A Comparative Analysis of Variations in Synthetic Biology Regulation

by

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Dedication

No research project can succeed without the help of others. Even more so for qualitative research, which is inherently driven by collaboration, patience, and a significant amount of good luck. This dissertation has my name as its author, but in truth is the result of so many dozens of people who agreed to lend a helping hand one way or another.

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Chapter 1:

Introduction – Understanding Variations in Synthetic Biology Regulation

1.1 Introduction

Emerging technologies (or those technologies with novel characteristics or components that differ from conventional options) challenge the understanding of policymakers and regulators to understand the technology's potential risks and benefits due to the uncertainty that such technologies inherently possess (Ludlow et al 2015). With regards to their scope, a report issued by the United States' Presidential Commission for the Study of Bioethical Issues describes emerging technologies as revolutionary and/or evolutionary technological and scientific advances that are geared to improve various aspects of human life (PCSBI 2010). This report specifically sought to review the risks and regulatory concerns of novel biotechnologies, and noted on behalf of the United States government that the technologies' uncertainties make regulatory reform for such technologies difficult to accomplish without further experimentation and research (PCSBI 2010). Further, the report also acknowledges that many such technologies have 'dual use' concerns, where the perceived benefits from a particular technology or innovative product may also be coupled with risks driven by an intentional misuse of technological innovation for deliberately hazardous purposes (PCSBI 2010). For such emerging technology enterprises, understanding the differences between novel and generally unconventional health risks versus well-understood conventional health risks is of high importance to regulators and decision makers (Bates et al 2015). This is driven by concerns where novel risks may arise from the emerging materials or engineering processes that traditional regulatory paradigms may or may not be able to properly cover (Carter et al 2014).

However, not all emerging technologies possess the uncertainty and novel health risks that key stakeholders must consider when reviewing an emerging technology's governance. All innovation poses some degree of uncertainty and risk, yet a contrasting point for those

emerging technologies containing uncertain risks includes their novel physical characteristics which could drive them to act in an unpredictable and irreversible manner (Moe-Behrens et al 2014). Current examples of this includes nanotechnology and synthetic biology. For the former, Maynard (2007) notes that "some purposely made nanomaterials will present hazards based on their structure—as well as their chemistry—thus challenging many conventional approaches to risk assessment and management", indicating that the chemical and structural novelties of such nanomaterials pose possible novel yet uncertain threats to human and environmental health. Likewise for synthetic biology, the substantial modification of an organism's DNA may contribute to the transfer of novel genetic information to the natural environment that could yield uncertain and irreversible risks to plant, animal, and human biology (Schmidt et al 2008; Cardinale & Arkin 2012; Dana et al 2012; Wright et al 2013; Dröge et al 1998).

1.2 Synthetic Biology

Synthetic biology is one of the more recent cases of emerging technology development, where the technology is purported to contain significant potential benefits to a variety of industries (Tucker & Zilinskas 2006; Neumann & Neumann-Staubitz 2010; Dormitzer 2013). The 'novelty' expressed within synthetic biology research includes several different factors, but generally includes the ability of synthetic biology research to generate greater control of genetic systems and the enabling of novel gene expression through the application of standardized engineering techniques to biology and thereby create organisms or biological systems with novel or specialized functions (Tabor et al 2009; PCSBI 2010).

The ability to alter, manipulate, and control cell expression has driven many scholars to hypothesize the technology's potential benefits within fields ranging from medicine (Dormitzer et al 2013; Paddon et al 2014) to ethanol production to insect population control (Georgianna and Mayfield 2012; Nading 2015). One specific area of this includes pharmaceutical development, where synthetic biology has been purported to provide several benefits to this field (Weber and Fussenegger 2009; Weber and Fussenegger 2012). Such discussed benefits include the ability to speed up the rate of drug and vaccine production (Dormitzer 2013; Rojahn 2013), facilitate the production of pharmaceutical components that are expensive or scarce

naturally (Paddon et al 2014), or even advance research on vaccines and drugs for diseases with limited to no vaccine, treatment, and/or cure (Barocchi and Rappuoli 2015; Ando et al 2014; Bugaj and Schaffer 2012). Such benefits have worldwide implications for delivering treatments to areas around the world suffering from debilitating disease (Barocchi and Rappuoli 2015; Paddon et al 2014), and improve public health response times and treatment capabilities to various pandemics (Dormitzer 2013).

This potential has already been partially realized for the treatment of malaria (Keasling 2012; Nandagopal and Elowitz 2011). Researchers have successfully produced the antimalarial drug precursor known as artemisinic acid from engineered Saccharomyces cerevisiae yeast, which has shown promise in malaria treatment (Paddon et al 2014; Ro et al 2006). In 2004, Keasling et al received a $42.5 million grant by the Bill and Melinda Gates Foundation to develop this research for eventual distribution in malaria-stricken countries (Cameron et al 2014). The drug was launched for commercial use by Sanofi in April 2013 (Sanders 2013). By May 2015, 15 million treatments were shipped to Africa, with projections of 100-150 million treatments to be produced via this method for use in Africa, Asia, and South America per year (TwistBioScience 2015). Stöhr (2014) and Vohra and Blakely (2013) note that other diseases have been targeted for future synthetic biology research, such as limiting the incidence and health consequences of diarrheal disease, mass-producing drugs for HIV treatment, and reducing the timeline needed to produce influenza vaccinations.

However, synthetic biology may also yield potential novel health risks. While synthetic biology product development may generate conventional health risk that are relatively well understood and known from non-synthetic biology drug and vaccine use, considerations of how the technology may generate problems for biosecurity and biosafety require a measured response by regulators and policymakers (Kelle 2009). From a biosafety perspective, this includes the concept of horizontal gene transfer (the transfer of genes between organisms in a manner other than traditional reproduction), where horizontal gene transfer is a particular problem of concern for synthetic biology as such gene transfer “is a common and somewhat uncontrolled trait through the microbial biosphere.” (Schmidt et al 2008; Cardinale and Arkin 2012). A specific concern of horizontal gene transfer includes the notion that modified cells may

transfer synthetic information to the natural environment and yield negative or unanticipated consequences (Schmidt et al 2008; Cardinale & Arkin 2012; Dana et al 2012; Wright et al 2013; Dröge et al 1998).

Likewise for biosecurity, concerns by policymakers and regulators reflect fears that a nefarious agent or bioterrorist could utilize principles of synthetic biology to produce a biological weapon, and with disastrous consequences (Kelle 2009; National Research Council 2004). The central issue here includes the notion of 'dual use concerns' raised in the PCSBI (2010) report noted above, where such nefarious actors utilize synthetic biology research in a manner that deliberately yield harms to humans, animals, or the environment. As with synthetic biology's benefits, synthetic biology biosafety and biosecurity risks will be discussed in Chapter 3.

The novel and uncertain health risks produced by synthetic biology research includes the substantial genetic modification of cells that, under certain circumstances, could have deleterious effects upon humans and/or the natural environment (Mukunda et al 2009; Moe-Behrens et al 2014). Given such uncertainties, regulators and key stakeholders may or may not seek to consider whether or not traditional measures of governance are sufficient to protect humans and the environment from significant health risk (Wiek et al 2012; Kuzma & Tanji 2010). The pathways of such risk may include, among others:

i) exposure in a laboratory setting (Rabinow & Bennett 2012),

ii) accidental releases in an occupational/production setting (biosafety) (Schmidt 2008),

iii) intentional release of potentially harmful microorganisms (biosecurity) (Vogel 2014),

iv) acute risk concerns to individual human health upon commercialization (Fatehi & Hall 2014), and

v) improper disposal of such microorganisms upon their end-of-life disposal and their unintended proliferation in the environment (Traavik 2000; Myhr & Traavik 2011; Ho et al 2001).

In this way, attempts to review risk of synthetic biology products such as pharmaceuticals must consider collective biosafety and biosecurity concerns that could generate health concerns to humans, animals, and/or the environment (Bates et al 2015; Carter et al 2014). Normatively, to protect against uncertain technological risks associated with synthetic biology's biosecurity and biosafety concerns, policymakers and key stakeholders within a given country must engage in active governance of the field based upon their perceptions of how serious such risks actually are.

However, local regulation and governance does not occur in a vacuum, where contextual factors such as with regulatory history and institutional culture may influence how technologies are regulated in a unique manner from one government to another (Parthasarathy 2012; Kelemen 2011; Kagan 1991). Synthetic biology is no exception to this rule, where individual governmental systems such as with the United States, the European Union, and Singapore have all adopted differing approaches to regulate and govern the process of synthetic biology development despite limited information regarding technological risks and hazards (Bar-Yam et al 2012; Bates et al 2015). Such differing approaches serve as the focal point of this dissertation, and are expanded upon below in Section 1.3. Overall, however, this dissertation seeks to understand the extent of how various elements of risk culture as independent variables explain varations in synthetic biology regulation within the three cases noted above.

Where Sections 1.1 introduced the general issue of accounting for emerging technology risk under high uncertainty and 1.2 further applied this concern to synthetic biology, the remainder of this chapter outlines both the general focus of this dissertation as well as the key concepts that will be used throughout the remaining chapters. Specifically, Section 1.3 outlines the focus of this dissertation upon explaining variations in synthetic biology regulation. Further, that section also outlines the explanatory hypotheses regarding the drivers of such variations, where these hypotheses are tested to determine the effect that specific elements of risk culture may have upon generating these regulatory variations for synthetic biology across the three governments examined here. Later, Section 1.4 defines and unpacks key terms that are essential to understanding regulatory variations for synthetic biology, including (i) regulation,

(ii) governance, and (iii) legalism. Lastly, Section 1.5 lays out the structure for the overall dissertation.

1.3 Identifying Variations in Synthetic Biology Regulation – Driving Theories for the Dissertation

After understanding the general concerns raised by the uncertain and potentially risky nature of emerging technologies like synthetic biology noted in Sections 1.1 and 1.2, this section outlines how this dissertation reviews one area of concern that arises amidst such uncertainty – the differing regulatory stances taken by various governments engaged with the technology's research and development. In this way, this dissertation seeks to explore two general research questions, including (i) do variations for synthetic biology regulation exist across specific case countries, and (i) if so, why do such variations occur?

In this manner, this study takes a comparative approach to review the regulatory instruments and actions of the United States, European Union, and Singapore that capture the process of synthetic biology pharmaceutical development. As such, this dissertation will review whether such regulatory variations exist between the three cases, and if so, review whether elements of risk culture may influence such variations. Overall, this dissertation adopts the stance that elements of legalism and risk culture may explain the differing regulatory approaches utilized within each of the three cases studied here (Vogel 2001; Jasanoff 1986; Jasanoff 1987).

Further, this dissertation argues that the factors of path dependency (i.e. how the historical path of regulatory reform and decision making influences future decision making) and governmental legalism (the style of regulatory dispute resolution possessed by each individual government) serve as key variables of consideration for this research question. For the former, Jasanoff (1986), Vogel and Lynch (2001), and Parthasarathy (2012) indicate that such path dependence may have a role not only in binding the regulatory options available to govern emerging technology risks, but also influencing how those risks are perceived by local policymakers and stakeholders. This dissertation argues that this factor is the strongest element of risk culture to influence regulatory variations on synthetic biology, where path dependency

in each of the three cases has influenced the regulatory authority and mechanisms available to govern the process of synthetic biology development (Carter et al 2014; Bar-Yam et al 2012).

For the latter, Kelemen (2011), Kagan (1991), and Volcansek (2014) contend that the inherent cooperational or adversarial style of legalism within a given government influences regulatory decision making, and can have a strong influence upon whether such governments can adapt quickly to emerging risks such as with emerging technologies. This dissertation argues that such legalism has a lesser but still significant effect upon regulatory variations. This is particularly due to the ability of an adversarial style of legalism to favor the regulatory status quo and increase the political resources needed to generate regulatory reform, where a cooperational style of legalism is less encumbered by such formal and resource-intensive barriers to adaptive and anticipatory regulation.

Below, risk culture is further defined and unpacked inclusive of the factors described above as well as other considerations that may or may not influence variations upon synthetic biology regulation within the United States, European Union, and Singapore.

1.3.1 Risk Culture and Variations on Synthetic Biology Regulation and Governance

Within each government, risk culture serves as the sum of local culture, politics, and institutions within a given government that influences governmental perception of risk and ability to act against potential challenges and emerging risks (Lash 2000; Van Loon 2002; Douglas and Wildavsky 1983; You 2015). One particular avenue of this includes emerging technologies, where the unique institutional and political factors within a government may cause it to regulate a particular emerging technology in a manner entirely different with other governments – even in the presence of identical information on the technology's hazard, exposure, and health consequences (Wildavsky and Dake 1990; Parthasarathy 2012).

In this way, risk culture in this dissertation focuses on factors ranging from government structure to history of regulatory development to perceptions of technological benefit. Further considerations include the style of legalism and 'legal culture' within each government (Kelemen 2011; Kagan 1991), which are also tested alongside more traditional considerations of risk culture such as with regulatory path dependency (Jasanoff 1986). However, risk culture in

this context does not consider unique demographic factors (local considerations of religion, race, ethnicity, population size/makeup, etc.), economic considerations (i.e. the economic strength or capabilities of a state), or existing scientific capability (i.e. the degree of advancement and complexity within synthetic biology research). Many of these factors are introduced and discussed within each case's background, but are not studied as potential independent variables to explain variations in government regulation of synthetic biology (for similar approaches and discussion, see also Douglas and Wildavsky 1983, Jasanoff 1986, Kelemen 2011, and Volcansek 2014).

Further for this dissertation, the different avenues of risk culture and legalism are respectively operationalized:

i) the degree of centralization in government power (autocratic/authoritarian, multipolar democratic, etc.) (Kagan 1991; Knutsen 2015; Kelemen 2011)

ii) how disputes in regulatory decision making are resolved (i.e. formally via courts, or informally via government-stakeholder meetings) (Kelemen 2011; Volcansek 2014),

iii) the historical path of regulatory reform (Vogel and Lynch 2001; Jasanoff 1986),

iv) the perceived practicality and benefits of the technology to a nation (in other words, will the technology be useful and provide substantial benefits and minimal risks versus more conventional options?) (Lofstedt and Schlag 2016; Söderholm et al 2015).

This case study sought to test how societies interpret and regulate risk in a unique manner. In other words, a government's risk culture influences not only how regulators and legislators perceive risk within a potentially hazardous practice, but also the ability, willingness, and drive of such government actors to reform existing regulations or establish sui generis regulation for an emerging technology altogether. Further, the concept helps account for the institutional and bureaucratic histories, interactions, and interdependencies to execute regulation and governance for emerging technologies – something noted as crucial for the study of governance by Levi-Faur (2013) and Abbott and Snidal (2012). As such, each of these

characteristics of risk culture are used as hypotheses to test, via qualitative expert elicitation, which factors if any have influenced the three comparative cases to produce differing and divergent regulatory policies for synthetic biology in general and pharmaceutical production in particular. Ultimately, these four hypotheses are tested individually to review the qualitative strength that these factors have individually upon influencing variations in synthetic biology regulation across differing governments.

The three geographic cases within this comparative assessment include the United States, European Union, and Singapore. The United States and European Union were chosen at the onset of this research due to their status as housing various research centers and institutions engaging in synthetic biology research, alongside the growth of various conferences focused on the technology's development being held in both areas on a national and international scale since at least 2004 (Cameron et al 2014; Kuiken 2015). Both cases here are examples of transparent authorities with power-sharing across different actors of government.

Divergent from the initial two examples, Singapore is, instead, more authoritarian in its approach to regulation and governance, and is less transparent than its Western partners. Further, it remains several orders of magnitude smaller than the other two cases in the size of its research capacity, gross domestic product, and population count. However, its state funding for local universities such as with the National University of Singapore and Nanyang Technological University on the subject of synthetic biology and medical products such as pharmaceuticals make it relevant for study regarding the promotion of adaptive regulation and governance of synthetic biology products (Mitchell 2011; Oldham et al 2012). Additionally, Singapore's extensive commercial and research connections in higher education with other Asian nations such as China, Sri Lanka, Malaysia, Indonesia, and others also makes it a potential window by which to assess an Asian example of synthetic biology research and development alongside the challenges of balancing precaution and proaction as it matures (Welch 2015).

1.4 Factors for Consideration for Governmental Risk Culture: Key Definitions and Concepts

After outlining the general research question and hypotheses for this dissertation, this section further unpacks the various terms and theories that will be deployed throughout the

remaining chapters. Specific considerations include (i) adherence to a precautionary or proactionary mindset towards risk regulation, (ii) the hard and soft law regulatory instruments available to capture the process of synthetic biology development within a given government, and (iii) the instrinsic style of governmental legalism as outlined by Kagan (1991) and Kelemen (2011).These considerations directly relate to the four components of risk culture and style of legalism noted above, where such factors explain how power is centralized within governments, which priorities and considerations governments are required to consider when engaging with regulatory reform, and how easily such reform is accomplished. In turn, these considerations offer tools by which the four hypotheses may be comparatively reviewed across the three cases included here.

1.4.1 Precaution versus Proaction: Engaging in Synthetic Biology Research and Development

Looking first at precaution and proaction, governments have adhered to the precautionary principle to varying degrees in their risk management of emerging technologies like synthetic biology. The precautionary principle has roots pertaining to the aphorisms such as "better safe than sorry" in 1980s publications on government regulation in Europe (Christiansen 1994), and was established in German environmental law as the concept *Vorsorgeprinzip* in the late 1970s and early 1980s (Boehmer-Christiansen 1994). At its core, the precautionary principle serves as a motivational philosophy to drive risk management (Lofstedt 2003).

Later, the precautionary principle became an established international norm via the Rio Conference of 1992, which contributed to an international statement by the United Nations dubbed 'The Rio Declaration' (Harremoës et al 2013). Specifically, the Rio Declaration stated that:

> "*In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*" (Harremoës et al 2013). The purpose of the Rio Declaration was to promote sustainable development in a manner that promotes human welfare and advancement while preserving environmental health and quality internationally (Viñuales 2015).

Further extensions of the precautionary principle after the Rio Declaration included the Cartagena Protocol on Biosafety, which sought to protect biological diversity from threats posed by genetically modified organisms (Ansari and Wartini 2013; Gupta 2015). Passed in 2000 and in effect since 2003, the Cartagena Protocol reaffirmed the precautionary approach adopted in the Rio Declaration with applications the genetically modified organisms. Specific to this point, the Cartagena Protocol noted the importance of uncertainty within the decision making context for such organisms, where the Protocol insists that signatories take appropriate steps to avoid or minimize adverse effects of modified organisms in all cases regardless of the availability of scientific information (Gupta 2015).

In the aftermath of these international conventions, the precautionary principle has been interpreted in a number of different ways. Some of the more common interpretations include (O'Riordan 1994; Tosun 2013):

i) preventative anticipation

ii) safeguarding of ecological space

iii) proportionality of response or cost-effectiveness of margins of error, and

iv) duty of care, or onus of proof on those who propose change

O'Riordan (1994) states that items one and two are driven by the need to prepare for and protect against risks from uncertain or unknown technological developments until more evidence is available to facilitate their risk assessment. For item one, focus is centered on the need to "to take action in advance of scientific proof of evidence of the need for the proposed action on the grounds that further delay will prove ultimately most costly to society and nature, and, in the longer term, selfish and unfair to future generations" (O'Rioran 1994). On the other hand, item two seeks to establish the notion that the limits of risk tolerance amongst humans and the environment should not even come close to being approached – let alone breached (Origgi 2014).

Item three takes a different approach by indicating that the selected degree of precaution or restraint does not pose undue or excessive cost to developers and other stakeholders in favor of technological development (Origgi 2014; O'Rioran 1994). In other words, this approach requires risk managers to account for cost *and* benefit in their risk

calculations – something that Origgi (2014), O'Rioran (1994), and Tosun (2013) argue is inherently difficult due to the uncertain nature of emerging technologies. Further, O'Rioran (1994) states that such a mindset introduces bias into cost-benefit calculations by potentially allowing for inaccuracies in general risk perception.

Lastly, item four encourages risk managers and regulators to adopt an approach where innovators are required to overcome a burden of proof that their products cause no undue harm, and such innovators and developers are required to compensate those harmed by their products (Owen et al 2013). O'Rioran (1994) argues that this approach may or may not seek to balance potential technological advances and economic benefits against environmental and human health risks, yet generally seek to outline clear liability and damage amelioration by innovators and developers should any risky events arise.

The precautionary principle is often discussed within the context of emerging technologies research, where the need to avoid potentially harmful risks is an important task for regulators to fulfill within the scope of technological uncertainty and development (Kelle 2013; Grunwald 2012; Kelle 2009). For synthetic biology, this includes the need to avoid the potential for horizontal gene transfer and other potential novel risks associated with human and environmental health alongside the need to prevent the rise of biosecurity threats (Kelle 2009; Dana et al 2012; Wright et al 2013; Dröge et al 1998). Such calls for the precautionary principle in such research stem from the Cartagena Protocol related to genetically modified organisms, organisms engineered via synthetic biology processes fall under the category of 'living modified organisms' and share similar uncertainties relative to their impact upon natural organisms (Kuiken 2015).

For purposes of this dissertation, the precautionary principle is discussed as where the introduction of a new product or process whose ultimate effects are disputed or unknown should be resisted (Sandin 1999; Kriebel et al 2001). As a risk management tool, this mentality falls within *preventative anticipation* and *safeguarding of environmental space*. Within such an arrangement, regulators and risk managers are required to prepare for and protect against risks from uncertain or unknown technological developments until more evidence is available to facilitate their risk assessment (O'Rioran 1994; Origgi 2014).

Such an approach was discussed and reinforced at the Asilomar Conference on Recombinant DNA of 1975 (Ansari and Wartini 2013; Hurlbut 2015). At the Conference, 140 professionals (including biologists, physicists, lawyers, and others) met to discuss the potential risks that may arise from novel and developing field of genetic engineering (Ansari and Wartini 2013). Specifically focused on the potential risks of recombinant DNA (or the ability to bring together DNA from multiple sources – creating sequences that would not be found in nature), discussants voiced opinions that the potential biosafety risks associated with the technology's use warranted a moratorium on such recombinant research (Carmen 1985). The lasting impact of the Conference was to apply the precautionary principle to research on recombinant DNA and other work on genetic engineering as well as to propose voluntary agreements to improve the governance of such research via soft law (Friedberg 2014).

An opposing perspective to the precautionary principle includes the proactionary principle (Chen et al 2015; Newson 2015; Suppan 2014). Proponents of proaction seek to advance technological prowess by reducing governmental and regulatory impediments to the technology's development (Fuller and Lipinska 2014). Further, proponents of the proactionary principle seek to consider the opportunity costs associated with limiting innovation via a restrictive measure against potential risks and damages posed by the new technologies, as opposed to consideration of damages by themselves (Fuller and Lipinska 2014). Synthetic biology has such proponents, where a proactionary approach is stated as the manner in which synthetic biology advances in medicine, industry, and various other fields will develop and mature (Murray 2010).

Such a proactionary context must account for the need for a 'responsible stewardship' of the technology in the midst of potential risks to human and environmental health (Colussi 2014), yet generally is framed from the perspective of the technology as providing eventual benefits to health that far outweigh risks, which are occasionally framed as minute or highly unlikely (Glick 2012; Beyleveld and Brownsword 2012). Overall, however, the proactionary principle has remained limited in scope and driven as a response to those who argue that the precautionary principle hinders technological development (Bennett et al 2009; Colussi 2013). Tenets of the proactionary principle have not been formally adopted by any government on the

subject of technology regulation (Colussi 2013), although it does serve as an emerging school of thought on the subject of emerging technology regulation that government regulators may consider in the near future for synthetic biology and genetic modification (Kaebnick et al 2014; Fuller and Lipinska 2014).

1.4.2 Hard and Soft Law

Aside from considerations of precaution and proaction, another important term to understand synthetic biology regulation within each government is the use of hard and/or soft law to capture the process of synthetic biology development. Hard law, or the formal legislation passed and implemented by legislative authorities within a given government, serves as a resource-intensive yet legally binding approach to regulate risky activities (Trubek et al 2005; Mandel et al 2014). On the other hand, soft law serves as a more flexible yet nonbinding approach for agencies to indicate recommendations and best practices for technology development (Mandel et al 2014). Generally speaking, these concepts are key to understanding the regulatory tools and instruments available to individual governments for the governance of synthetic biology, and serve as central considerations for both legalism (i.e. how are differing governments able to shape/reform emerging technology governance) as well risk culture considerations of path dependency (i.e. how previous regulations, recommendations, and best practices of the past shape current and future capabilities for technology governance reform). As such, these terms will be utilized throughout each case in Chapters 4-7.

Schaffer and Pollack (2010) and Blauberger (2009) describe hard law as the legally-binding instruments taken by legislatures and executed by regulatory agencies to govern specific activities. An advantage to the development of such hard law is that once passed and implemented, it has the advantage of possessing the full force of law of and thereby must be followed as described (Gluck 2011). Further, such hard law has the ability to establish new executive agencies or expand the power of existing ones to cover regulatory activity as established in the law (Mandel et al 2014). Using such authority, regulatory actors can capture synthetic biology development under their existing pre- and post-market reviews which allow them to gauge the safety and efficacy of a given product. Within such legislative change,

innovators and developers would generally be unable to bring a new substance or product to market without such approval or a corresponding waiver from the given regulatory agency in a manner identical to existing pharmaceutical regulation (Markell 2014; Carter et al 2014).

However, the development and implementation of hard law can be hindered by the political and institutional difficulties with getting desired legislation passed in an effective and efficient manner (Mandel et al 2014). In the United States, for example, hard law often requires significant political resources and support in order to pass a government's legislature, and thereby can be significantly delayed, altered, or otherwise prevented from being passed due to political disagreements and/or an unwillingness to expand the power of certain government agencies (Schaffer and Pollack 2010). Kelemen (2011) and Kagan (2008) also state that such hard law also requires political resources and manpower in the European Union, although they note that this may be alleviated somewhat by the cooperational nature of European legalism (see Section 1.4.4 below). Concerns of hard law passage and implementation are less problematic for Singapore due to the high degree of power centralization and informal approach to dispute resolution, yet hard law changes are generally minimized in order to avoid perceptions of abuse of power and to maintain public trust in a predictable and fair regulatory system (Turner 2015; Reilly 2016; Ortmann 2012; Olds 2007).

While the passage of new legislation is often burdened by the need for significant political resources and compromise in order to get such law passed, soft law empowers certain governments with the ability to avoid such logjams by allowing for the imposition of guidelines, best practices, and rules to indicate proper behavior and actions by innovators and developers (Marchant et al 2013; Mandel et al 2014). Virtually all national governments have some capability to foster and implement variations of soft law, yet for some this task is a much more common and politically feasible task (Brady and Vogel (2001; Volcansek 2014). As such, considerations of soft law are important for this dissertation where the differing levels of potential use of soft law by the three case governments may indicate how certain governmental systems institute regulatory reform easier than others, and serve as mechanism to better understand the legal elements of risk culture (i.e. adversarial and cooperational legalism) within each case country.

Such soft law can come in various forms such as with voluntary programs, consensus standards, partnership programs, codes of conducts, principles, and certification programs that developers and innovators are asked to abide by (Schaffer and Pollack 2010; Trubek 2006). Such guidance documents and recommendations created by regulatory agencies are established outside of the traditional route of lawmaking, making them politically easier to develop and utilize by agencies with cases of technology regulation like synthetic biology (Bradley and Posner 2006). Further, soft law approaches initiated by members of industry via multi-stakeholder, public-private, or industry-NGO arrangements further outline voluntary best practices and codes of conduct that seek to drive technology development towards reducing risk via best practices (Mandel et al 2014).

A crucial consideration here includes the fact that soft law includes both government and non-governmental activity – particularly within key stakeholders in industry (Cini 2001; Shaffer and Pollack 2010; Senden 2005). Specific to synthetic biology, Marchant and Scheckel (2014) state that the private standards, guidelines, codes of conduct, and partnership programs utilized by industry to meet emerging challenges and enable relevant researchers to advance development of commercial products. Further, Marchant and Scheckel (2014) note the importance of both government and industry players relative to soft law development for a given technology, where positive relationships between both sets of players are important to overcome adversarial relationships that potentially hinder technology regulation and governance.

Mandel et al (2014) further note that soft law can "impose substantive expectations or requirements", yet "are not directly enforceable" in a manner similar to legislation or Executive Orders, nor offer regulatory agencies the same coverage and legitimacy in action as with hard law. However, Guston and Sarewitz (2002) and Mandel et al (2014) do indicate that soft law approaches to governance can work within "new governance modes of oversight", where government oversight capabilities are broadened to include the participation of other relevant stakeholders such as within industry, subject experts, and non-governmental organizations. In such a model, Mandel et al (2014) contends that soft law governance can be extended beyond

national and regional borders to influence international governance of a technology's regulation.

1.4.3 Regulation, Governance, and Risk Governance

A further crucial consideration includes the definition and scope of regulation, governance, and risk governance that will be used throughout the remainder of the dissertation. Such terms are central to understand regulatory variations for synthetic biology, where their common usage has produced multiple definitions for various applications in government oversight and activity. However, for purposes of this dissertation, the definitions used in this section are explicitly focused with respect to technology development.

1.4.3.1 Defining Regulation

Looking first at regulation, Levi-Faur (2011) notes that regulation is hard to define because it maintains so many different meanings to different people. From a state-centered disciplinary focus, Laffont (1994) argues that regulation centers on the development and execution of state-made laws. This perspective is similar to scholars of public administration, where examples such as with Coen and Thatcher (2005) and Gilardi (2005) view regulation as the scope of state authority as laid out by regulatory authority. However, Levi-Faur (2011) also notes that scholars of global governance discuss regulation as including the soft norms and standards that drive international conventions and agreements (see also Dejlic and Sahlin-Andersson 2006).

Further, some scholars have discussed the potentially normative nature of regulation, where such government action may be 'good' or 'bad' depending on perspective and context (Hood et al 2001; Hutter 2001). Levi-Faur (2011) describes this normative question as being centered on considerations of cost and benefit, where regulations may hinder or amplify economic activity by establishing best practices and standards to follow. Consideration of such regulatory costs and benefits have even been reviewed and predicted via regulatory impact analysis assessments, where such tools of risk management seek to understand whether a regulation will offer net-positive results to a society (Sunstein 2002).

Both Levi-Faur (2011) and Black (2002) argue that based upon the complexity and numerous perspectives on the field, establishing a catch-all definition of regulation is unproductive and limits the ability of scholars to review the causes and effects of regulation within specific contexts. With this in mind, Selznick (1985) does note that the study of regulation is inherently focused on the connection between legislative bodies and regulatory agencies to develop and implement new standards for society to follow. Using this core understanding of regulation, this dissertation adopts the viewpoint of Laffont (1994), Coen and Thatcher (2005), and Gilardi (2005), where regulation serves as the development and execution of state-made laws. However, this dissertation acknowledges that a focus only upon state authority would limit discussion of technology regulation, where consideration of non-state and industry activity within regulation and governance are noted below in Section 1.4.3.2 (see also Levi-Faur 2011).

1.4.3.2 Theory of Governance

A central element of risk culture inherent within a given government includes the style of governance utilized to capture the process of synthetic biology development and manage its potential risks. In other words, the differences in the style of governance serve as a main concern that this dissertation seeks to review, where different elements of risk culture and legalism are individually hypothesized as contributing to such variations in governance-style.Multiple viewpoints and definitions of governance have arisen, such as with Levi-Faur (2011), Kersbergen and van Waarden (2004), Fukuyama (2013), and Börzel and Risse (2010). For starters, Fukuyama (2013) defines governance as "a government's ability to make and enforce rules, and to deliver services, regardless of whether that government is democratic or not." This perspective is helpful for this dissertation, where cases included for discussion are both democratic and undemocratic in nature. Levi-Faur (2013) acknowledges Fukuyama's (2013) perspective, but argues that governance is broader than the state-centric approach inferred by Fukuyama. Further, Levi-Faur (2013) and Levi-Faur (2011) state that governance is more than just government capacities, but also includes the involvement of the private sector

and other non-government entities. Levi-Faur (2013) and Kersbergen and van Waarden (2004) use this perspective by defining and describing governance as:

> *"the approach is pluricentric rather than unicentric. Second, networks, whether inter- or intraorganizational, play an important role. These networks organize relations between relatively autonomous, but interdependent, actors (e.g., business firms in a sector, public and private organizations, EU Member States). In these networks, hierarchy or monocratic leadership is less important, if not absent. The formal government may be involved, but not necessarily so, and if it is, it is merely one – albeit an important – actor among many others. Third, one finds an emphasis on processes of governing or functions as against the structures of government. These processes are relatively similar in the public and private sectors, and concern negotiation, accommodation, concertation, cooperation and alliance formation rather than the traditional processes of coercion, command and control. Fourth, the relations between actors pose specific risks and uncertainties, and different sectors have developed different institutions to reduce these in order to make cooperation possible or easier. Finally, many approaches are normative. They prescribe an ideal as well as an empirical reality. This holds in particular for the 'good governance', 'corporate governance', 'new public management' and 'multilevel governance' approaches."*

Within such an approach noted above, Levi-Faur (2011), Kersbergen and van Waarden (2004), and Börzel and Risse (2010) do not argue that researchers should ignore or minimize the importance of the state within the study of governance. However, the authors do argue for the need for multi-level approach to governance that includes non-governmental actors such as within industry. Further, Levi-Faur (2013) and Abbott and Snidal (2012) note that the study of governance should also account for the interdependencies and interactions by different institutions and bureaucratic agencies within the regulatory development process, where the scope and magnitude of such interactions can shape how regulatory reform is carried out and implemented.

For this dissertation, governance is reviewed as the processes and capabilities of a given government to manage or govern an activity, regardless of whether the state is democratic or

not (Fukuyama 2013; Pierre 2000; Perry & May 2007; Bevir 2008). These processes and capabilities may vary with respect to the regulation and governance of synthetic biology, where elements of risk culture and legalism are hypothesized as being the potential cause of this. Further, while regulation focuses on governmental authorities and instruments, governance includes the involvement of both governmental and non-governmental actors involved with the risk management of emerging technologies (Kersbergen and van Waarden 2004; Levi-Faur 2011). This multi-level arrangement is all reviewed under the consideration of the institutional interactions and relationships that influence how regulation is established and implemented – something that will prove to be important for the study of 'risk culture' in Section 1.4.4 below (Abbott and Snidal 2012).

1.4.3.3 Introduction to Risk Governance

Where synthetic biology's high uncertainty related to potential novel health risks and limited guidance may challenge existing national governance paradigms dedicated to chemical and traditional genetic engineering, synthetic biology requires the use of risk governance to assess technological risk while suggesting ideal hard and soft law to govern synthetic biology moving forward. According to the International Risk Governance Council, risk governance applies the principles of good governance to the identification, assessment, management and communication of risks in situations of high risk and uncertainty alongside multiple stakeholders (IRGC). For synthetic biology and pharmaceutical research and development, risk governance requires a consideration of both hard and soft law in order to govern the field in a way that neither exposes humans to undue risk nor is too prohibitive with respect to allowing a potentially beneficial field to mature and develop (Mandel et al 2014). In this way, synthetic biology regulation and governance requires an inherent consideration of the precautionary and proactionary principles, respectively (Newson 2015; Gutmann 2011; Bubela et al 2012).

However, a significant challenge to promoting effective risk governance and balancing the precautionary and proactionary divide includes the notion of regulatory pacing, where Kuzma and Tanji (2010) and Kuzma (2013) argue that pacing of more complex genetic engineering capabilities like synthetic biology may outstrip the capabilities of existing

regulations to adequately cover synthetic biology product governance. Such discussion was further echoed by Carter et al (2014) and Bar-Yam et al (2012), and which noted that as synthetic biology products become increasingly artificial in their genetic makeup, they will come to challenge the ability of existing regulatory structures to cover the product's research, production, sale, and disposal. Further, Carter et al (2014) state that such pacing problems are already occurring in the United States, where regulatory agencies like Animal and Plant Health Inspection Service, the Environmental Protection Agency, and the Food and Drug Administration are losing their ability to regulate certain synthetic biology products. Overall, as synthetic biology's pacing problems challenge the ability of governments to cover a particular product's risks, the need for governance reform via hard and/or soft law may become necessary to update such regulation and governance over time (Paradise et al 2009; Wolf et al 2012).

An avenue to improve regulation for synthetic biology products and prevent the development of pacing problems outlined in Kuzma (2013) includes the concept of adaptive or anticipatory governance, where more flexible and less politically-intensive soft law approaches may provide flexible yet temporary guidance mechanisms to promote oversight, codes of conduct, and best practices for synthetic biology's pharmaceuticals (Mandel et al 2014; Guston 2014). This adaptive approach allows regulatory bodies to maneuver in a more active fashion in the face of developing technologies such as synthetic biology without requiring significant political resources or action by leading lawmakers that are traditionally less capable of developing quickly (Gorman 2012; Mandel et al 2014).

Adaptive and anticipatory governance was posited as potentially necessary by the Presidential Commission for the Study of Bioethical Issues, where regulators are able to revisit past regulatory decisions related to synthetic biology product risks and amend guidelines and rules as necessary based upon the availability of new information that warrants a change in the product's overall governance (PCSBI 2010). Under this purview, Mandel et al (2014) advocate for the use of soft law governance as it "can often be adopted more rapidly and amended more quickly than traditional regulation, providing a more adaptive oversight system." Such a framework also allows for greater flexibility with adjusting rules and guidelines to anticipate

incoming challenges for synthetic biology governance (Fatehi and Hall 2014; McNamara 2014), where new activities, products, or areas of novel risk may warrant a review by regulators with respect to whether or not existing guidance is sufficient to monitor and regulate risks from such products. Tucker and Perkins (2010) agree with Mandel et al (2014) in that not only can soft law be shifted on an as needed basis more rapidly than hard law legislation, it may also be extended beyond regional and national boundaries and be taken up as a collaborative model that review the international exchange of synthetic biology products in a safe yet efficient manner. This is a helpful notion as synthetic biology research and development is international in scope, making a common understanding of synthetic biology risk and governance beneficial as the technology's products are produced, consumed, and disposed of on an international scale.

1.4.4 Adversarial and Cooperational Legalism

A significant benefit of accounting for the unique political and institutional influences that make up a government's risk culture includes an understanding of the legal obligations and political possibilities relative to driving for regulatory change (Kelemen 2011; Kagan 2009). For the former, legal obligations via existing hard law includes those statutes and binding obligations that compel certain behavior in the regulatory process. These include formal requirements in the risk assessment process (i.e. what type of information and assessment is mandated within the context of emerging technology governance), clear notations of potential divisions in authority (i.e. which agencies or ministries have the legal mandate to execute such governance, and how does legal and/or regulatory change arise), and the formal requirements to drive regulatory change (see Carter et al 2014, Renn and Roco 2006, and Stirling 2008). These factors are all crucial to the regulatory development process within a given government, where those seeking reform must understand who has authority to legislate and institute new policy change (Jasanoff 1986; Kelemen 2011).

For the latter, the institutional and political realities behind regulatory change must be accounted for in order to craft governance that works within the government in question and yields the desired changes in regulation in a legal, expedient, and practical manner. Considerations here center on the behaviors and tendencies that policymakers, regulators, and

stakeholders express in the process of regulatory reform, where such behaviors and interactions can facilitate or complicate regulatory reform (Kelemen 2011; Kagan 1991). One of the concepts here includes the notion of adversarial/cooperative legalism, which is noted by Kagan (1991) and Kelemen (2011) as including notions of a government's (i) process to resolve regulatory disputes, (ii) requirements for transparency related to the dissemination of information, (iii) reliance upon formal or informal approaches to propose new technological governance, and (iv) the degree of combativeness that may be expected via legal challenges to regulatory proposals.

According to Kelemen (2011) and Kagan (1991), adversarial legalism is defined by (i) strict transparency and disclosure requirements in the regulatory reform process, (ii) legalistic approaches to regulatory enforcement and dispute resolution, (iii) financially costly legal contestation by companies and governments involved in regulatory disputes, and (iv) active judicial review of administrative decision related to regulatory reform. In this way, Kelemen and Sibbitt (2004) and Kelemen (2011) envision adversarial legalism in the United States as being notable for "enforcing legal norms through transparent legal rules […], empowering private actors to assert their legal rights." Overall, Kelemen (2011) and Kagan (2009) argue that legal requirements for transparency alongside formal and combative regulatory disputes within the courtroom contribute to a regulatory environment that makes it difficult for hard law to quickly or easily be passed and implemented within an environment of adversarial legalism.

Likewise, cooperational legalism is defined by (i) a reliance upon informal approaches to dispute resolution between actors in government, industry, academia, and non-governmental institutions to foster regulatory reform, (ii) limited use of legal disputes and judicial resolution to resolve disagreements amongst key actors in the reform process, (iii) often, less stringent requirements for transparency and disclosure of all activity related to government actions pertaining to reform, and (iv) coordinated discussion amongst stakeholders across government, industry, academia, and non-governmental institutions to drive regulatory best practices in a manner that is inclusive of various viewpoints and needs (Kagan 1991; Kelemen 2011; Kelemen and Sibbitt 2004).

Adherence to either an adversarial or cooperational approach to legalism is driven by a variety of factors, including, among others, the historical path of legislation for technology governance, the separation of powers and lawmaking capabilities within government, and cultural practices regarding the relationship between industry and government via regulatory disputes (Kagan 1991; Jasanoff 1986; Kelemen 2011). Each of the three cases in Chapters 5 – 7 will be reviewed for individual and unique elements of the respective government's risk culture that drive it towards and adversarial or cooperational style of legalism – an important driver of the types of regulatory reform that may be instituted without significant political, legal, and/or institutional resistance

The concept of adversarial and cooperative legalism was included in this dissertation due to its ability to explain key elements of a country's risk culture, with particular emphasis on how regulatory disputes are resolved within a given government. In other words, legalism as discussed above and expressed by Kelemen (2011) and Kagan (1991) offers a clear explanation regarding how and why regulatory change is easier to produce in certain governmental contexts than others.

1.4.5 Structure and Content of the Dissertation

Given the discussion noted above, the central argument of this dissertation is that elements of risk culture and legalism have a direct influence upon generating variations in the regulation and governance of emerging technologies within individual governments. As noted by Bar-Yam et al (2012), Carter et al (2014), and Bates et al (2015), the uncertainty behind the risks and hazards of such technologies create an environment where limited objective information is available by which to shape regulations and guidance for specific emerging technology developers, leaving such regulators and policymakers to utilize their existing authorities to capture the process of such technology development until sui generis regulation is justified. Synthetic biology is one such example of an emerging technology, where the technology's high uncertainty has contributed to diverging opinions on how the process and products of synthetic biology should be regulated and governed (Mandel et al 2014; Bar-Yam et al 2012; Carter et al 2014). Ultimately, this study finds that such variations in early stage

synthetic biology regulation are attributable to various elements of risk culture and legalism, with particular emphasis on the effect of the path dependence via historical regulation and legislation to limit the feasible options to apply existing regulation and future reform to synthetic biology and its various enabling technologies (for similar perspectives on path dependence fostering diverging regulatory and governance structures, see Vogel and Lynch 2001, Jasanoff 1986, and Parthasarathy 2012).

Looking towards the structure of the dissertation, Chapter 2 discusses the methodological approach to the literature review, subject interviews, and discourse analysis used to generate and assess qualitative data for this dissertation. The methodological approach described within this chapter was carried out in three phases for subject experts in the United States, Europe, and Singapore, and represents the demonstration regarding how each of the cases (i) perceive the novel health risks associated with synthetic biology research and development, (ii) discuss existing regulatory options to monitor and regulate such risks that account for the specific country's political, social, economic, and scientific drivers that influence local synthetic biology governance, and (iii) achieve regulatory change to improve coverage of synthetic biology development where necessary and helpful. Information generated from this methodology is used to drive the three-system comparative assessment in Chapters 4-7.

Next, Chapter 3 includes a more targeted discussion on synthetic biology, including information related to the field's history, the search for its definition, the scientific principles guiding synthetic biology research, the risks and benefits of such research, and existing conversations and debate for the technology's governance from 2000-2016. As such, this chapter provides a general understanding of the existing scientific capabilities expressed by synthetic biologists over time, and offers insight into the developments of synthetic biology's use with pharmaceutical development in particular.

Chapters 4-6 include these respective cases, which unpack the perceptions of synthetic biology pharmaceutical benefits, risks, and regulatory needs/capabilities as discussed by identified interview subjects and literature analysis collectively. Using the methodological approach described in Chapter 2, each case is respectively broken down into several parts, including:

(i) the relative strength of synthetic biology research within the country,

(ii) perceptions of synthetic biology health risk for pharmaceutical products across the product life cycle by subject experts within that country,

(iii) discussion of existing regulatory frameworks used to address synthetic biology risk within that given country, and

(iv) discussion of the efficacy of such government regulation, alongside perceptions by experts of what extensions of those existing regulatory paradigms are needed to better regulate the risks and promote the benefits of synthetic biology in the future.

Lastly, Chapter 7 includes a synthesis of the dissertation's findings, and discusses how the various veins of risk culture may cause variations in the regulation of synthetic biology within different governments. Specifically, this chapter will include a comparative analysis from the cases to review which elements of risk culture, if any, influence regulatory decision making and technological risk perception in a unique manner within each of the three cases.

Chapter 2:

The Qualitative Method Chosen for this Dissertation: Subject Expert Interviews & Discourse Analysis

2.1.0 Statement of the Problem and Subsequent Selection of Method

2.1.1 Statement of the Problem: Regulating Synthetic Biology Under Uncertainty

As described in Chapter 1, a small number of emerging technologies possess unique physical characteristics that make it difficult to understand their potential risks to human and environmental health (Maynard 2007). The uncertainty posed by such technologies makes their regulation a more complicated task than with technologies that possess more predictable and well-known risk profiles (Pierre 2000; Perry & May 2007; Bevir 2008). Within such situations, individual governments chose unique measures to regulate and govern such technologies in the midst of high uncertainty – the measures of which may be driven by various elements of local risk culture. Synthetic biology serves as one example of such a technological approach that possess a unique genetic structure may pose uncertain and consequential risks to humans or the natural environment (Carter et al 2014; Bar-Yam et al 2012; Mandel et al 2014).

Given the technology's uncertainty and novel potential risk profile, governments have already begun to adopt diverging approaches to synthetic biology regulation (Bar-Yam et al 2012; Carter et al 2014). These differing approaches are generally not driven by local data on technological risk, hazard, and exposure, but may instead be the result of unique cultural, political, and institutional factors that influence technology regulation within each government (Jasanoff 1986; Kelemen 2011). This dissertation seeks to explore more direct causes of why such variation might exist, where such variation is hypothesized to be caused by one or more factors that comprise a government's risk culture as noted in Section 1.3.

Qualitative methods offer multiple approaches that may address various angles of synthetic biology risk analysis and regulation. However, given the specific focus on this

dissertation regarding the potential risks that may arise within the process of synthetic biology development and the need to review regulatory capabilities to cover such risks, this dissertation made use of narrative discourse analysis via subject expert interviews alongside a literature analysis.

2.2 General Project Description

Given the central focus on reviewing how elements of risk culture generate variations in synthetic biology regulation, the following sections specifically describe the methodological underpinnings of this study and the specific hypothesis that were reviewed. To begin with, this dissertation focused explicitly on the following two research questions, including:

1. Do stakeholders in the United States, European Union, and Singapore approach risks to synthetic biology in differing manners?
2. If so, what factors cause them to do this?

Collectively, addressing these research questions will allow for an improved understanding of whether the three included cases have adopted differing approaches to the risk perception and regulation of synthetic biology as well as offer some explanation regarding why this is the case. As such, research findings are centered on (i) the potential biosafety and biosecurity risks as noted by local subject experts that may arise from synthetic biology, and (ii) the regulatory and governance mechanisms required to address such concerns.

To test these research questions and review how risk culture may influence variations in synthetic biology regulation, this dissertation explores the effect of several elements of risk culture, including:

ii) The degree of formality in regulatory dispute resolution

iii) The degree of centralization in government power

iv) The general appetite by local stakeholders for risk acceptance

v) The perceived domestic benefit of a particular innovation

Where these factors serve as the main components of risk culture operationalization in this dissertation, such research may allow for an improved understanding of which elements of risk culture, if any, may cause governments to regulate and govern synthetic biology in a

culturally unique manner from their peers. As noted in Section 1.2 and 1.3, this dissertation hypothesizes that the specific factors of regulatory path dependency (i above) and style of local regulatory legalism (ii above) are the strongest influencing factors to generate variations in synthetic biology regulation across the three cases studied here. Further, it argues that regulatory path dependency has the strongest influence, where Jasanoff (1986) and Vogel and Lynch (2001) argue that such path dependency limits the political and policy options available to generate regulatory reform in various governments. On the other hand, the style of local regulatory legalism is hypothesized as having a lesser but still significant effect upon such regulatory variations, where Kelemen (2011) notes that an adversarial style of legalism can make regulatory reform too politically costly for regulators and policymakers to engage with. The remaining factors noted above are hypothesized as having lesser degrees of influence upon such regulatory variations, where instead considerations of regulatory path dependence (Jasanoff 1986; Vogel and Lynch 2001) and legalism (Kelemen 2011; Volcansek 2014) are argued as having more substantial effects.

To address these research questions, a holistic approach was undertaken to review the entire lifespan of the pharmaceutical's life cycle stages in order to integrate all potential relevant factors to societal health risk through the use of literature analyses and subject expert interviews. This was undertaken due to the need to consider both the existing published scholarly opinion as well as qualitative subject expert input with respect to synthetic biology risks during the production, manufacturing, consumption, and disposal life cycle stages. Methodologically, such a focus is essential to obtain a more context rich view of where synthetic biology risk may arise as well as to indicate which areas may be more difficult for regulators to address when shaping new guidance or regulation for the technology or its products (see Mohan et al 2012 and Bates et al 2015 for similar approaches to nanotechnology and synthetic biology).

Driven by the need to better understand the uncertainty regarding the potential risks of synthetic biology development, the first portion of research centers on the need to discuss novel versus conventional synthetic biology health risks across a pharmaceutical product's life cycle, both from a general perspective (a typical pharmaceutical) and with specific cases

currently within development (notably, Keasling's artemisinic acid, Novartis' influenza vaccine production, and the potential for a synthetic biology-derived probiotic). The goal here is to gain insight into the novel risks associated with synthetic biology for pharmaceutical products in order to map out where, if at all, these hazards may occur and damage human health. This is a difficult exercise due to the uncertain nature of synthetic biology research and the need to think speculatively about the interactions and exposure between synthetic and human cells, yet taking a case-by-case approach offers some insight into the various bounds of risk that developers must account for in separating conventional pharmaceutical health risk versus novel risk generated through complex genetic manipulation.

Further, concerns of proprietary knowledge and trade secrets complicate horizon scanning and anticipatory decision making, where private companies do not fully disclose the novel circuit and biological engineering developments that may contribute to novel health risk (Konig et al 2015). With these complications and impediments in mind, research here seeks to acquire insight into areas across the pharmaceutical life cycle that may produce novel risks due to the exposure of biologically active synthetic DNA utilized within synthetic biology research and development.

Qualitative approaches, with the notable inclusion of narrative analysis via subject expert interviews, can serve as an avenue to generate information regarding where these risks such as with threats to biodiversity or horizontal gene transfer may occur along a synthetic biology product's life cycle. Such information may in turn be used to review variations in both the perception of synthetic biology risk as well as the regulatory mechanisms available to regulate and govern the technology's development. A review of such risks is an essential piece of this review, where such risks may or may not possess irreversible and harmful consequences due to the presence of synthetic DNA within the engineered cells (Redford et al 2013; Dana et al 2012).

Lastly, to better understand the effect of the political and institutional factors that drive the regulatory risk culture of a given government, the next portion of research seeks to identify existing regulatory structures within specific cases (United States, European Union, and Singapore) that have been discussed as being applicable to synthetic biology regulation across

the process of product development. Through subject expert elicitation, this also includes the need to identify trends in opinion regarding the ability and effectiveness of those hard and soft law to govern said technological products, and discuss (if necessary) the novel extensions of hard and/or soft law that may be implemented to strengthen a specific case's regulation. Strategies explored will include those intended to perceive, monitor, manage, and mitigate risk amongst multiple stakeholders – a critical component of the International Risk Governance Council's definition of what proper regulation and governance of emerging technologies should include (IRGC 2009).

With regards to defining metrics for success or failure, the three primary goals of this framework are to (i) identify the institutional and political factors that may influence the regulation of synthetic biology within specific countries, (ii) acquire expert insight into the potential risks posed by synthetic biology pharmaceuticals, and (iii) review how specific institutional and political factors that comprise risk culture influence variation in synthetic biology risk perception and regulation. Given this, methodological success is determined by whether a diverse set of subject experts may be acquired for interview and whether a mixture of literature and expert assessment can identify the political and institutional factors of the government's risk culture which influence their regulatory decision making.

With this in mind, the joint literature-expert interview approach taken here is used to both review the existing discourse related to synthetic biology and government regulation while also gaining insight from targeted subject experts related to their perception of synthetic biology risks and the regulatory mechanisms available to cover such risks. For the former, the literature analysis generates background knowledge regarding the various issues and concerns raised about synthetic biology risks and benefits. The results of this study can both frame the initial areas of study and interview questions pertaining to the process of synthetic biology development – something that was undertaken in this dissertation (Pickering and Byrne 2014; Green and Hall 1984). For the latter, subject expert interviews and subsequent discourse analysis can help researchers build off of their initial understanding of synthetic biology regulation from literature and gain expert insight into specific questions about the field in general, particular areas of risk specifically, or even both (Bogner et al 2009; Kvale and

Brinkmann 2009; Seidman 2013). As such, the joint approach utilized here is complementary, where literature analysis allows researchers to gain a general overview of emerging challenges in the field whileexpert interviews subsequently allows them to gain more in depth understanding and analysis.

The following sections detail (i) the literature analysis methodology undertaken to review scholarly analysis of synthetic biology regulation, and (ii) the interview protocols and analysis utilized to acquire, organize, and understand information offered within the three phases of subject expert interviews undertaken specific to this research project.

2.3 Literature Analysis: Description and Approach

With respect to this dissertation's literature analysis, this dissertation sought to incorporate literature from three streams of thought, including (i) synthetic biology health risk in general, (ii) synthetic biology health risk from pharmaceutical products, and (iii) synthetic biology regulation (inclusive of hard and soft law options used by governments to cover synthetic biology risk).

Methodologically, this dissertation utilized the ISI Web of Knowledge to identify papers from peer-reviewed journals that discuss synthetic biology health risks along with the mechanisms that potentially contribute to these risks for the technology in general and for pharmaceutical products in particular. These efforts were initially conducted in tandem with an additional Alfred P Sloan Foundation grant entitled *Designing a 'Solution-Focused' Governance Paradigm for SynBio: Case Studies of Improved Risk Assessment and Creative Regulatory Design*, of which I served as a co-investigator in 2013. Outlined below, this general framework was repeated in 2014 and 2015 to update my literature base to include those publications and gray literature (or information that falls outside the mainstream of published journals and literature) released after the initial 2013 search.

By September 2013, 8 keyword search phrases were identified with the assistance of other participants in the Sloan Foundation grant that were used within the ISI Web of Knowledge along with Google Scholar. ISI was utilized to identify formal publications within peer-reviewed journals, while Google Scholar was used conduct the 'forward to backward

search' described below (Webster & Watson, 2002; Levy & Ellis, 2006). ISI Web of Knowledge was utilized due to its recognition as one of the primary collections of academic literature worldwide (Chadegani et al 2013, Huang et al 2011). Within this initial search, each keyword was utilized in a case-sensitive manner (where these terms and phrases are listed below) to acquire a list of publications related to synthetic biology risk and regulation from a general perspective, and for pharmaceuticals and therapeutics in particular. After conducting these initial searches, articles were culled using a variety of criteria, which are described further below.

By March 2014, this initial literature analysis was refocused explicitly on synthetic biology pharmaceutical regulation. As such, the literature analysis was undertaken for a second time with the specific focus of this targeted application of synthetic biology. This included the removal of one irrelevant search term specific to a different case under the abovementioned Sloan Foundation Project (Synthetic Biology Biofuels), and included the addition of one search term to amplify the search's capability to acquire articles relevant to the concept of anticipatory governance, respectively.

Several criteria were used to cull articles that were not topically related to synthetic biology regulation as defined by me and with guidance from certain literature sources as Cameron et al (2014). The first criteria used included considerations of article publication date, where the initial search was focused around those articles published between January 2000 and September 2013, the second search from 2000-March 2014, and the third search serving as an update for April 2014-July 2015. The initial date was identified due to the publication of two significant articles in *Nature* that discussed the deliberate creation of biological circuit devices by combining genes within E. coli cells and subsequently triggered discussion and research related to systems and circuit engineering that served as an important launch point for modern synthetic biology research (Elowitz and Leibler 2000; Collins et al 2000). The significance of this start point was later emphasized by Cameron et al (2014), who described it as one of the early origins of research engaged directly at the concept of 'synthetic biology'.

The next criteria used for literature analysis evaluation included the removal of duplicate and near duplicate entries. While pure duplicates (or exact copies of the article under

consideration) were relatively rare (approximately 1% of articles used for review), certain publications contained material very similar in nature that warranted the inclusion of only the original publication within the literature analysis sample (approximately 17% of articles used for review). Examples of this included conference proceedings or book chapters by certain authors that were derived from their previously published material. As a rule, an article was only deemed a 'near duplicate' if the research methodology, abstract, and general discussion of synthetic biology was identical to previously published work, and at least one author matched for both the original and near duplicate paper (consistent with Hart 1998 and Dillon and Gabbard 1998). In cases where this occurred, the earliest published document within a peer-reviewed journal was kept in the review for further analysis to maintain consistency in the review process. Further, articles that appeared for multiple search terms were eliminated in this stage of the article culling process.

After filtering out duplicates and near duplicates, the next round of evaluation included focusing only those articles published in English as well as removing irrelevant or extraneous material. For starters, only papers published in English were kept for analysis, consistent with Huang et al (2011) and Juni et al (2003). The next step included removing those articles not directly related to synthetic biology, where such articles did not contribute to this dissertation's discussion of synthetic biology regulation in general and for pharmaceuticals in particular. Such a process involved reviewing for articles that did not explicitly state the phrase 'synthetic biology' (except for the search term 'synthetic biology engineering', where the term had not become widely used until 2004-2005), where this culling process for term relevance is consistent with Hart (1998) and Huang et al (2011).

To supplement the literature search and to ensure that it was thorough, a forward and backward search (Webster & Watson, 2002; Levy & Ellis, 2006) was undertaken. Backward searches reviewed papers that were cited in studies and scholarly discussion previously identified for review, while forward searches allowed for a review of papers that cited the selected studies to see if those should also be included for assessment. Articles identified here were assessed using the same exclusion criteria noted above. Further, this entire process was

repeated in March 2014 (prior to Phase I interviews) and July 2015 (prior to Phase III interviews). The resulting list of publications is noted below in Table 1.

Search Terms	2013		Mar-14		Jul-15			
	Queried	Selected	Queried	Selected	Queried	Selected	Duplicates	Final Count
Synthetic Biology - Synthetic Bacteria	826	24	1257	216	147	35	52	199
Synthetic Biology Biofuel	123	21	0	0	0	0	0	0
Synthetic Biology ethics	85	19	112	75	38	17	15	77
Synthetic Biology Medicine	78	24	207	54	98	23	9	68
Synthetic Biology Pharmaceutical	47	9	82	33	95	21	0	21
Synthetic Biology Risk Governance	6	6	17	14	7	4	4	14
Synthetic Biology Risk Management	2	2	7	5	4	3	0	8
Synthetic Biology Governance	35	7	77	29	14	8	10	27
Synthetic Biology Anticipatory Governance	0	0	2	2	3	3	0	5
Total	1202	112	1761	428	406	114	90	419

Table 1. Breakdown of Literature Search Statistics Across 3 Years

Article analysis was conducted in terms of whether the papers were driven by experimental research, social science/implications research, or both. For experimental research, information was gathered regarding the biological, chemical, and engineering processes utilized by researchers to foster advancement in circuit and metabolic engineering relevant to synthetic biology research. These articles were used to inform the dissertation chapter on synthetic biology's history, development, risk, and overall regulatory concerns. For social science/implication research (or those articles that discussed the implications, consequences, and future outlook of synthetic biology research), these articles were used to frame Phase 1 and Phase 2 interviews, which are described further below. As the smallest third of the subdivided literature, those that discussed both biological and engineering information related to synthetic biology research alongside the social science and implications considerations were used to inform the specific cases of synthetic biology pharmaceuticals and therapeutics (Keasling's antimalarial, Novartis' influenza vaccine production, and a theoretical probiotic), while also informing on general discussion of synthetic biology questions for interviews in Phases 1 and 2.

Looking at the final list of 419 articles chosen for review, general percentages were derived regarding the timeline of article publication (i.e. the count of articles published across the timespan covered here) as well as how the articles were framed (i.e. as articles with a focus on social science and implications discussion, the presentation of experimental and/or

methodological information related to the science of synthetic biology research, or a mixture of both). Categorically, articles dedicated to discussion of social science and/or implications research of synthetic biology research and development accounted for 53% of articles included in the 419 article sample, with Experimental (37%) and Both (10%) accounting for the remainder (Figure 1). Temporally, publication across all three literature categories grew in number throughout most of the timeline mentioned here (Figures 3 and 4).

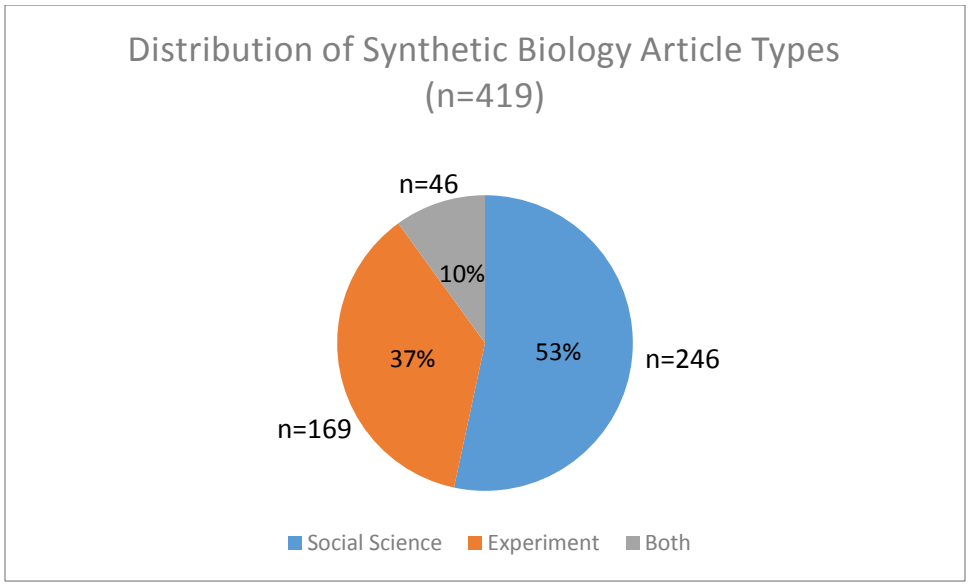

Figure 1. Categorical Breakdown of Literature Analysis Articles

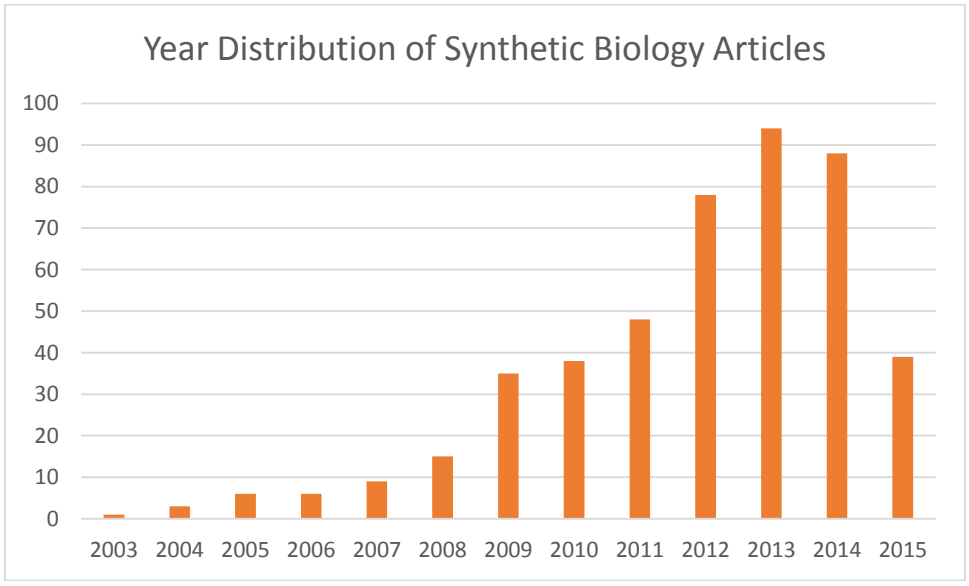

Figure 2. Distribution of all Articles from 2003 – July 2015.

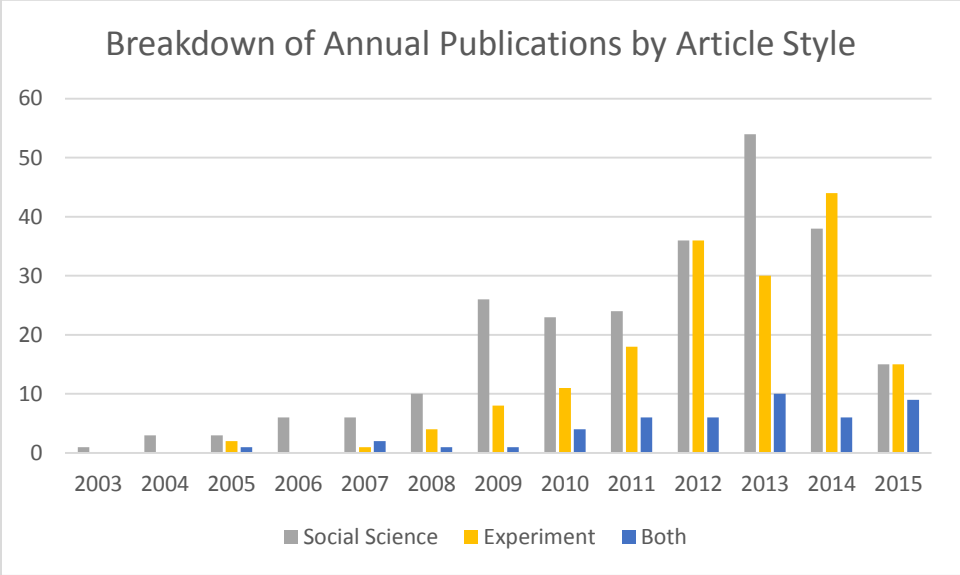

Figure 3. Breakdown of Article Categories by Year

Given the growth of articles pertaining to synthetic biology research and regulation above, certain trends have begun to emerge related to the regulatory landscape of the process of synthetic biology development as well as concerns pertaining to future regulation of synthetic biology products. For the former, Carter et al (2014), Bar-Yam et al (2012), Pei et al (2012), and Heavy (2012)discuss the challenges associated with regulating synthetic biology in the United States and European Union. In their discussion, authors such as Mandel et al (2014), Allan et al (2015), and Buhk (2014) note that for most governments as with the United States and European Union, no new hard law has been developed to explicitly cover synthetic biology health risks. Instead, Carter et al (2014), Bar-Yam et al (2012), and Buhk (2014) discuss how such risks are covered under extensions of existing law, such as with the Toxic Substances Control Act or the Food, Drug, and Cosmetic Act in the United States. Such law derives from the regulation of chemical and genetically engineered materials (respectively) on one hand, as well as from specific product regulation on the other (Suppan 2014; Kuzma 2015), Kuzhabekova and Kuzma 2014).

For the latter, scholars such as Douglas and Stemerding (2014), Calvert (2013), Serrano (2007), Landrain et al (2013), and Way et al (2014) all note the difficulties facing governments relative to the future of synthetic biology regulation. In this vein, Douglas and Stemerding

(2014), Carter et al (2014), Landrain et al (2013), and Bar-Yam et al (2012) all note that whereas the United States and European Union regulate the process and products of synthetic biology under existing chemical and genetic modification laws and guidance, such law will become increasingly unable to cover synthetic biology risks as the resultant organisms become increasingly artificial in their genetic structure. While the discussion of such regulatory challenges was noted in the mid-2000s as a theoretical concern (Tucker and Zilinskas 2006; Serrano 2007; Maurer et al 2006), such discussion has grown in significance since 2014 as synthetic biology research continues to mature in various fields such as pharmaceuticals, biofuels, and rodent control (Mandel et al 2014; Roberts et al 2015; Carter et al 2014; Allan et al 2015; Winter 2015).

A further point of discussion related to difficulties facing synthetic biology regulation includes the pressures by government regulators to develop policy and guidance without robust experimental data or commercialization of synthetic biology products. This is not a unique challenge for synthetic biology, where Malloy (2008) and Beaudrie et al (2013) describe similar concerns related to the regulation of nanotechnology. However, Bates et al (2015), Roberts et al (2015), Bubela et al (2012), and Moe-Behrens et al (2014) do note that such challenges complicate synthetic biology regulation and governance by making it difficult for such regulators to foster guidance and policy that adequately addresses potential risks of synthetic biology products. Further, Kuzma and Tanji (2010) and Colussi (2013) indicate that such uncertainty can exacerbate regulatory pacing problems as the technology becomes more refined (further discussion in Chapter 1).

Relative to the potential risks posed by the development of synthetic biology, authors in the United States, European Union, and Singapore have continually noted concerns of biosafety and biosecurity, respectively (White and Vemulpad 2015; Simirenko et al 2015; Guston 2014; Winter 2015; Douglas and Stemerding 2014). Specifically, Guan et al (2013), Church et al (2014), Carter et al (2014), and Garfinkle and Knowles (2014) state that the presence of novel genetic information in organisms modified within synthetic biology research pose specific problems if accidentally or deliberately misused and/or exposed to an unintended target. For biosafety, unintentional release outcomes have been described as potentially problematic for several

reasons, including (i) the potential for engineered organisms to act as invasive species and negatively impact biodiversity, (ii) concerns of exposure of engineered organisms to unintended human and animal targets, and (iii) the inability to control engineered organisms – particularly bacteria – once they are taken outside of a contained environment (Wright et al 2013; Schmidt 2008; Church et al 2014). Such concerns are noted both for commercial research (Bubela et al 2012; Saukshmya et al 2010) as well as for academic competitions and 'do-it-yourself' developments such as with iGEM (Guan et al 2013; McNamara 2014). However, more recent biosafety discussion has centered on the regulation of research intended for eventual commercialization due to advances in the technology's development for several potential product applications (Moe-Behrens et al 2014; Chugh et al 2015; Schmidt and de Lorenzo 2016).

For biosecurity, emerging trends of discussion center around questions of access (i.e. how nefarious agents could gain expertise and materials to misuse synthetic biology research for harmful purposes) and plausibility (i.e. how likely are biosecurity events). For the former, early concerns of biosecurity include the potential for synthetic biology research to have 'dual-use' implications, where a nefarious agent could use technological capabilities to develop harmful substances like a genetically modified virus (Kelle 2007; Tucker and Zilinskas 2006; Selgelid 2009). Discussion here has developed to focus more specifically on how biosecurity threats may be mitigated in specific regulatory areas, including export control (Shaw 2016), screening of synthetic biology research prior to public dissemination (Krishna 2014; Edwards 2014), and regulatory approval of proposed experiments for dual-use implications and harms (Chugh et al 2015; WHO 2016; Oye 2012).

With respect to the likelihood of biosecurity issues, scholars have taken varying positions on whether such concerns are plausible. On one hand, Jefferson et al (2015), Jefferson et al (2014), and Marris et al (2014) argue that such concerns may be unfounded and induce unnecessary fear in synthetic biology research within commercial and academic research alike. On the other, Chen et al (2015), Mukunda et al (2009), and Tucker and Flanagan (2010) contend that such risks may grow in likelihood as the technology matures, and that governments have an ethical imperative to protect against dual use threats to human and environmental health.

The diverging opinion of these two schools of thought is particularly noted within the context of pharmaceutical development, where scholars argue from both a scientific and ethical standpoint about biosecurity issues. Relative to scientific concerns, authors note that biosecurity risks are plausible (Chen et al 2015) or implausible (Jefferson et al 2014). For ethical concerns, scholars argue that governments have a responsibility to protect against perceived biological threats from engineered organisms (Tucker and Flanagan 2010), or that governments have a responsibility to facilitate synthetic biology research in order to unlock potentially life-saving advances that such research may provide (Wimmer et al 2009; Vohra and Blakeley 2013).

Overall, the literature analysis conducted for this exercise served as the key background work to acquire an understanding of the progression and current status of the field and general scholarly opinion and research into regarding synthetic biology health risks. This exercise also served to elucidate some of the existing research questions related to synthetic biology regulation, where issues such as whether existing regulatory paradigms within the three case governments studied here are sufficient to cover synthetic biology products serve as necessary information to inform interview questions for the second half of this study.

2.4 Subject Expert Interviews and Narrative Discourse Analysis

Alongside a formal literature review of synthetic biology regulation, this dissertation included three rounds of interviews with synthetic biology and emerging technology subject experts within Europe, Singapore, and the United States between May 2014 and December 2015 (entirely separate from the interview transcripts acquired from Drs. Kuzma and Cummings). These interviews were constructed to acquire information regarding the perceived risks by experts within the three case governments pertaining to synthetic biology development in general and for pharmaceutical production in particular. Specific discussion here centered on the general likelihood that such risks may arise, the mechanisms which contribute to novel risks to human and environmental health, the potential consequences of such risks, and discussion of regulatory capabilities currently available within a given country's national government to

cover such risks. This section describes the methodological approach of these subject Expert interviews, including:

(i) case selection within the United States, European Union, and Singapore,

(ii) the general interview protocols used for the three interview phases,

(iii) how each interview was analyzed and information was organized to identify common points of discussion for synthetic biology risk regulation, and

(iv) the limitations of this narrative analysis approach.

2.4.1 Case Selection

After acquiring a University of Michigan Internal Review Board Exemption (HUM00090576) for human subjects research, this research project sought to engage with various experts within industry, academia, government, and non-governmental organizations directly engaged with synthetic biology research and regulatory discussion. This section details this dissertation's case selection philosophy utilized for the three phases of interviews undertaken for this research project.

Case selection was accomplished across two axes: geographic and vocational. The motivation of this was to provide metrics for comparison regarding the general background and scope of work for the various experts interviewed for a given country – see Table 2 for a breakdown of completed interview responses. Further, these results may be reviewed comparatively across geographic lines, with this case including assessment from the United States, European Union, and Singapore.

	Vocational Axis				*Locational Axis*			
Interview Phase	**Academia**	**Industry**	**Government**	**NGO**	**Singapore**	**USA**	**Europe**	*Total*
1	14	5	2	1	22	0	0	22
2	10	3	3	2	0	13	5	18
3	5	2	1	1	1	4	4	9
Sloan	26	5	8	6	0	33	12	45
Total	55	15	14	10	23	50	21	94

Table 2. Breakdown of Completed Interviews by Location and Vocation

A limiting factor in the search for expert interviews included the fact that synthetic biology is a relatively new field, and does not have more than a few hundred subject experts that could be called upon to give their opinion. Given such limitations, case selection was determined via a stratified and purposeful sampling of synthetic biology experts and scholars (whose status was determined by their publication of synthetic biology research in a peer-reviewed journal with an impact factor of at least 1, or published at least 3 papers in peer-reviewed journals or conference proceedings). Such published research could include experiments or proposals for experiments related to synthetic biology research, as well as discussion of synthetic biology regulation and policymaking. The vocational axis included respondents from industry, academia, government, and other non-governmental organizations. The locational axis was assessed between the United States, Europe, and Singapore. These twin axes allow for a comparison of both disciplinary and political/cultural similarities and differences associated with synthetic biology risk perception and regulation. Due to the sensitive nature of the field, all responses are kept anonymous, where identifying information for any single respondent is removed for discussion.

For the vocational axis, interview subjects were selected due to their theoretically differing motivations related to the role of synthetic biology research and development alongside the need for regulation to both protect human health while promoting technological development for those products utilizing synthetic biology. Bates et al (2015) and Linkov et al (2012) took a similar strategy towards comparing semi-structured interview responses across vocational lines, with Bates (2015) particularly noting the need to balance potentially conflicting points of view from members of industry and members of government.

All interviewees for research conducted within this dissertation alongside the interview transcripts donated by Dr. Jennifer Kuzma and Dr. Christopher Cummings fall into one of the four vocational subsections. Generally speaking, all interviewees have a PhD-level education in biology, chemistry, or similar field in science, or have a PhD in a social science background pertinent to the risk analysis and regulation of emerging technologies. Overall, academia is the most represented group (58.5% of total completed interviews) due to the emerging nature of

the field and the relatively preliminary nature of most commercial and industrial research. However, including early perspectives from other groups is important to elucidate the differing perspectives available to the field – particularly those that directly discuss risk acceptance or aversion based upon desires to protect public health or advance technological capacities.

On the other hand, the locational axis was used to identify different cases by which the qualitative approach described within this dissertation could be used to acquire and assess information related to synthetic biology's potential health risks alongside the regulatory capabilities that may or may not be available within the given country to cover such risk. While Kuiken (2015) claims that accurately measuring the level of effort related to synthetic biology research and development is currently improbable, both Kelley et al (2014), and Check (2015) describe the United States and European Commission as being two of the primary funding bodies for synthetic biology research while also serving as the area of operations of dozens of research projects related to a variety of synthetic biology applications, pharmaceuticals included.

For the case of Europe, Kuiken (2015) notes that various funding bodies within the European Union have grown their funding for synthetic biology research every year, and eclipsed $100 million in 2014. The European Union has also actively engaged with synthetic biology implications research such as with dual-use challenges related to biosecurity and biosafety, leaving organizations such as SYNBIOSAFE, COSY, and the International Associated Synthetic Biology to actively debate the role of regulation needed to cover synthetic biology's novel risks within European borders.

As with the United States, Oldham et al (2012) assert that Europe's status as one of the two major financiers of synthetic biology research alongside a willingness to engage with implications-based research and discussions of regulation (something that Kuiken 2010 described the United States as taking a limited approach towards) makes it one of the primary regions of focus for synthetic biology research moving forward. Collectively, the United States and Europe serve as two case studies that cover well financed and scientifically advanced regions with a growing appetite for synthetic biology innovation (Oldham et al 2012; Kuiken 2015).

An important comment to note relative to case selection centers on the unconventional nature of the cases reviewed here. Specifically, the respondents regardless of vocation come from three very different environments, and do not reflect the classic cases in comparative research that seek to explain certain outcomes in the United States or European Union. Specifically, the inclusion of Singapore differs from traditional comparative research, where the smaller gross domestic product, geographic size, and population count of Singapore causes it to differ inherently from the larger and wealthier United States and European Union. However, the inclusion of Singapore as a case study brings unique benefits to this dissertation, which are described below.

Singapore was chosen as a third case for this dissertation for two reasons: (i) its growing interest in funding and conducting research of synthetic biology product development, and (ii) the need to promote generalizeability and external validity to this study by reviewing regulatory variations of synthetic biology for an Asian economy heavily invested in emerging technologies research (Olds 2012). For the former, Chapter 6 will discuss the growing level of funding and research capabilities within Singapore's universities, although it is noting that Singapore's Nanyang Technological University, the National University of Singapore, an A*Star all maintain research facilities with research directly related to synthetic biology and pharmaceutical research (Mitchell 2011; Oldham et al 2012; NUS 2015), with the Singaporean government investing $15 million in 2015 to advance such research at the National University of Singapore. For the latter, it is important to understand that Singapore's research capacity for work pertaining to synthetic biology is growing within academia and industry, and reflects a developing interest and millions of dollars of investment in emerging technology and synthetic biology research in Asian countries like South Korea, China, Japan, and Singapore, among others (NUS 2015). Particularly for the case of China and Singapore, these countries possess differing governmental structures that may be equally influenced by legalism and risk culture with respect to their early stage decisions for synthetic biology regulation, and should be reviewed alongside their counterparts in the United States and Europe to strengthen the dissertation's generalizeablility. As such, Singapore offers an opportunity for such generalizeability, and

serves as a vehicle to review potential synthetic biology research and development in China due to the strong research and development connections between the two countries.

A further justification of using qualitative methods across an international scale includes the notion that regulators and stakeholders within a given country will naturally be interested in understanding the perceptions of risk as well as the regulatory options used for synthetic biology. This is driven by the global supply chains and the potential exchange and trade of synthetic biology products from one country to another, where the risk culture of one country may drive it to regulate and govern new pharmaceutical products in a manner different from others (Jasanoff 1986; Jasanoff 1987).

2.4.2 Interview Collection

Interview collection was carried out in three main phases based upon funding availability and stakeholder access. Phase 1 was completed during May-September 2014, the entirety of which was spent within Singapore. Stakeholders within industry, academia, and government were particularly targeted for interview, with on-site interviews successfully conducted at The Institute of Occupational Medicine in Raffles Place, Nanyang Technological University, the National University of Singapore, A*Star in Biopolis, and various contacts within Singapore's City Hall. The purpose of these interviews was to both (i) begin to understand the novel versus conventional human health risks fostered by synthetic biology products, and (ii) gain insight into the perception of these risks by local Singaporean emerging technology scientists and synthetic biology researchers. In this stage, 22 formal interviews were completed, with approximately 20 unofficial discussions with experts that offered some insight into Singaporean technology development and regulation. Formal interviews were semi-structured and roughly one hour in length on average, with a range of 30 minutes to two hours based upon interviewee availability and expertise on the subject. The instrument (interview protocols) for this and the other two phases will be attached in the dissertation's Appendix 3. Interview responses are kept anonymous within this dissertation. Percentages regarding interview completion are noted above in Table 2.

Phase 2 interviews began on October 2014 and ran through March 2015. Interviews were typically conducted over telephone or video conference calls from Ann Arbor, Michigan. Similar to Phase 1, interviews conducted here were centered on i) the novel versus conventional human health risks fostered by synthetic biology products, and (ii) the ability of regulatory capabilities within the respondent's national regulatory regime to adequately cover such novel risks should they arise. Interview questions included a mixture of those included in Phase 1 interviews alongside new points of inquiry raised from Phase 1 interview transcripts. Stakeholders specifically targeted here included American and European stakeholders across each element of the vocational axis.

Phase 3 interviews began on July 2015 and concluded December 2015. Rather than a dedicated search for new interview contacts, this phase of inquiry instead focused upon tracking down leads suggested by previous interview contacts (consistent with Goodman 2011 and Cohen and Arieli 2011). As such, these interviews were dedicated towards resolving any preliminary gaps in analysis, particularly on the subject of specific applications of synthetic biology pharmaceuticals and their subsequent options to manage risk. Interviews were carried out both in-person and over the phone, with locations including Singapore, Denver, Colorado, Washington DC, and Ann Arbor, Michigan. Supplementing discussion here includes interview transcripts and surveys from the external Sloan Foundation Grant *Looking Forward to Synthetic Biology Governance: Convergent Research Cases to Promote Policy-Making and Dialogue.*

At the onset of all interviews, respondents are asked for their permission for their interview to be recorded using a Philips DVT5500/00 Digital Voice Tracer. Of the 49 interviews conducted, 29 (59%) agreed to be recorded provided their identifying information was kept off of the record and transcription information was coded exclusively by me. If permission was not granted, respondents were asked for their permission for the interviewer to take notes throughout discussion. Of the remaining 20 respondents, 19 gave their permission for such note taking (95%), with one preferring that no written notes be taken during the interview. For that single case, important quotes related to the interview questions were written down shortly after the interview concluded, and were placed alongside the pool of other interview responses.

2.4.3 Interview Protocols & Instrument

Structurally, interview protocols were formed with five general sections. Section 1 of each interview included statements where each respondent was asked to state their general familiarity with synthetic biology, the type of research and scholarship they perform, and their level of exposure with discussion and research of synthetic biology pharmaceutical products. Sections 2 and 3 included specific questions which ask the respondent to articulate their perceptions of synthetic biology risks in general and for pharmaceutical cases in particular, with the specific aim of fostering conversation related to conventional versus novel risks alongside the potential mechanisms by which novel risks may be exposed to humans and the environment. Questions here sought to focus discussion related to placing perceptions of risk along the product's life cycle, where respondents were asked to articulate where they believe novel health risk may occur throughout a product's lifespan along with the relative likelihood and severity of such risk (if that level of detail was available). Section 4 included interview questions related specifically to the regulation of synthetic biology in general and pharmaceutical products in particular, where respondents where explicitly asked about their familiarity with relevant regulations within their country geared to cover synthetic biology risks, the effectiveness of such hard and soft law regulation to actually do this, and where (if at all) new regulation is needed to strengthen state capabilities to monitor, manage, and mitigate such risk. Lastly, Section 5 gave respondents the opportunity to indicate where they believe synthetic biology research may develop and evolve into, and offer general insight into how state regulation should move to 'keep up' with the shifting technological landscape relative to health risk.

Accounting for bias across interview subject responses, the three-tiered structure where interviews were conducted in a variety for phases is consistent with Chenail (2011), who argued that 'pilot studies' serve as an avenue to test instrument rigor as well as control for any biases that may have appeared within early interview protocols. The first round of interviews served as a check on the rigor of the interview instrument, where questions that generated initial

respondent confusion or lack of response were removed, and other questions were added based upon the common streams of discussion raised by groups of interviewees.

To account for bias within individual interviews, subjects were given definitions of key terms such as with synthetic biology (discussed in Chapter 3, and included in the dissertation Appendix 3). Such material was provided in the initial email contact with each interviewee, as well as within the initial in-person discussion but prior to any interview questions being asked. Respondents were asked to provide their insight into discussion of synthetic biology risk and regulation based upon such guidance, and were asked to state their exposure to and expertise on the subject at the beginning of each interview. Such an approach allows for increased standardization and reduced bias within individual interviews as noted by Boyce and Neal (2006) and Turner (2010).

2.4.4 Interview Discourse Analysis

As with many interview projects, the assessment of qualitative interview material requires a robust discourse analysis to make sense of the various streams of logic described by interviewees (Wetherell et al 2001; Phillips and Hardy 2002; Starks and Trinidad 2007). Often, such discourse analysis is driven by the quantification of key terms and phrases, where the frequency of occurrence of such phrases denotes a relative strength of agreement or disagreement on a subject alongside a general understanding of its magnitude within a given subject (Wetherell et al 2001; Phillips and Hardy 2002). However, due to the lack of standardization within emerging technology and synthetic biology research (including a common list of definitions), traditional keyword or phrase searches are ineffective to assess information from transcribed interviews (Bates et al 2015). Such complications are only furthered by the international scope of this project, where the description and understanding of regulatory tools for high-risk, high-uncertainty projects and products may differ strongly within separate cultural or political contexts (Bates et al 2015; Silverman 2010; Gee 2014).

Given this, a more generalist approach towards discourse analysis was utilized to make sense of interview data from the United States, Europe, and Singapore. Discourse analysis is a technique within the narrative analysis family of qualitative approaches that includes the

analysis of language in order to "shed light on the creation and maintenance of social norms, the construction of personal and group identities, and the negotiation of social and political interaction" (Starks and Trinidad 2007). Potter and Wetherell (2002) argue that one vein of discourse analysis is centered on understanding how scientists construct their talk and text to formalize knowledge and express meaning within their research (Mulkay et al 1983). Related to yet unique from content analysis, discourse analysis seeks to gain greater meaning into the context of what is being said, with emphasis placed upon how discussants frame their thoughts and opinions in differing manners (Thorne 2000; Burck 2005). In this way, discourse analysis differs from content analysis by focusing on the social, historical, and knowledge-driven differences in projecting opinions and ideas for a given topic, which is particularly beneficial where specific linguistic framing and conventions for discussion are still emerging as with the case of synthetic biology (Potter and Wetherell 2002). Similarly, Charmaz and McMullen (2011) state that one of the functions of discourse analysis is to review how knowledge is constructed within specific groups or organizations given the experiences, knowledge, and beliefs of those groups.

Discourse analysis begins with the analyst turning to readings related to their topic at hand and gaining perspective related to the important research questions specific to a given topic alongside various strains of discussion related to it (Potter and Wetherell 2002). After reviewing written literature, Potter and Wetherell (2002) and Charmaz and McMullen (2011) state that the next task for a discourse analyst is to obtain verbal feedback in the form of interviews, where Wengraf (2001) notes semi-structured interviews as being sufficiently organized and focused to keep discussion rooted on a particular subject while also affording interview respondents the capability of framing discussion on their own terms and based upon their existing knowledge and beliefs. Later, the analyst uses responses from such interviews (and, if possible, transcripts of interview discussion) to assess the meaning behind interviewee responses to particular questions (Wood and Kroger 2000; Potter and Wetherell 2002). Within this exercise, Wetherell (1998) contends that it is the job of the discourse analyst to acquire certain shared claims and beliefs relative to a specific topic, where the quotes and information used within interview discussion is chosen by the analyst to describe knowledge constructions

for a given area. As such, Wetherell (1998), Wood and Kroger (2000), and Potter and Wetherell (2002) state that it is impossible to divorce analyst views and perceptions from the analytical process, where the analyst is inherently required to review a large body of interview responses and text to determine which statements are relevant and interesting for a given topic.

Given such concerns, strategies to reduce bias by the interpreter are centered around proving that the researcher offered a realistic assessment of qualitative information that limits the potential for personal bias or error (Shenton 2004). Three strategies particularly noted by Shenton (2004) include (i) triangulation, (ii) iterative questioning, and (iii) building towards a larger sample size. For this study, research was triangulated via a comparison of interview information between interviews conducted in Rounds 1-3. Second, this study engaged within iterative questioning, where questions related to the various topics discussed within the interview instrument were asked in various manners to view if interview responses changed or wavered. Lastly, this project sought to acquire as many interviews as feasible within the given timeframe and budget available, and when combined with information loaned by Kuzma et al, offers a rich sample size as defined by Guest et al (2006) ($n \geq 60$) by which qualitative information may be drawn relative to synthetic biology regulation (see also Johanson and Brooks 2009).

Using guidance from Potter and Wetherell (2002), Wood and Kroger (2000), and Charmaz and McMullen (2011), this project's discourse analysis involved the perusal of each interview for certain elements of discourse that illuminated beliefs behind emerging technology and synthetic biology risk. Where interview protocols were divided into sections geared specifically on interview responses towards potential synthetic biology risk, the mechanisms driving such risk, and the regulatory options to cover such risk, this discourse analysis was facilitated by reviewing these targeted responses relative to expert perception of these issues.

Lastly, analysis of expert feedback included a review of whether novel extensions and improvements of such regulation was necessary to (i) better regulate against risk, (ii) better enable the efficient research and development of synthetic biology products, or (iii) a mixture of both. These efforts fostered the creation of a transcript index, or a collection of general terms and phrases that serve as placeholders for identified quotes from various interviews on a

given subject. This is consistent with Potter and Wetherell (2002), Wetherell (1998), and Wood and Kroger (2000), which collectively contend that discourse analysts must review and organize response information in a manner that describes beliefs and behaviors in various observed subjects, with this case serving as synthetic biology regulation. Overall, the index included 26 unique entries, with relevant quotations aggregated for each entry.

Creation of index terms was facilitated by the semi-structured nature of each interview. Typically, interviews were framed in a small number of self-contained subsections, including (i) potential synthetic biology novel health risk (generally speaking), (ii) potential synthetic biology novel health risk (pharmaceuticals), (iii) synthetic biology regulation within the process of the technology's development, and (iv) differences in cultural risk perception. Given this framework, the interview index was sub-divided into these four subsections. Individual quotations within a given index line item retained interview codes assigned to each individual interviewee, allowing for a vocational and locational analysis of each index item.

Additional qualitative discourse analysis was used to generate simple metrics related to expert perceptions of where novel synthetic biology risk may occur across the life cycle of a typical pharmaceutical product (Wetherell 1998; Wood and Kroger 2000). Specifically, interview discussion included considerations of where within a product's life cycle, if at all, novel health risk and the mechanisms to generate such hazards may arise within the process of pharmaceutical product development.

Further, Kelle (2009)'s use of qualitative subject expert interviews to test the general level of familiarity of various respondents of the hard and soft law regulatory tools was used to acquire a general understanding of how interview respondents perceived existing regulation of synthetic biology within their country. Kelle (2009) expressed familiarity with synthetic biology regulatory authority on a binary metric, where respondents were either aware of the authority and its ability to govern synthetic biology health risk or not. This dissertation took Kelle's (2009) approach further by breaking down respondent familiarity with such regulation and authorities by reviewing responses based upon the respondent's general line of work (the vocational axis). Further, this dissertation expanded Kelle (2009)'s coding approach, where respondents were able to indicate differing levels of familiarity with synthetic biology regulation, including (i) no

knowledge or awareness of regulation and relevant policymakers and regulators, (ii) awareness of a particular regulatory authority but not specific regulation or vice versa, and (iii) intimate awareness of both the regulatory body and regulatory codes dedicated to synthetic biology regulation within their given country.

Aside from the general review of respondent opinions of synthetic biology life cycle risks and regulatory capabilities, the ultimate output of this discourse analytic approach is to foster an index of quotations on various subjects related to synthetic biology regulation. The specific index terms will be included in the dissertation Appendix 2.

2.4.5 Supplemental Interviews: Sloan Foundation Project "Looking Forward to Synthetic Biology Governance: Convergent Research Cases to Promote Policy-Making and Dialogue"

Further bolstering this interview framework includes the use of qualitative expert interviews and ordinal surveys conducted within a project funded by an Alfred P. Sloan Foundation grant (#G-2013-3-02) entitled "Looking Forward to Synthetic Biology Governance: Convergent Research Cases to Promote Policy-Making and Dialogue." The project's researchers conducted a 4 round expert elicitation for several different applications of synthetic biology, with the similar goal of identifying areas of potential health risk alongside technological economic benefits and the corresponding regulatory options to promote such benefit. Researchers for this project (led by Dr. Jennifer Kuzma and Dr. Christopher Cummings) made use of semi-structured interviews for Rounds 1 and 4, with more structured survey questions for Rounds Two and Three (see Table 3 below). For purposes of this dissertation, information generated from Rounds 1 and 4 are used in tandem with subject expert interview information acquired within the scope of this project, although specific takeaways or indicators of risk and regulation from Rounds Two and Three were utilized on an as-needed and as-applicable basis.

Round 1 interview transcripts were parsed using the same analytical approach described below, where these transcripts were reviewed for particular discussion on synthetic biology health risk, the mechanisms that may drive this risk, and the regulatory options available and necessary to cover those novel risks discussed by stakeholders. All interviews here were

transcribed and coded to retain respondent anonymity, where only information related to their geographic region and general vocation was utilized for coding purposes specific to this dissertation's methodological approach. Information responses within Phase 1 as well as survey responses in Rounds 2-4 were used to triangulate interview findings discussed within interviews from Rounds 1-3, and allowed for the expansion of subject expert perceptions of synthetic biology health risks and the appropriate level of regulation to cover the novel risks that may or may not arise from the technology's use. While also adding to various quotes to this dissertation's discourse analysis, the use of these interviews served also as a method to review potential bias or interpretation errors from the resultant transcripts.

Round	Method	Description
One	Standardized open-ended interview protocol; n=45	Participants responded to a variety of questions about risk analysis, regulation, and societal issues for different cases of synthetic biology product development. Interviews were approximately 75 minutes in length.
Two	Online quantitative survey; n=34	Designed from preliminary round one findings. Included various scaled items regarding regulatory issues associated with the case studies.
Three	Face-to-face workshop and ordinal ranking exercise; n=35	Focused on concept-mapping and mind-mapping exercises to generate lists of challenges and opportunities for SB regulation. Also included an ordinal ranking exercise of ideal regulatory characteristics.
Four	Online qualitative and quantitative survey; n= 35	Open- and closed-ended items and scales assessing factors that may influence future policy and regulatory options concerning the case studies.

Table 3. Breakdown of 4 phase research designed from Alfred Sloan project (#G-2013-3-02)

2.5 Limitations to This Approach

Such an approach has natural limitations. Firstly, discourse analysis contains elements of subjectivity that are essentially impossible to remove. This is exacerbated by the differing terms, phrases, definitions, and mindsets deployed by each interview contact to describe their understanding and familiarity of emerging technologies like synthetic biology, requiring any transcript analysis to 'read between the lines' to understand exactly what is being discussed for individual interview questions (Wetherell 1998; Potter and Wetherell 2002). Second, discourse analysis within this application is generally descriptive rather than causal or quantitatively

driven, where this research is better able to describe the existing state of the emerging technology regulatory universe rather than draw strict causal conclusions regarding how risk and uncertainty may be measured and understood. Further, the primary motivation of such a discourse analytic approach is to take into account the conditions and contexts which interview statements are made and account for the methods and measures used by interview respondents to make sense of synthetic biology regulation (Potter and Wetherell 2002). These limitations are frequently noted in emerging technology and synthetic biology literature, particularly due to the lack of quantitative risk, hazard, and exposure data by which to make traditional risk-based decisions on the technology's health risk (Bates et al 2015; Kuzma and Tanji 2010).

Other limitations important to note here include the instrument design used within each interview phase. Specifically, interview questions were scoped around explicit considerations of synthetic biology potential risk and benefit such as with biosafety and biosecurity considerations. While this does allow for more targeted discussion around notable issues raised within scholarly literature about synthetic biology risk, this level of scoping may prime interview responses in a manner that would potentially influence respondent answers to discuss only the prompted risk categories instead of raising other issues that may not be as well understood or known to arise (Wheeldon and Faubert 2009). Such targeted responses allow for greater comparability between interview answers along the lines of specific risk issues, yet also potentially reduces the richness of interview responses that may allow for greater discussion of implications concerns and less discussed risks pertinent to synthetic biology research (Hollway and Jefferson 2000).

2.6 Discussion

Overall, the maturation of synthetic biology may produce dramatic improvements to medicine and public health in a rapid and systems-wide fashion. Similar to other emerging technologies like nanotechnology, however, synthetic biology may also pose environmental and human health risks if not developed and implemented responsibly. Further, the uncertainty behind such risks may cause regulators within different governments to govern the process of

synthetic biology development in differing manners (Kelemen 2011; Jasanoff 1986). Qualitative approaches such as with narrative discourse analysis may enable researchers to acquire insight into how such variation occurs, where this dissertation explicitly sought to review whether and to what extent specific elements of risk culture drove such variation within the United States, the European Union, and Singapore.

Even in the absence of robust guidance regarding hazard and exposure data for such emerging materials, subject experts can offer preliminary thoughts and opinions that effectively bound the field's uncertainty, and offer a general framework with how to proceed forward with effective yet responsible innovation for fields ranging from systems engineering and synthetic biology to nanotechnology to nanorobotics. Such insight is helpful to gauge both local perceptions of risk as well as beliefs by interviewed experts regarding the regulatory mechanisms need to cover such risks – information that is essential to study variations in synthetic biology regulation across different governments.

This dissertation does not seek to completely rewrite our existing understanding of how emerging technologies are used within society and produce risks to individual health. Instead, it leverages available information from an international body of subject experts, and use such information to explore a) whether variation in synthetic biology regulation exists within the United States, European Union, and Singapore, and b) if so, whether elements of risk culture may be the cause of this.

Chapter 3:
Synthetic Biology – Background, Applications, and Risks

3.1 Introduction

Synthetic Biology has the potential to revolutionize the development and production of pharmaceutical products (Barocchi and Rappuoli 2015; Ando et al 2014; Bugaj and Schaffer 2012). However, there is uncertainty over the potential novel health risks it may present to humans and the environment (Marris 2015; Kelle 2009; Carter et al 2914). This dissertation does not seek to resolve the various worries and problems that drive uncertainty of synthetic biology's regulation, where it would be impossible to do so given the current state of the field in its earliest stages of development. Instead, it seeks to understand whether variations in synthetic biology regulation exist within three noted case studies, and review whether elements of risk culture are the cause of such variation. In this vein, this chapter lays the groundwork for how synthetic biology is framed based upon an exhaustive literature review of the technology's scientific underpinnings, potential risks, potential benefits, and perceived regulatory needs within the three cases included for study.

To accomplish this aim, Section 3.2 lays out the history of synthetic biology – both from its early roots in late 19th through mid-20th Century work on biological and genetics research. This is coupled with discussion of modern synthetic biology research (2000-2016), where cellular modification evolved to incorporate more complex engineering concepts. Next, Section 3.3 will include a general discussion of potential synthetic biology health risks given the technology's various potential products and applications. Section 3.4 builds off of this by offering differing perspectives on efforts within scholarly literature to define synthetic biology. Lastly, Section 3.5 will focus upon a more substantial discussion regarding the potential pharmaceutical risks and benefits yielded by early developments in the field.

3.2 History of Synthetic Biology

3.2.1 Redesigning Living Systems in a Lab: Early Aspirational Ideas from 1900-1940

Despite its relatively recent development as scientific practice, principles of 'synthetic biology' have discussed in English language literature at least since the early 20th Century. One of the earliest known of the term comes from French biologist Stéphane Leduc in 1912, who spent his career exploring the mechanical and chemical foundations and operations that make up living organisms (Leduc 1912; Keller 2003). While several eminent scientists in the late 19th Century did seek to explain some of the core principles and functionalities of cells and molecules, Leduc differed in his focus on identifying certain mechanistic conditions by which cells could be manipulated or created through the use of osmotic pressure (Leduc 1910). Specifically, Leduc argued that such mechanistic manipulation through the use of various chemical substances could contribute to a manipulation of individual cells for differing purposes than they were organically produced to achieve (Pereto and Catala 2007).

For Leduc, the fledgling focus of early synthetic biology included both the synthesis of organic molecules and cells to even more complex biological tissues and structures – a notion that carries over to the modern synthetic biology community today even in spite of its various scholarly and intellectual differences. Between 1910 and 1922, Leduc published three manuscripts on his general philosophies regarding this early manipulation and reorganization of cells for certain purposes, and made use of several experiments using various chemicals to produce his intended outcomes. One of these publications in particular (*La Biologie Synthétique* - 1912*)* served as the first manifestation of 'synthetic biology' as an academic term (Leduc 1912). Discussion within Leduc's work serves as an early precursor to more modern synthetic biology, specifically relative to the notion of manipulating biological organisms on a systemic level to produce cellular change (where more modern synthetic biology takes this beyond a theoretical concept and applies concepts of modern engineering for synthetic biology research experiments) (Leduc 2012; Pereto and Catala 2007). However, the failure of many of Leduc's experiments alongside extensive criticism from the Roman Catholic Church (often derived from perceptions that Leduc sought to find evidence of spontaneous generation of cells) and

academic peers such as Jacques Loeb prevented the early scientific notions of synthetic biology from taking root (Pereto and Catala 2006; Pereto and Catala 2007).

Even with Leduc's theories and assertions being largely resisted by various academics of his time, certain ideas of cell and molecule manipulation individually and in larger biological systems took root for some who criticized Leduc's failed experiments but considered the potential of artificial organic life (Pauly 1996; Loeb 1912). One particular case included biochemist Jacques Loeb, who, despite criticizing Leduc for attempting to engage in research that was beyond the scope and capability of contemporary science, did acknowledge that "nothing indicates […] at present that the artificial production of living matter is beyond the possibility of science" (Loeb 1912). Loeb eventually argued that it was imperative for biologists to produce living organisms artificially and in a directed manner, or at the very least identify those conditions that make such research impossible (Pereto & Catala 2007).

For Leduc and Loeb's time in the early to mid-20th Century, practical applications of engaging with work on the artificial production of life and its cellular functions was quite elementary by modern standards, with only a small number of research facilities and laboratories available in the world to conduct such research (Pereto and Catala 2007). Even within these contexts, such early attempts at synthesizing biotechnology research did not differ too strongly from the experiments towards selective breeding and basic exposure to emerging chemical solutions of the time (Pauly 1996; Pereto and Catala 2007). Beyond a small number of intrepid universities and research facilities, scholarly opinion was largely set against the pursuit of fostering artificial life. This was driven particularly with those scientists with funding from religious institutions decrying such work on the possibility of spontaneous generation (or the creation of a novel cell from scratch rather than the asexual production of the given cell from a previous parent cell) as being against the religious ideas of a divine Creator as being the progenitor of all life from a single starting point (Pereto and Catala 2006).

Russian biologist and chemist Aleksandr Oparin sought to navigate this hostile environment by concluding that while spontaneous generation was an improbable phenomenon, biochemistry should seek as a long term goal the ability to synthetize the various compounds of living cells (Pereto and Catala 2007). In his 1924 treatise and later 1936 work,

Oparin argued that "life originated as a result of a process of chemical evolution on a primitive Earth, where the right components, ingredients and physical conditions coincided, giving rise to the first elementary cells" (Procar and Pereto 2014). Oparin's widely publicized and discussed works allowed for a maligned yet mildly optimistic collection of early synthetic biology scientists to continue their work under the guise of not clashing too seriously with the prevailing biological opinions of the time (Pereto and Catala 2007). However, all were cautious to acknowledge the technological limitations of the day, with a general understanding that many of life's basic principles were largely unknown beyond larger-scale molecular and systemic activity (indeed, the structure of a deoxyribonucleic acid, or DNA, was not fully described until 1953 by James Watson and Francis Crick).

3.2.2 Advances in Biology and Genetic Engineering: 1953 - 1990

Biological research advanced during the mid- to late-20th Century via the development of genetic engineering due to breakthroughs in understanding of DNA and its synthesis. One of the early advancements here includes the discovery of DNA as having a double-helix structure (Watson and Crick 1953). Similar developments included the reconstruction of viruses and bacteria in a laboratory setting. One example includes the 1955 artificial reconstruction of the tobacco mosaic virus, where researchers Heinz Fraenkel-Conrat and Roblay Williams at the University of California at Berkeley engaged in the elementary composition of macromolecular components of the virus (Fraenkel-Conrat and Williams 1955).

Driven by Watson and Crick's description and growing technological capabilities to study DNA and cellular structures, a later substantial development in early biotechnology and genetic engineering included the ability to sequence DNA genomes (Sanger et al 1977). Specifically, a Stanford University team led by Dr. Fred Sanger conducted a genomic synthesis of the PhiX174 virus, which was the first synthesis of a virus' genome that remained biologically vigorous (Sanger et al 1977). This breakthrough even got the attention of President Lyndon Johnson, who exclaimed that *"[this] is going to be one of the most important stories you ever read, […] some geniuses at Stanford University have created life in the test tube*!" (Porcar and Pereto 2014).

Improvements in understanding of genetics facilitated the development of the first organism to be artificially engineered in a laboratory setting. In 1983, researchers engineered tobacco cells to contain resistance to an antibiotic – the results of which were successfully developed into full plants (Lemaux 2008). Further advancements included the creation of the first transgenic animal in 1985 (pigs), as well as transgenic corn in 1988 (Klein et al 1988). These advancements eventually contributed to the rise of genetically modified organisms being sold in markets, such as with the engineered tomato in 1994 (Uzogara 2000). Generally speaking, the development and maturation of genetic engineering during this period focused on addition, deletion, or substitution of specific DNA base pairs, where more substantial genetic modification of cellular systems was limited by technological constraints of the day (Cameron et al 2014). However, the computational and engineering advancements from 2000 – onward would enable more complicated research to take place.

3.2.3 Modern Synthetic Biology: 2000 - Present

After decades of similar and incremental improvements in biochemical and genomic science from the 1950s-1990s, modern synthetic biology began to take root in the 1990s and early 2000s as an attempt to engage in more complex systems engineering of viruses and bacteria. During the 1990s, Cameron et al (2014) note that "automated DNA sequencing and improved computational tools enabled complete microbial genomes to be sequenced, and high-throughput techniques for measuring RNA, protein, lipids and metabolites enabled scientists to generate a vast catalogue of cellular components and their interactions" (Cameron et al 2014). This, coupled with a systems engineering approach to biology, served as the core principles that made modern synthetic biology possible (Porcar and Pereto 2014; Cameron et al 2014). In other words, genetic engineering around this time began to ponder questions of whether complex cellular networks could be viewed as an engineered system, where deliberate biological engineering of a cell's DNA could yield complex changes to how those systems operate.

In 2000, the journal *Nature* published two articles that discussed the deliberate creation of biological circuit devices (where biological parts inside a cell are designed to perform logical

functions mimicking those observed in electronic circuits) by combining genes within E. coli cells (Elowitz and Leibler 2000; Collins et al 2000). One of these papers discussed how the authors (Alon 2006; Collins et al 2000) were able to construct a genetic toggle switch which influenced "the expression of mutually inhibitory transcriptional repressors" (Cameron et al 2014). For the other paper, Elowitz and Leibler (2000) engineered an oscillatory circuit that, when activated, "resulted in the ordered, periodic oscillation of repressor protein expression" (Cameron et al 2014). It has been suggested that these publications spurred the further development of research centered on circuit engineering and synthetic circuit construction to influence a cell's network design, including the ability to influence cell to cell communication and interactions (Weiss and Knight 2001). Further, the early 2000s included early attempts to "rewire post-translational regulation using protein–protein interaction domains and scaffold proteins", which was accomplished through the manipulation of *S. cerevisiae* (Park et al 2003; Cameron et al 2014).

It was during this time that the field of systems biology emerged as a mature and independent field of inquiry pertaining to the computational and mathematical modeling of complex biological systems (Kitano 2002; Ideker et al 2001). Among the central aims of the field is to better understand the various properties of cells, tissues, and the systemic infrastructure that comprises living organisms (Hucka et al 2004; Hood et al 2004). This is generally undertaken by researching cell signaling networks, or the signals and stimuli that govern and control cellular actions (Ingber 2003; Kitano 2002). Coupled with earlier principles of genetic engineering, the technological and scientific advancements derived within systems biology serve as some of the driving forces behind the development of synthetic biology research (Andrianantoandro et al 2006; Khalil and Collins 2010).

By 2003, nascent synthetic biology research grew both from an academic and professional standpoint. Professionally, the conference "Synthetic Biology 1.0" in June 2004 at the Massachusetts Institute of Technology served as the first international conference explicitly dedicated to synthetic biology research (Ball 2004). At this meeting, an interdisciplinary collection of professionals ranging from biology and chemistry to computer science, and centered on the desire to design, build, and characterize biological systems and interactions

(Ferber 2004). This conference series spurred further international meetings known colloquially as the SBx.0, with the latest iteration as of this writing held in Imperial College, London in 2013 (SB 6.0). Cameron et al (2014) note that this conference series furthered discussion around blending elements of engineering with molecular biology, with a general goal of describing whether or not synthetic biology could become as developed an engineering field as electrical engineering or materials science. Specifically, Endy (2005) and Cameron et al (2014) described these early efforts as an attempt to produce a collection of modular parts and improve design pathways for engineered cells – with the idea that modifying specific cell circuit designs could deliberately change the behavior or interactions of that cell with its local environment.

Within the period from 2004 and 2010, various elements of synthetic biology research began to materialize in the form of circuit design and metabolic engineering, which became collectively known by Purnick and Weiss (2010) as "the second wave of synthetic biology" (Purnick and Weiss 2009; Isaacs 2004). For the former, this includes attempts to expand RNA-derived cellular systems to broaden biological circuit engineering from "transcriptional control" into post-transcriptional control vehicles and capabilities (Bayer and Smolke 2005). Generally accomplished using *E. coli*, various scientists sought to expand circuit and part designs, with one such circuit dedicated to the conversion of light into gene expression for a collection of *E. coli* cells (Levskaya et al 2005). For the latter, a group of scientists at the University of California, Berkeley engaged in research on isoprenoid biosynthesis, which enabled the production of artemisinic acid, or the component precursor to the wormwood *Artemisia annua* (Ro et al 2006). Using a collection of organisms including *S. cerevisiae* and *E. coli,* this group under the leadership of Dr. Jay Keasling was able to produce antimalarial components of the artemisinin plant in a faster timeline and more efficient use of resources than occurs naturally with plant growth.

Artemisinin combination therapies have been utilized by the World Health Organization as the primary initial treatment for *P. falciparum* malaria, which destroys the majority of parasites in a patient's blood immediately upon the drug's consumption (Nosten and White 2007; Van Agtmael et al 1999). However, where the plant maintains erratic price points (ranging from $120 to $1200 USD per kilogram between 2005 and 2008), the natural

production of artemisinin for antimalarial drug use is often too expensive for distribution in Africa and Southeast Asia (Mutabingwa 2005; White 2008; Kindermans et al 2007). Furthermore, the lack of production remained a concern for much of the 2000s, where artemisinin farmers in China, Vietnam, and East Africa did not maintain steady levels of plant production in the midst of large-scale market swings (Kindermans et al 2007; Mutabingwa 2005). One approach to resolve such concerns includes the subsidy and controlled development of artemisinin crops to prevent substantial price swings, ensure steady and predictable production, and help make artemisinin-based treatments more accessible and affordable to populations in Africa and Southeast Asia (Mutabingwa 2005; White 2008).

However, another potential approach includes the synthetic production of artemisinic components to remove the reliance upon natural crop cycles and growth of artemisinin plants. This included the research accomplished by Keasling's team, where Keasling's semi-synthetic artemisinin precursor is seen as an improvement over traditional production measures of artemisinin due to its capability to produce the medicinal properties of the plant using fermented yeast cells, and in controlled and pre-planned settings (Ro et al 2006; Hale et al 2007). By 2013, the World Health Organization prequalified the use of semi-synthetic artemisinin, allowing Sanofi (the pharmaceutical producer who commercialized Keasling's product) to begin distributing such products, with an initial shipment of 1.7 million artemisinin treatments sent largely to Africa in August 2014 (Singh and Vaidya 2015). Among other things, this advancement in synthetic biology research demonstrated the ability of the technology to yield therapeutic benefits for human health while also yielding commercial products for various industries such as with pharmaceuticals (Hale et al 2007; Westfall et al 2012; Kong and Tan 2015).

Outside of academia and industry, another development within synthetic biology discussion and work by 2003 included the International Genetically Engineered Machine (iGEM) competition, which is an annual event where high school students, undergraduate students, graduate students, and entrepreneurs compete to build synthetic biological systems using pre-defined parts as a team (Kelwick et al 2015). Normally, groups register and are given a kit of biological components by which they are asked to build biological systems and operate them in

living cells (Kelwick et al 2015; Mercer 2015; Stemerding 2015). The competition's membership grew to 130 teams worldwide by 2010 and 280 teams by 2015, with at least one team from every habitable continent on Earth (iGEM 2016). Within such competitions, however, Tocchetti and Aguiton (2015) and Kwik (2015) note that there exist concerns about the potential for biosafety and biosecurity risk when enabling 'do-it-yourself' research. Responding to such concerns, Tocchetti and Aguiton (2015) and Evans and Frow (2015) state that iGEM participants are screened and reviewed by multiple judges for safety concerns. Nevertheless, Guan et al (2013) states that some stakeholders in government and the lay public remain concerned about the potential for such risks.

3.3 Synthetic Biology's Recent Development: 2008-Present

Where the period between 2003 and 2007 saw a rise in circuit design and eventual characterization alongside the growth and development of the synthetic biology research community, Cameron et al (2014) notes that by 2008 the technology's development had accelerated to include the creation of more complex biological circuits and greater control of systemic biological behavior within cells. In this timeframe, circuit engineering was advanced by a decline in the cost of gene synthesis alongside the development of high-throughput DNA assembly approaches (Engler et al 2008; Gibson et al 2009; Cameron et al 2014). This enabled greater control genetic systems and enabled novel gene expression such as with light sensing circuits within bacteria (Tabor et al 2009) along with faster and more complex pattern formation in *E. coli* swarms (Liu et al 2011). Overall, this period drove greater connections between synthetic biologists with network engineers in order to engage with greater attempts to control and alter the form and function of cellular networks on a systems level (Cameron et al 2014).

Perhaps one of the more widely publicized developments within this timeframe includes the advancements made by the James Craig Venter Institute (Gibson et al 2010; Ellis et al 2011; Elowitz and Lim 2010). In 2010, the James Craig Venter Institute announced the creation of the first synthetic cell (Gibson et al 2010). Using a modified *Mycoplasma mycoides* genome, Venter's team fostered a proof of principle regarding the notion that genome design may be

"constructed on a computer, chemically made in the laboratory and transplanted into a recipient cell to produce a new self-replicating cell controlled only by the synthetic genome (JCVI 2010). In their experiment, Venter's team synthesized a version of the *M. mycoides* genome, which was subsequently transferred and transplanted into a *Mycoplasma capricolum* bacterial shell that had its DNA previously removed (JCVI 2010; Cameron et al 2014; Gibson et al 2010; Ellis et al 2011). The ultimate result of this process was to foster a self-replicating bacteria cell that only contained Venter et al's synthesized genome – with proof that digital synthesis of genetic base pairs on a computer for assembly and transplantation of an entirely artificial genome within biological material was a viable process for synthetic biology research (Gibson et al 2010). Less than a year later, a research team led by Jef Boeke at Johns Hopkins University was able to utilize a similar synthesis of *S. cerevisiae* in yeast (Dymond et al 2011).

The technological breakthrough by Venter's team was a turning point for synthetic biology research, which now had proof that the process of computerized genome construction and editing for physical transplantation of a fully synthetic genome in a bacterial cell was viable in controlled settings (JCVI 2010; Gibson et al 2010). One such development includes the multiplex automated genome engineering platform (MAGE), where a team led by George Church developed a platform to rapidly alter multiple loci in the *E. coli* genome (Wang et al 2009; Cameron et al 2014). This platform enabled the "proof-of-principle replacement of all TAG stop codons with the synonymous TAA codon" (Isaacs et al 2011; Cameron et al 2014; Wang et al 2009). Another prominent technological development includes the clustered regularly-interspaced short palindromic repeats system (or CRISPR-Cas, for short), which was utilized by Jiang et al (2013) and DiCarlo et al (2013) to serve as a genome-editing tool that helped to generate genomic mutations within a cell. This increased the ability of geneticists to alter bacterial and yeast genetic structures (Jiang et al 2013; DiCarlo et al 2013). Another genetic editing technique includes zinc fingers, which are particularly useful to engineer proteins that target specific genes (Klug 2010). Specifically, zinc finger manipulation facilitates synthetic biology engineering capabilities by allowing scientists to selectively switch specific genes on and off (Heinemann and Panke 2006; Klug 2010), and helps enable the more complex genetic manipulation of larger eukaryotic organisms (Khalil et al 2012).

Based upon these developments, synthetic biologists have within the current period through 2016 become increasingly able to alter cell DNA and produce systemic-level change to the cell's genome and behavior. However, significant challenges remain specific to the science of synthetic biology research, such as with the high variability of cellular part and circuit performance to overall cellular circuit construction (Nandagopal and Elowitz 2011; Cameron et al 2014). Smith et al (2014), and Baltes and Voytas (2015) further note that variability within a complex intracellular environment difficult to prevent or avoid.

Purnick and Weiss (2009), Andrianantoandro et al (2006), Ellis et al (2009), and Cheng and Lu (2012) sought to work around this problem by constructing libraries of synthesized cellular parts and rigorously quantify the behavior and activity of these parts under certain conditions. The general goal of such libraries is to enable the assembly of cellular circuits from these thoroughly researched collection of parts, which would then be screened and improved as necessary for a particular function or project. One such library project in this aim includes the International Open Facility Advancing Biotechnology (BIOFAB), which serves as a facility geared towards constructing and characterizing libraries of bacterial promotors and transcription terminators (Mutalik et al 2013; Cambray et al 2013). Specific to this aim, BIOFAB is currently looking to foster a reliability score for individual cellular parts, which allows for greater understanding of the potential flaws that each part may express and has been shown to assist with debugging efforts within circuit engineering exercises (Mutalik et al 2013).

3.4 Synthetic Biology Today: Defining the Field

A complicated issue that still faces the field today includes defining what 'synthetic biology' actually means, and the processes that are implied by it. Such a formal definition remains elusive and misconstrued even as of December 2015. Voosen (2013) described it as" arguably the world's hottest and most poorly defined scientific discipline." Schmidt (2010) further stated that if you ask 10 experts to define synthetic biology, you are likely to get 10 different answers (Schmidt 2010). Likewise, the Royal Academy of Engineering (2009), the President's Commission on the Study of Bioethical Issues (2010), The National Bioeconomy Blueprint (2012), and the Synthetic Biology Engineering Research Center (SYNBERC 2013) all state and

describe their own definitions of 'synthetic biology' and the various processes and scientific techniques involved within its research in differing ways (see Table 4 below)– although they come to some fundamental agreement on the technology as being 'the deliberate design and construction of novel biological parts and systems for pre-identified purposes.'

Institution	**Definition**
UK Royal Academy of Engineering	"Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems."
SYNBERC	"Synthetic biology is a maturing scientific discipline that combines science and engineering in order to design and build novel biological functions and systems. This includes the design and construction of new biological parts, devices, and systems (e.g., tumor-seeking microbes for cancer treatment), as well as the re-design of existing, natural biological systems for useful purposes (e.g., photosynthetic systems to produce energy).
President's Commission on the Study of Bioethical Issues	"…apply standardized engineering techniques to biology and thereby create organisms or biological systems with novel or specialized functions"
European Commission Scientific Committees	"SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms"

Table 4. List of Synthetic Biology Definitions by Selected Organizations

For this dissertation, the definition presented to interview contacts centers on 'the deliberate design and construction of novel biological parts and systems for pre-identified purposes'. This definition is consistent with discussion by PCSBI (2010), SynBERC (2013), the UK Royal Academy of Engineering (2009), and the European Commission Scientific Committees (2014) – all of which are important resources for the field's discussion and eventual regulation. After reviewing this general definition, more expansive discussion centered around SynBERC (2013)'s explanation of the field. This was chosen for two reasons. The first includes the fact that SynBERC also included governmental definitions of synthetic biology from other prominent

publications as the President's Commission on the Study of Bioethical Issues (USA) and the European Union – factors that are important to consider when reviewing the technology's regulation. The second reason is that SynBERC directly states that they sought to balance biological and engineering perspectives of synthetic biology to be inclusive of the various approaches taken to develop the field. Overall, SynBERC's definition at its core is consistent with other definitions in the field, and served as the up-to-date account of synthetic biology discussion at the onset of this dissertation (2014). SynBERC's full definition is listed here:

> *"Synthetic biology is a maturing scientific discipline that combines science and engineering in order to design and build novel biological functions and systems. This includes the design and construction of new biological parts, devices, and systems (e.g., tumor-seeking microbes for cancer treatment), as well as the re-design of existing, natural biological systems for useful purposes (e.g., photosynthetic systems to produce energy). As envisioned by SynBERC, synthetic biology is perhaps best defined by some of its hallmark characteristics: predictable, off-the-shelf parts and devices with standard connections, robust biological chassis (such as yeast and E. coli) that readily accept those parts and devices, standards for assembling components into increasingly sophisticated and functional systems and open-source availability and development of parts, devices, and chassis."* (SynBerc 2013).

3.5 Synthetic Biology and Health Risk

Aside from issues surrounding the field's definition from an administrative standpoint, further discussion related to synthetic biology research has focused on the pathways of potential risk to humans and the environment (Carter et al 2014; Moe-Behrens et al 2014). Two such early topics of risk-based discussion in the early 2000s related to synthetic biology research include the concepts of *biosafety* and *biosecurity* (Kelle 2009; Guan et al 2013; Carter et al 2014). Specific discussion on these topics centers on the potential for irreversible and/or hazardous outcomes from the process of synthetic biology product development, either from deliberate misuse (biosecurity) or unintended consequences (biosafety) (Kelle 2009; Guan et al 2013; White and Vemulpad 2015).

Noted above, the two major potential risk categories associated with synthetic biology include biosafety and biosecurity. The former includes accidental release and exposure scenarios, where novel genetic material may produce harms to humans, animals, and the

environment (Schmidt 2008; Guan et al 2013). Biosafety concerns are relevant and challenging for synthetic biology research, where accidental release of modified organisms could potentially yield risks to local biodiversity as well as contribute to horizontal gene transfer of artificial genetic material into natural cells. For the latter, biosecurity risk focuses on dual-use concerns, where technological advancements may be deliberately misused to produce potential harms to humans and the environment (Garfinkle and Knowles 2014; Church et al 2014). Such concerns have been noted by Garfinkle and Knowles (2014) and Perkins and Nordmann (2012) as potentially enabling bioterrorists and other nefarious agents in their abilities to produce harmful biological agents like an engineered virus. In the following sections below, each potential risk category is discussed from the perspective of how such risks are viewed in the literature.

3.5.1 Biosafety

Biosafety considerations generally consider the unintentional release of genetically-modified material that may subsequently alter or overwhelm its local environment and incur negative health consequences (Wright et al 2013; Schmidt 2008; Seyfried et al 2014). Such concerns may occur across the life cycle of a given synthetic biology material, including at the research and development stage (i.e. biological material accidently escapes lab containment and reaches unintended human or environmental hosts), the manufacturing stage (i.e. concerns of occupational health due to unintended exposure to modified cells), the commercial stage (i.e. unintended use amongst consumers), and the end-of-life stage (i.e. improper disposal or treatment of synthetic biology byproducts and waste) (Bates et al 2015). Across all stages, an important consideration includes how such an event could occur alongside the magnitude of health consequences that it may produce.

One potential biosafety risk concerns noted in the literature includes the concept of horizontal gene transfer (Schmidt et al 2008; Cardinale & Arkin 2012; Dana et al 2012). Generally referring to the transfer of genes between organisms in a manner other than traditional reproduction, horizontal gene transfer is a particular problem of concern for synthetic biology as such gene transfer “is a common and somewhat uncontrolled trait through

the microbial biosphere" (Wright et al 2013; Dröge et al 1998). Davison (1999) and Wright et al (2013) state that horizontal gene transfer occurs by transduction, conjugation, and/or transformation of modified cells within the natural environment. For each of these three methods of transfer, transduction involves the active transfer through bacteriophages, conjugation through pili, and transformation via "sequence-independent uptake of free DNA from the environment" (Wright et al 2013).

Synthetic biologists have begun to explore avenues to prevent horizontal gene transfer via one or more of these avenues, yet the process of fully resolving the 'transformation' gene transfer avenue is challenging due to the potential for lingering cell DNA to persist in the environment well after cell death (Thomas and Nielsen 2005). Neilsen et al (2007) note that even months after a cell is placed within certain environmental conditions, extracellular DNA can be detected. Further, such extracellular DNA may be actively assimilated by bacteria along with some unicellular and multicellular eukaryotes (Lorenz and Wackernagel 1994; Wright et al 2013; Boschetti et al 2012). While Khalil and Collins (2010) describe how engineering a 'self-destruct' option can limit some vectors of horizontal gene transfer by programming the cells to die under certain conditions or time intervals, Wright et al (2013) and Lorenz and Wackernagel (1994) discuss how even with cases of cell death, extracellular DNA may be scavenged and absorbed by other natural cells afterwards. Callura et al (2010) and Wright et al (2013) discussed how self-destruct mechanisms serve as the best available tool to prevent synthetic material from escaping control and interacting with the environment, where engineered cells could be preprogrammed to self-destruct en masse if cell population density becomes too great.

Wright et al (2013) and Townsend et al (2012) go on to state that monitoring the rates of horizontal gene transfer is a complicated process due both to the large swarms of cells required to monitor for gene transfer along with the extended timeframe needed to monitor whether or not a rare genetic mutation was able to grow into larger populations of cells. Nielsen and Townsend (2004) and Wright et al (2013) further argue that horizontal gene transfer events are difficult to monitor due to their limited rate of occurrence, where the frequency of transformation of microbes in soil is less than 1×10^{-7} per bacterium exposed, with

transformation generally capable only within a few hours to days after the release of novel cellular material into the environment. However, Pruden et al (2012) note that despite the general rarity of horizontal gene transfer, certain DNA elements have been shown to proliferate through large and complex ecosystems. One of these includes antibiotic-resistance genes, which Mulvey & Simor (2009) describe as cases of horizontal gene transfer where antibiotic-resistance spreads in environments such as hospitals and produces antibiotic resistant superbugs. From the perspective of biosafety, Wright et al (2013) argue that such antibiotic-resistant genes should not be utilized by synthetic biologists unless absolutely necessary, although such genes remain "commonly used as markers during plasmid construction."

Aside from cellular self-destruction, another approach to promoting biosafety includes making it easier to identify where cells escaping containment may have originated from in order to fix existing containment issues and prevent future breakout events. Wright et al (2013) describe that synthetic operons within cellular DNA may be fashioned to contain a genetic 'barcode' that may be indexed within a database in order to facilitate cellular recognition and communicate the cell's origin point to identifiers. Another approach described by Gibson et al (2010) includes the introduction of a 'DNA watermark' into several locations on the cell's genome, which acts as an identifier similar to that describe above. Wright et al (2013) further argue that such a watermark or barcode may also have proprietary benefits, where such unique codes may be used for commercial purposes to 'brand' a cell's DNA with unique identifying information in the event of theft.

Even should these approaches to reduce the opportunities for horizontal gene transfer fail, the chance for mutated genes that are harmful to humans to transfer and proliferate are minute (Arber 2014; Wright et al 2013). In other words, it is rare that transferred traits are evolutionarily beneficial to targeted organisms that are also detrimental to human and ecosystem health in a natural setting (Rossi et al 2014). However, White and Vemulpad (2015) note that synthetic biology may increase the potential for harmful gene transfer due to the use of artificial gene sequences. Even in such scenarios, however, Armstrong et al (2012) argue that such concerns are more likely in deliberate biosecurity situations rather than through accidental release and random gene transfer.

3.5.2 Biosecurity

Biosecurity, or concerns of risk driven by the use of synthetic biology for nefarious or deliberately harmful means (i.e. bioterror), centers on the 'dual use' concerns associated with emerging technology development (Perkins and Nordmann 2012; Marris et al 2015). Such concerns include fears that technological developments may also be utilized for deliberately harmful purposes (Marris et al 2015). Dual use concerns have been discussed within synthetic biology research since at least 2004, when the World Health Organization outlined certain guidelines to promote lab safety while reducing the potential for malicious use of synthetic biology's concepts and tools at cellular manipulation (WHO 2004; Mandel et al 2014).

Particularly within the United States, federal policymakers increasingly concerned with the potential for life sciences research to be misused in warfare or terrorism began to assize their own inquiries with respect to synthetic biology biosecurity, with the first such council including 'The Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology' of 2004 – colloquially known as the Fink Committee (National Research Council 2004; Kelle 2009). Specific to synthetic biology, the Fink Committee was asked to review those "practices that could improve US capacity to prevent the destructive application of biotechnology research while still enabling legitimate research to be conducted" (National Research Council 2004). Specific recommendations produced by the Fink Committee include:

1) To educate the scientific community

2) Review experiment proposals and plans related to genetic manipulation and experimentation

3) Likewise, to review submitted manuscripts in this field prior to their publication,

4) Foster the creation of a national science advisory board related to combatting bioterrorism and other threats arising from the misuse of life sciences research like synthetic biology,

5) To "harmonize international oversight" (Kelle 2009)

6) To achieve a more active role for the life sciences in efforts to prevent biosecurity concerns.

In response to the Fink Committee's recommendations, the US National Research Council established the Committee on Advances in Technology and the Prevention of their Application to Next Generation Bioterrorism and Biological Warfare Threats, which later also became known as the Lemon–Relman Committee (Kelle 2009). To more specifically address potential biosecurity risks and threats of emerging life sciences research such as with early synthetic biology, the committee established a four-group classification methodology which included:

1) Technologies that seek to acquire novel biological or molecular diversity,

2) Technologies that seek to generate novel but predetermined and specific biological or molecular entities through directed design,

3) Technologies that seek to understand and manipulate biological systems in a more comprehensive and effective manner, and

4) Technologies that seek to enhance the production, delivery and 'packaging' of biologically active materials (National Research Council, 2006; Kelle 2009).

Under the Lemon-Relman categorization, synthetic biology falls into categories 1 and 2, with Committee recommendations for the technology to have increased awareness and oversight for biological capabilities to damage, for example, host homeostatic and defense systems or for constructing synthetic organizations with limited control and/or the potential for deliberate negative health risk (National Research Council 2006). A primary outcome of the Lemon-Relman Committee and its subsequent categorization was an increased call for government oversight and monitoring related to the potential for dual use applications in life sciences research (Choffnes et al 2006).

Further, discussion from both committees, with particular discussion from the Lemon-Relman Committee which called for increased consideration of the societal implications of and access to synthetic biology research, was discussed at the SB2.0. Specifically, SB2.0 conference attendees produced a collective statement that discussed some of the biosecurity implications of DNA synthesis, including calling for an open working group to "improve existing software

tools for screening DNA sequences" and promote further discussion on options for national governments in Europe and the United States to govern DNA-synthesis technology that may be produced in synthetic biology research (Conferees SB2.0 2006; Kelle 2009).

3.5.3 Considerations of Hard and Soft Law in Synthetic Biology Regulation

Aside from government-directed discussion on biosecurity issues, one of the early descriptive papers on the regulation of synthetic biology biosecurity concerns includes Church (2004). Specifically, Church called for a biosecurity paradigm where oversight agencies would screen any genetically modified material with various research projects based upon the product's oligonucleotide and DNA information to identify and similarities between the discussed organism and other traditional pathogenic organisms. To limit the proliferation of such research outside of institutions with clear external oversight and regulation, Church (2004) also called for the licensure of certain instruments and reagents involved in the production of genetically modified material deemed similar to harmful pathogens (Church 2004; Kelle 2009).

Despite these calls for expanded government oversight of synthetic biology research, Maurer and Zoloth (2007) and Bügl et al (2007) argued instead for a governance paradigm driven by synthetic biologists instead of preemptive national regulation. Specifically, Maurer and Zoloth (2007) placed emphasis on the need for self-governance without external interventions or intrusive oversight. In a similar vein, Bügl et al (2007) argued for a governance structure that, while incorporating external oversight from government, placed companies squarely within the governance-building process.

Overall, Kelle (2009) identifies two distinct strands of discussion related to biosecurity regulation that emerged with the second and early third waves of synthetic biology. First, industry and DNA-synthesis companies generally emphasize the "formation and implementation of best practices across the industry" where "oversight and enforcement of these standards […] is not regarded as falling into the purview of industry itself, but rather as a governmental task" Kelle (2009). For the second element, Kelle (2009) acknowledges the growing discussion of self-governance within the synthetic biology community, which Maurer and Zoloth (2007) and Kelle (2009) describe as not easily reconciled with governmental wishes

to strengthen external oversight over an industry they perceive as advancing potentially threatening technological capabilities if nefarious agents were able to gain access to them.

Kelle (2013) and Grunwald (2012) describe the former as generally precautionary in approach, which while reducing the probabilities of bioterrorism and similar risks would potentially limit the advancement of the field by reducing the ability to disseminate knowledge freely and quickly. Likewise, Murray (2010) describes discussion similar to the latter as relatively proactionary (or behavior geared towards advancing a particular aim of science in spite of potential risks or hazards), where limited to no oversight hinders the ability of regulators and decision makers to understand emerging trends in the field of synthetic biology and identify areas of concern related to biosecurity.

3.6 Synthetic Biology and Health Risk: Pharmaceutical Development

3.6.1 Background

As noted in Chapter 1, one of the emerging applications of synthetic biology is for pharmaceutical development (Neumann & Neumann-Staubitz 2010; Carter et al 2014). From a perspective of contemporary synthetic biology research beginning around 2000, pharmaceutical and therapeutic research has remained one of the primary focal points of synthetic biology scientists, with a focus upon improving access and production options for certain drugs while producing novel vaccines for those viruses lacking any vaccine approved for commercial distribution. More specifically, such development is driven by one or more benefits that synthetic biology approaches offer, including:

1) The ability of synthetic biologists to produce pharmaceuticals and pharmaceutical components on a faster and less expensive timeline, and

2) The ability of synthetic biologists to potentially synthesize and engineer drug and vaccine treatments for diseases that traditionally lack a vaccine or lack effective treatments to control disease symptoms or provide novel health benefits relative to current pharmaceutical offerings.

Both areas of research are being discussed by synthetic biologists vested in research of various pharmaceutical and therapeutic treatments. The first option has already seen some

advancement, such as with the case of Keasling's antimalarial drug. The second option, however, is more elusive due to the more intensive gene synthesis and engineering required to produce a safe and effective pharmaceutical treatment (Carter et al 2014; Pade et al 2015; Haelmann and Fusnegger 2015).

3.6.2 Synthetic Biology for More Efficient Production of Pharmaceuticals

With respect to the ability of researchers to produce pharmaceutical material in a faster and less costly timeframe, synthetic biologists have advocated for a systems engineering approach to produce specific drugs and vaccines (Paddon and Keasling 2014; Oberg et al 2011). One of the first instances of this includes the research group at University of California, Berkeley led by Dr. Jay Keasling, which was briefly discussed above as an attempt to produce semi-synthetic artificial artemisinin to treat those suffering with malaria (Paddon and Keasling 2014). Keasling's process involved the synthesis of antimalarial precursors in the form of artemisinic acid, which facilitated a faster, cheaper, and more reliable alternative to traditional artemisinin to be used to alleviate malarial conditions experienced by the afflicted (Singh and Vaidya 2015). By 2014, pharmaceutical producer Sanofi produced 1.7 million doses of artemisinin treatment using Keasling's method (Singh and Vaidya 2015).

Another synthetic biology pharmaceutical in this category includes an early attempt to mass produce the influenza vaccine on a more rapid time scale than within conventional production measures. Specifically, the Swiss pharmaceutical company Novartis International AG (or Novartis, for short) began in 2012 an attempt to utilize principles of synthetic biology to reduce production times for influenza vaccine production (Rojahn 2013). Novartis Head of Virology Dr. Philip Dormitzer stated in a public presentation at the National Academy of Sciences in October 2013 that such an effort was geared towards addressing the lag time between the initial onset of a viral outbreak and the distribution of a viable vaccine to the masses (Dormitzer 2013).

Dormitzer further noted that using current vaccine production methods (generally, growing large numbers of the pathogen in question in chicken eggs to use as starting material for a vaccine), approximately 40% of cases of viral infection of influenza will occur before any

vaccine is made available to the public – largely due to the time needed to produce the vaccine material in significant quantities for large-scale manufacturing (Dormitzer 2013). Rappuoli and Dormizer (2012) stated that the time lag for H1N1 in 2009 was approximately three months, where the virus' detection in March initial vaccine manufacturing in June, and initial widespread vaccine distribution by November had delayed vaccination to a point where the virus' incidence had already begun to subside (Perkel 2015). To help resolve this lag time and speed up vaccine production for emerging strains of influenza, Novartis utilized synthetic biology approaches to sequence strains of the influenza virus, reprogram said virus on a computer, and then use that computer code to facilitate vaccine production at sites across the globe (Perkel 2015).

The first case of this technological process included influenza strain H7N9, which was first sequenced by Chinese epidemiologists in March 2013. Using this information, a joint team from Novartis, the James Craig Venter Institute, Synthetic Genomics, and a few others were able to review the H7N9 gene sequence over the internet and subsequently synthesize artificial genes within the gene sequence. Later, this modified virus was "inserted […] into a pre-existing viral backbone" and subsequently used to infect eukaryotic Madin-Darby canine kidney (MDCK) cells in a cell culture for subsequent growth and harvesting over the course of 2-3 days (Dormitzer et al 2013; Bart et al 2014). The entire process from downloading the Chinese gene sequence to growing material needed for early vaccine production was approximately 100 hours, did not involve the physical shipment of any vaccine material to research labs, and ultimately reduced vaccine production times from about 6 months down to approximately 1 week (Dormitzer et al 2013).

The key novelty associated with this vaccine production process centers on the ability to synthesize, modify, and engineer virus material on a computer that could then be used to develop vaccine material. Dormitzer et al (2013) note that not only does this process dramatically reduce the time requirements needed to produce vaccine material needed for manufacturing, but it also allows for the rapid geographic distribution of digital vaccine material for localized work at laboratories around the world. Further, the ability to modify and reprogram material via a computer allows for greater control over the genetic engineering

process, and allows biologists and engineers to engage in more complicated and systems-wide genetic modification of biological material (McGuigan 2016; Ulmer et al 2015).

3.6.3 Synthetic Biology for Novel Pharmaceutical Production

Aside from facilitating the development of existing pharmaceuticals, the ability to use synthetic biology to synthesize and produce novel pharmaceuticals for diseases which currently lack an approved vaccine or effective treatment such as with the ebolavirus, malaria, and the dengue virus has been discussed as a futuristic application of the technology (Weber & Fussnegger 2012; Tucker & Zilinskas 2006; Barocchi & Rappuoli 2015). Similar applications include the development of engineered probiotics to assist with digestion and improve overall human health (Ando et al 2014; Bugaj and Schaffer 2012; Folcher and Fusnegger 2012). Each of these potential treatments respectively has the ability to provide health benefits that are either currently unavailable or advance health improvement capabilities beyond traditional and conventional pharmaceuticals, both from the perspectives of preventative and acute medical care (Weber and Fusnegger 2012).

However, the health benefits generated from such novel drug and vaccine creation as well as the *in vivo* use of genetically modified biological agents also inherently possess greater uncertainty regarding the scope of potential health risks that they may potentially pose to humans and the environment. This uncertainty centers on, among others, the potential risks from the *in vivo* use of biological agents (Ruder et al 2011). Ruder et al (2011) and Church et al (2014) note the need for greater attention to be paid to the potential for novel health risks of such pharmaceuticals to arise throughout the material's life cycle, such as the potential for unintended exposure to humans and the environment and subsequent gene transfer. Getino et al (2015) argue that research is needed and becoming increasingly available to mitigate the horizontal transfer of synthetic genetic material such as those transferred by plasmids, although other avenues of horizontal gene transfer exist as noted above that have a small probability of occurring within human and environmental cells.

One specific application within this category includes the production of synthetic probiotic bacteria, or an improvement of existing probiotics that are purported to confer health

benefits to users such as the decrease of potentially pathogenic microorganisms, improvement in the body's immune system, reduced gastrointestinal discomfort, the improvement of bowel regularity, and others (Danino et al 2015; Ray 2015; Rijkers et al 2011). However, the medical benefits derived from conventional probiotic use have not been causally confirmed (Rijkers et al 2011). Synthetic biologists have discussed the potential for certain bacteria to be synthesized and engineered in a manner that incurs health benefits such as screening for disease *in vivo* (Danino et al 2015; Ray 2015) or improving gastrointestinal health and function (Zhang and Nielsen 2014; Piñero-Lambea et al 2015).

Of these two general categories of probiotic benefit, the former (disease detection *in vivo* such as with cancer) is closest to commercial medical use (Danino et al 2015; Ray 2015). Slomovic et al (2015) describe how bacterial cells such as with *E. coli* have been reprogrammed to serve as a diagnostic tool for cancer screening, and could in the future be repurposed for therapeutic delivery *in vivo* and directly upon a tumor target site. Further, Danino et al (2015) note that such semi-synthetic *E. coli* can "noninvasively indicate the presence of liver metastasis by producing easily detectable signals in urine", where no harmful health effects of the treatment were observed in mice within 12 months after oral delivery of the engineered probiotic. While this stage of engineered probiotic testing is in the earliest stages of animal testing, Danino et al (2015) and Ray (2015) note that the limited approach to engineering various bacterial cells will likely yield little novel health risk.

Aside from disease detection, the use of probiotics to improve gastrointestinal health and metabolism is an emerging application of synthetic biology research with significant potential benefits yet more elevated levels of risk than with its disease-detecting cousins (Zhang and Nielsen 2014; Burrill et al 2011). This is due to the enhanced complexity and involvement of gene synthesis and engineering needed to deliver therapeutic treatment *in vivo* (Piñero-Lambea et al 2015), along with the potential need for other novel technologies to assist with drug delivery and probiotic control such as with micro robotics and nanomaterials (Tripathi et al 2013). Further, such probiotics may yield acute and risky side-effects to an individual's cardiovascular and/or gastrointestinal systems such as the disruption of 'good' bacteria populations and the uncontrolled production of unhealthy gut bacteria (Tang et al 2013),

although such findings remain uncertain due to the lack of clinical testing and commercial development in the field on humans. From an environmental perspective, the potential introduction via misuse or accidental release of modified material into the environment (Halling-Sørensen 1998) may contribute to opportunities for horizontal gene transfer (Endy 2005) and subsequent environmental invasion and proliferation, although the probability of this is very small (Wright et al 2013).

Chapter 4:

Synthetic Biology and Risk Regulation – The Case of the United States

4.1 Introduction

Since the early 2000s, synthetic biology research has been studied by research facilities across United States (Kuiken 2010; Kuiken 2015; Stephanopoulos 2012; Cheng and Lu 2012). Ranging from government laboratories to universities and early private sector research, synthetic biology innovation has grown for both military and civilian purposes each year since at least 2008 (Kuiken 2015). Such spending (approximately $200 million annually by 2014) is geared for a variety of purposes, such as with the financing and improvement of circuit and metabolic engineering to improve the science of synthetic biology (Wright 2014; Georgianna and Mayfield 2012). One particular application of this includes research into pharmaceutical and therapeutic improvements, including options to facilitate the more efficient and less costly production of existing products and further inquiry into elusive drugs and vaccines (Paddon and Keasling 2014; Wright 2014; Weber and Fussenegger 2012).

This chapter indicates how each case was addressed from an analytical perspective. While each individual case maintains its intricacies related to the availability of interview subjects, the regulatory environment that synthetic biologists must operate under, and the degree of scientific achievement and progress, these cases cover three general sections, including:

(i) the history and current status of synthetic biology research within the given case (where this is partially covered within the Chapter 3),

(ii) The perceptions expressed by subject experts regarding where synthetic biology pharmaceutical product health risk may arise along the technology's life cycle as well as the mechanisms that may contribute to such harms, and

(iii) discussion of existing hard and soft law regulation available to cover synthetic biology products within a given country, including discourse analysis and respondent perceptions of whether or not these mechanisms are capable of adequately regulating the field moving forward.

Within this framework, the goal of such discussion is to review how differing elements of risk culture have influenced the regulation of the process of synthetic biology. Specifically, this includes the need to review in this Chapter how the regulatory history and institutional and political structure has come to foster a risk culture in the United States that is formal, transparent, and generally adversarial in nature, and makes any attempt at regulatory reform in the United States a politically difficult task. Specifically, Sections 4.2 and 4.3 seek to unpack the political and institutional factors that cause the American government to favor the regulatory status quo and adopt regulatory change slowly, while later sections review US-based expert perception of synthetic biology risk as well as the ability of existing regulatory instruments to capture the process of synthetic biology development.

4.2 Regulatory Instruments and Tools Relevant to Synthetic Biology in the United States

To better describe the regulatory capabilities and legislative instruments within the United States directed at regulating the process of synthetic biology development, literature and expert interview responses were used to review several considerations important for synthetic biology regulation. These include the need to (i) identify applicable hard and soft law that has been used directly or indirectly to cover synthetic biology research, (ii) discuss potential limitations of such regulation to cover novel risks associated with synthetic biology, and finally (iii) describe potential improvements (where necessary) to rectify these discussed shortcomings.

Looking first at describing the existing regulatory instruments and tools within the United States applicable to synthetic biology, such regulation is generally not geared towards synthetic biology but instead an extension of existing regulation and law to temporarily cover synthetic biology research (Carter et al 2014). Clift (2006) and Marchant et al (2009) state that other emerging technologies with potential risk and inherent uncertainty are also regulated

using existing legislation and regulatory policy until the need for sui generis regulation is deemed necessary (Marchant et al 2012). Further, Jasanoff (1995) and Dana et al (2012) contend that a product-driven focus for the regulation of new technologies such as with nanotechnology makes it necessary for regulators to review the context in which a technology will be used – not simply its inherent characteristics.

Carter et al (2014) state that American regulation related to genetically engineered products stems from a mixture of regulations and non-binding recommendations, which specifically centered on the 1976 National Institutes of Health (NIH) Guidelines for Research Using Recombinant DNA Molecules. These guidelines were explicitly targeted at addressing the potential biosafety risks that may arise from the research, production, use, and disposal of products containing genetically engineered material.

NIH (2013) and NIH (2012) maintain that such guidelines ensure within the current era of biotechnology research funded by NIH is conducted within set guidelines regarding the physical containment of genetically engineered material in order to (i) protect researchers from potential exposure to harmful material, and (ii) prevent as much as possible potential releases of such materials into the environment. Where Carter et al (2014) describe ongoing debates specific to the ability of existing regulation to adequately cover against biotechnology and genetic engineering risks, the Office of Science and Technology Policy in 1986 established their 'Coordinated Framework for Regulation of Biotechnology', which contended that established federal law appeared capable of governing products stemming from biotechnology research (OSTP 1986). As new products, processes, and risks stemming from technological innovation developed, however, OSTP (1986) also indicated that regulation needed to evolve over time to better protect against such risk. Such evolutions included OSTP (1992) and OSTP (2002), which further explained OSTP's position that agencies should regulate technologies with genetically engineered components on a product level.

Under the Coordinated Framework's guidelines that products derived from genetic engineering processes should be regulated in a manner similar to those produced via traditional means, three agencies were explicitly empowered to govern products utilizing genetic engineering capabilities (Carter et al 2014). These include the Environmental Protection Agency

(EPA), the Food and Drug Administration (FDA), and the Department of Agriculture's Animal and Plant Health Inspection Service (APHIS).

Looking first at the Department of Agriculture, APHIS regulates experiments and field trials of genetically engineered crops and plants, and "reviews requests to "deregulate" the crop or plant, which, if granted, allows it to be grown without a permit at a commercial scale" (Carter et al 2014). APHIS' authority within this context derives from the Federal Plant Protection Act of 2000, where the agency is granted the capability to inspect, seize, quarantine/isolate, remediate/treat, or dispose of imported plant and animal materials that are potentially harmful to U.S. agriculture, horticulture, forestry, and, to a certain degree, natural resources (Plant Protection Act 2000; House 2006). While this does not explicitly include pre-market assessment, Bundy (2012) argues that APHIS has 'strong authorities' to remediate contaminated sites and prevent the dissemination of modified plant material that could be harmful to humans or the environment (Bundy 2012). Specifically, these authorities derive from the Federal Plant Pest Act of 1957, the Plant Quarantine Act of 1912, and the Federal Noxious Weed Act, which were collectively incorporated into the Plant Protection Act of 2000 (Bundy 2012).

APHIS' authority over genetically modified organisms was first established in 1986 under the Federal Plant Pest Act of 1957 and the Plant Quarantine Act of 1912. These rules, along with the addendums established by the Plant Protection Act of 2000 (specifically 340), defined genetically engineered organisms pertaining to plants and noxious weeds as 'regulated articles', and explicitly states the ability of APHIS to monitor, control, and prohibit the importation, transportation, and release of such organisms unless said organisms are within the guidelines established by the PPA (Plant Protection Act 2000, Part 340). With respect to what a 'regulated article' actually is, 7414(a) of the Plant Protection Act indicates that the genetically engineered organisms in question must have "*some connection to DNA from a natural plant pest*" (Plant Protection Act 2000, Part 340; Bundy 2012).

Key provisions related to APHIS' regulatory authority over synthetic biology product development via the PPA include 7711(a), 7712(a), and 7414(a) (Bundy 2012). For 7711(a) and 7712(a), this includes the ability of APHIS to prevent the important, distribution, and

commercialization of plant pests without prior regulatory approval. Further, 7414(a) empowers APHIS with the ability to review and prevent the distribution of plant pests new to the United States environment in order to protect local environmental health. Statements of these provisions are noted below.

> PPA Section 7712(a) (7 USC 7712(a)): *"[t]he Secretary may prohibit or restrict the importation, entry, exportation, or movement in interstate commerce of any plant, plant product, biological control organism, noxious weed, articles, or means of conveyance, if the Secretary determines that the prohibition or restriction is necessary to prevent the introduction into the United States or the dissemination of a plant pest or noxious weed within the United States."*
>
> PPA Section 7414(a) (7 USC 7714(a)): *"[i]f the Secretary considers it necessary in order to prevent the dissemination of a plant pest or noxious weed that is new to or not known to be widely prevalent or distributed within and throughout the United States, the Secretary may hold, seize, quarantine, treat, apply other remedial measures to, destroy, or otherwise dispose of any plant, plant pest, noxious weed, biological control organism, plant product, article or means of conveyance that is moving into or through the United States or interstate, or has moved into or through the United States or interstate and the Secretary has reason to believe is a plant pest or noxious weed or is infested with a plant pest or noxious weed at the time of the movement or is otherwise in violation of this title."*

Given this defined authority, Bundy (2012) states that it is unclear whether a fully synthetic organism would qualify for cases where modified organisms do not contain plant pest DNA (even if the synthetic DNA was identical or nearly identical to its natural alternative). If APHIS' regulatory authority is challenged under such circumstances, they would lose the ability to review synthetic biology products prior to environmental release and commercial consumption (Carter et al 2014; Bundy 2012). Currently, however, APHIS has begun to assert its capabilities under Part 340, Sections 7411, 7412, and 7414 of the Plant Protection Act for various synthetic biology research enterprises such as with pharmaceutical development, which frequently uses plant bacteria such as *Agrobacterium tumefaciens* to transfer synthetic DNA into a host genome (Carter et al 2014; Bundy 2012). Overall, Carter et al (2014) and Bundy (2012) both argue that APHIS currently possesses the ability to protect environmental health from engineered plant pests, although this authority is hazily defined and may be challenged in court by developers.

Looking next at the United States EPA, the agency derives its authority over synthetic biology research via the Toxic Substances Control Act (TSCA 15 U.S.C. §2601), where it regulates genetically engineered microbes as novel chemical substances (Carter et al 2014). One specific section includes TSCA's Section 5, which provides the EPA with the power to regulate and monitor proposed chemical substances before their manufacture, importation, or commercial distribution. This Section gives EPA the authority to regulate new chemical substances prior to their manufacture, import, processing, or distribution for commercial purposes (Nabholz et al 1993; Wagner et al 1995). Using Section 5 of TSCA, the EPA has established rules indicating that novel yet artificially produced genetic sequences may be classified as novel chemical substances (EPA 2013a; EPA 2013b; EPA 1997).

Under these extensions of soft law governance and rulemaking, Carter et al (2014) discusses that the EPA may "require developers to notify EPA prior to testing any genetically engineered microorganisms outside of a contained environment when the organism will be used for a commercial purpose" via their Microbial Commercial Activity Notice (MCAN). This 'pre-post' notification process empowers EPA to review environmental health and safety concerns of emerging synthetic biology-derived products both before and after they have reached commercialization and market access, granting the EPA the capability of pulling such products if they have demonstrated the potential for health harms in various applications (Carter et al 2014). While TSCA has been applied to cover various activities such as with biofuel production (i.e. the conversion of algae to various biofuels – Glass 2015) or environmental remediation products (i.e. the remediation of brownfields or groundwater deposits – Schmidt 2012) (Mandel and Marchant 2014; Lohmann 2013; Rodemeyer 2009), their ability to engage in pre-post reviews of pharmaceutical products remains limited Carter et al (2014).

Next, the FDA serves as the main regulatory body charged with protecting public health by regulating various fields such as with food safety, pharmaceutical drugs, vaccines, and medical devices (Katz 2008). Where APHIS and the EPA have been discussed as having limited or questionable authority to review synthetic biology drug and pharmaceutical production, the FDA instead has much clearer regulatory authority to review, monitor, and approve such products as they seek to gain clinical approval and market acceptance (Carter et al 2014). The

legislative authority by which FDA derives its capability to monitor and regulate such products and materials includes Chapters 2 and 5 (Medical Drugs and Devices) of the Federal Food, Drug, and Cosmetic Act (1938) and Section 351 (The Regulation of Biological Products) of the Public Health Service Act (1944). Within Chapter 2 of the FDCA, drugs re defined as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals", or "articles (other than food) intended to affect the structure or any function of the body of man or other animals" (Fatehi and Hall 2014). Among other activities, this authority grants the FDA the capability to regulate the efficacy and safety of drugs and vaccines, where the drug is required to undergo a premarket approval requirement to test its safety and effectiveness according to FDCA Chapter 5 Section 505 (a-d) (Katz 2008). In this Section, the FDA's premarket regulatory authority is stated where:

> *"(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug. (b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug Included outputs from this exercise include labeling requirements detailing proper drug use alongside manufacturer reporting of adverse effects, furthering the FDA's post market authority to recall drugs with demonstrated harms to human health."* (21 U.S.C. 355).

As noted by Hutt (1990), Mathieu et al (2002), and Borchers et al (2007), the FDA's regulatory authority via the Food, Drug, and Cosmetic Act (FDCA) along with the Public Health Services Act provides the FDA with the legislative scope to regulate drugs in the United States. Where the end-products of synthetic biology pharmaceutical production remain drugs as defined by the FDCA, Bergeson et al (2014) as well as Keasling and Venter (2013) indicate that the FDA will have the power and authority to regulate such products. Specifically, the FDCA empowers the FDA to engage within pre-market regulatory assessment and approval of pharmaceutical products prior to their mass production and commercialization (Mathieu et al 2002). However, Carter et al (2014) notes that such authority has limited ability to consider the

environmental impacts incurred throughout the life cycle of drug production for any pharmaceutical product – something that Schmidt and de Lorenzo (2016) indicate as potentially being a significant risk for synthetic biology products.

One legislative instrument that has enabled the FDA to force developers to consider the environmental impacts of pharmaceutical development includes the National Environmental Policy Act (NEPA) (Anderson 2013). Specifically, NEPA gives the FDA the ability to consider the environmental ramifications related to pharmaceutical production (Anderson 2013). Under NEPA, the FDA can require those developers with products that may yield substantial risk to environmental health to generate an Environmental Impact Statement indicating the potential and consequences of such risk (Carter et al 2014). This is noted in Section 102 (c) of NEPA, where such Statements must:

> *"(C) include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on— (i) the environmental impact of the proposed action, (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented, (iii) alternatives to the proposed action, (iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and (v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented." (*42 U.S.C. 4321).

While the FDA cannot require environmental risk mitigations as part of its regulatory decision and approval under NEPA (Anderson 2013), the cost and time associated with constructing the Impact Statements serve as an incentive for developers to take steps to reduce such environmental risks on a voluntary basis (Carter et al 2014). As such, although the FDA has no regulatory authority to regulate based upon environmental impacts, their ability to require Impact Statements by developers does serve as one measure to increase transparency and awareness of potential environmental harms derived from the pharmaceutical's life cycle (Anderson 2013; Carter et al 2014).

Other regulatory bodies pertinent to synthetic biology research includes the Occupational Safety and Health Administration (OSHA) and the Recombinant DNA Advisory Committee (RAC). Via the Occupational Safety and Health Act of 1970, OSHA derives its legal authority to regulate workplace safety concerns that extend to research related to genetic

modification and synthetic biology (Mandel 2009; Pollack and Wilson 2010). Specifically, the Act's Section 5 'general duty clause' (Morgan and Duvall 1983), where employers:

> "*shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees"* (OSHA Section 5(1)).

While this clause has been applied to work related to the engineering of biological substances, its reliance on preventing against "recognized hazards" has limited the ability of OSHA to regulate against uncertain risk events to laboratory workers (Balbus et al 2006; Ramachandran et al 2011). Further, Section 8 requires the reporting of workplace accidents and potentially hazardous substances used within the workplace area (Ramachandran et al 2011).

To account for these and other uncertain threats, OSHA established a series of rules via Standards Regulation 1910.1200 (OSHA 2006). Such classifications include toxic substances, harmful physical agents, electrical hazards, fall hazards, hazardous waste, infectious disease, dangerous atmospheres, and others, where genetic modification and biological engineering research has fallen under guidance based upon the potential hazards promoted by the research topic (i.e. viral research would fall under 'infectious disease'). These rules have been applied to capture synthetic biology risks to workplace safety, although Balbus et al (2006) and Ramachandran et al (2011) note that 1910.1200 only loosely covers hazard protection from engineered biological substances until a given threat is proven plausible.

Relative to the RAC, this organization offers recommendations to the Director of the National Institutes of Health (NIH) relative to "basic and clinical research involving recombinant or synthetic nucleic acid molecules" (RAC 2016). Such guidance included recommendations that helped form the April 2016 "NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules", which includes information for safety practices for basic and clinical research funded by the NIH and utilizing enabling technologies for synthetic biology (NIH 2016). Specifically, the NIH Guidelines:

> *"detail safety practices and containment procedures for basic and clinical research involving recombinant or synthetic nucleic acid molecules, including the creation and use of organisms and viruses containing recombinant or synthetic nucleic acid molecules"* (NIH 2016).

These Guidelines require that a "*Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee"* for laboratories ranked at Biosafety Level 3 or 4 that conduct relevant research using NIH funding (NIH 2016).

Given that these regulatory bodies are primary agencies that shall have a role in regulating synthetic biology applications, interview respondents were asked to identify their government's relevant legislative instruments and regulatory bodies pertinent to pharmaceutical production in general and the process of synthetic biology development in particular. Figure 4 below includes the results of these interviews, with a general indication that all respondents were able to name at least one of the three regulatory agencies described above or a regulatory statute or guidance system applicable to synthetic biology regulation.

Of the 17 US-based respondents interviewed for this study, 47% (n=8) were able to describe in detail both the agencies and legal authorities involved with the process, with specific descriptions regarding the responsibilities and powers held by such authorities relative to the process of synthetic biology development. Further, 29% (n=5) were able to identify an agency but not a particular law. Lastly, 24% (n=4) were able to identify the legislative instruments that capture a portion of the process of synthetic biology development, but were unable to go into detail regarding how the relevant regulatory agencies executed and upheld such authority granted to them by law. Similar to the approach discussed in Kelle (2009), this general assessment indicates that there exists a general level of awareness of the regulatory authorities applicable to synthetic biology research amongst US-based respondents – where all respondents were able to identify and describe either the laws, regulatory bodies, or both factors that are relevant to the regulation of synthetic biology in the United States.

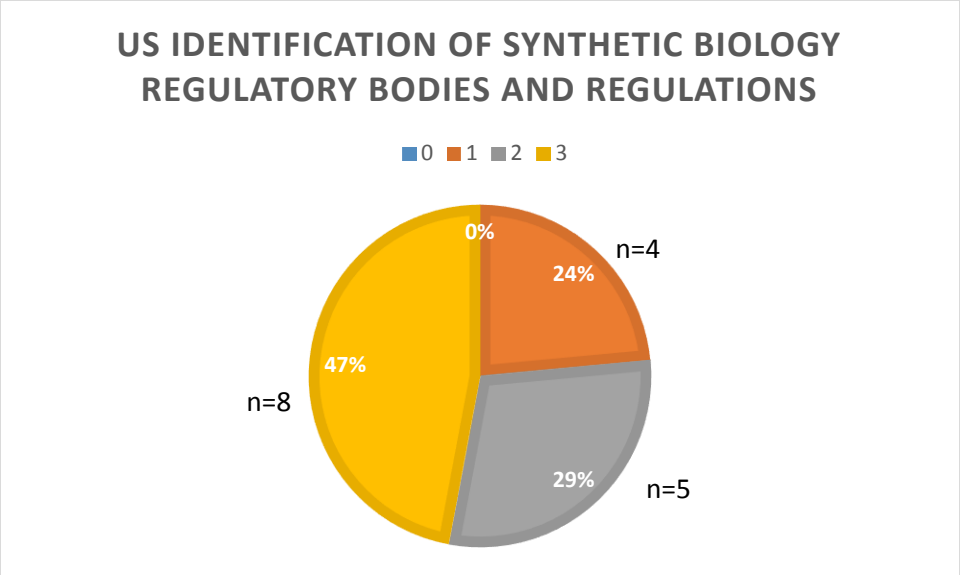

Figure 4. American Respondent Familiarity and Recognition of Synthetic Biology Regulation. 0 = no recognition, 1 = recognition of a piece of hard/soft law regulation but not an agency, 2 = vice versa, 3 = recognition of both hard/soft law regulation and relevant agencies. (n=17).

Another consideration that respondents were asked to offer tangential but relevant to existing regulatory authorities over synthetic biology research and development includes perceptions of how soon synthetic biology products will mature and commercialize for widespread consumption and distribution. Such discussion was speculative in nature and should not be taken as hard fact, where respondents were asked to only give a 'best guess' at when they thought that early cases of synthetic biology pharmaceuticals would enter commercialization. Despite such reservations, these questions do offer general insight regarding general beliefs of how quickly synthetic biology products may commercialize in a general sense.

Using such 'best guesses', Figure 5 below shows that most respondents (n=11, 65%) believed that such products would begin the process of commercialization not sooner than 5 years from December 2014 but prior to 2020, while equal proportions of respondents noted a belief that commercialization would occur either within the next 5 years, or more than 10 years. In other words, such products (i.e. a vaccine with a modified viral backbone, a drug created with semi-synthetic components, and a probiotic containing engineered bacteria to improve gut health) would begin to be explored beyond a theoretical standpoint and enter into clinical trials.

For the former, US Respondent 6 (Lab Researcher) noted that "we're already starting to see early commercialization, and I think this will only speed up the process for more synthetically-derived drugs." Likewise for the latter, US Respondent 7 (Lab Researcher) argued that "despite recent progress, we're still technologically very far away from building a fully synthetic cell that can perform reliably and efficiently, and it'll take many millions of dollars and years of research across the globe to develop technology to a point where these issues evaporate." This discussion was used as a segue to drive discussion related to evaluating existing regulatory options within the United States pertaining to synthetic biology, where weaknesses, gaps, and limitations in coverage may be reviewed within the lens of the fact that while synthetic biology innovation is currently underway. For pharmaceuticals, however, US Respondent 8 (Social Scientist) did note that "while commercialization may be years off, regulatory reviews [horizon scanning and/or updating relevant regulations] may occur sooner than we think […] maybe in two or three years, and we'll need to have proper guidance to regulate these products before then."

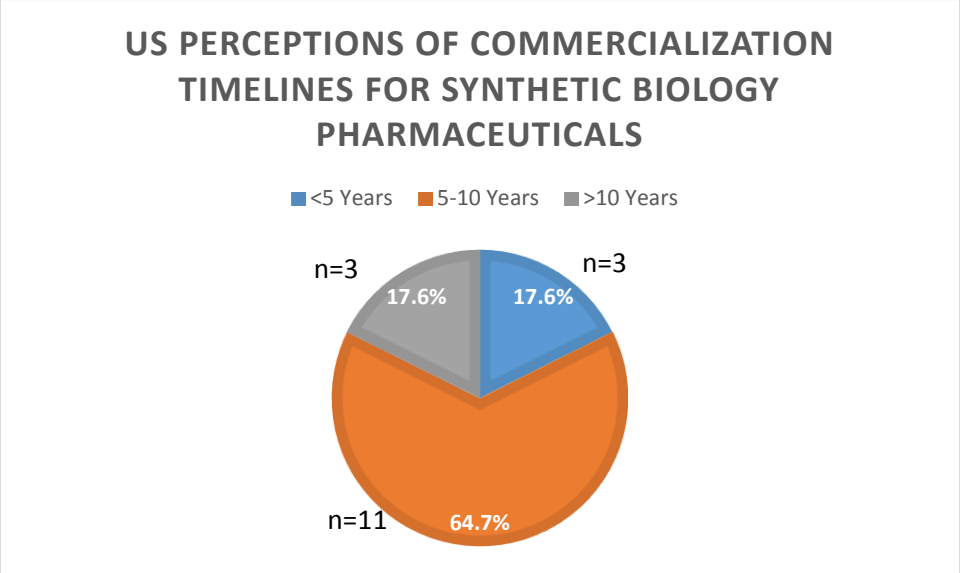

Figure 5. American Perceptions of Distance in Time for Synthetic Biology Products to Enter Marketplace (n=17) (from December 2014)

4.3. Regulatory Culture and Regulatory Decision Making in the United States

An important consideration to account for within each case includes understanding how each respective governments political and institutional circumstances drive relevant stakeholders to develop regulation and governance related to new scientific developments – synthetic biology included. For this chapter, this section includes a discussion of the regulatory system of the United States, with specific discussion related to (i) how existing regulatory frameworks have been applied (if at all) to cover the process of synthetic biology development, (ii) how different legal and institutional authorities influence behavior and regulatory change for synthetic biology, and (iii) considerations of what regulatory actions are probable based upon such regulatory history and institutional structure.

4.3.1 History and Background of the Political and Institutional Structure of Synthetic Biology Regulation in the United States

In order to review how elements of risk culture influence American regulation of synthetic biology, it is necessary to understand the political and institutional structure of the United States as it impacts regulatory change. For the former, power is shared both within the three branches that comprise the federal government, as well as between the federal and state governments (Smith 2004; Wilson 1961). This institutional framework influences policymaking by driving actors within the various branches of government to check the power and authority of each other and generally favor the status quo (Smith 2004; Wilson 1961). Laffont and Martimort (1998) argue that such relationships place high transaction costs for those seeking to develop policy reform in terms of legislation, executive orders, or court decisions. Given such transaction costs, Brady and Volden (1998), Epstein and O'Halloran (1999), and Cox and McCubbins (2007) argue that the power sharing and often adversarial nature of such policymaking often produces policy gridlock, where the development of new policy and law is slowed or halted by competing elements within Congress and/or between Congress, the Courts, and the Presidency.

Such political competition affects the development of technology regulation in differing manners (Kessides 2004; Hammond and Knott 1996; Marchant et al 2013). For hard law, or those formal statutes and laws passed by Congress or Executive Orders signed by the President,

political combativeness and the sheer number of actors involved in passing a bill into a law indicates that significant time and political resources are often required in order to make such lawmaking efforts successful (Bowling and Ferguson 2001; Marchant et al 2013). A specific impediment includes divisions between Congress and the Presidency, where entrenched political differences may cause such politicians to refuse to collaborate with one another on the development of new regulatory law (Pauley 2012; Curry 2014; Brady and Volden 1998). Within such a system, hard law reform is difficult to achieve due to an environment that generally favors the status quo and resists rapid and/or frequent change to regulatory law (Curry 2014; Mandel et al 2014).

This institutional structure also influences the implementation of new policy and law. Pressman and Wildavsky (1984) and Weaver and Rockman (1993) contend that adversarial relationships within a large and complex bureaucracy can derail and limit those policies and laws that are able to overcome transaction costs described by Epstien and O'Halloran (1999) and pass into law. Wilson (1989) asserts that bureaucracies and agencies tasked with implementing and administering policy reform are a product of their political realities, staffed by personnel with private agendas, and licensed for action by politicians with their own motives in mind. Further, Wright (2006) notes that bureaucracies are less concerned with brandishing political power, but rather operating as 'network managers' of the many complex actions and relationships within a particular area. Given such arrangements, Wright (2006), Pressman and Wildavsky (1984), and Wilson (1989) argue that bureaucracies often stymie or limit the intended development and execution of new policies and laws by executing their power in a manner inconsistent with the intentions of the lawmakers. Such concerns are exacerbated by unclear or confusing agency organization and distribution of power (Wilson 1989).

Given this discussion on technological hard and soft law in the United States, Section 4.3.2 below details the risk culture within US technological regulatory policy (see Lash 2000, Chapter 2). As will be argued further below, the political and institutional realities behind lawmaking and regulatory policymaking in the United States directly impact the approach to synthetic biology regulation that has been taken thus far by American regulators. Equally important includes the notion that these political and institutional factors shape the array of

regulatory options available for future regulation of the process of synthetic biology pharmaceutical development.

4.3.2 Risk Culture in the United States

Looking here at the risk culture of the United States' legislative bodies and regulatory agencies, this section details the political and institutional factors which influence the regulation of synthetic biology products. To accomplish this, this section begins by first discussing the historical path of regulation for chemicals and genetically-modified organisms – the history of which will be shown as an important guiding factor for synthetic biology regulation and governance in its current manifestation. Next, this section will discuss why options for future regulation are constrained by these political and institutional factors. Such discussion will be supplemented with discourse on how the risk culture of the United States directly influences expert responses within this dissertation's interview data in Section 4.4.2.3 below.

4.3.2.1 Historical path of synthetic biology regulation

Reviewing first the historical path for regulation and governance for synthetic biology, it is important to note that legislative instruments pertaining to the regulation of chemicals and genetically-modified organisms have been and continue to be gradually extended to cover applications of synthetic biology, including pharmaceutical production (Carter et al 2014; PCSBI 2010). Though specific regulatory items pertaining to synthetic biology will be discussed in further detail in Section 4.5.0 below, it is important to note here what hard and soft law has captured synthetic biology regulation and governance in its current iteration. One of these earliest precursors to synthetic biology regulation includes the TSCA, which is geared to regulate the production and sale of chemical materials and is administered by the EPA. Passed by Congress and signed into law by President Gerald Ford in 1976, TSCA represented at least 5 years of negotiation and discussion between various elements of the federal government and chemical producers alike (EPA u.d.).

Specifically, discussion regarding the need for government oversight of chemical research, production, sale, and disposal was raised in 1971 by the Council of Environmental Quality (CEQ) under the Executive Office of the President, where CEQ officials urged for greater oversight in for toxic substances, with synthetic chemicals representing the bulk of uncovered producers (Schierow 2009; Markell 2014). CEQ explicitly noted that existing regulations were unsatisfactory relative to the protection of human and environmental health throughout the process of chemical production and use, particularly due to the fact that such regulation was reactionary to hazardous spill events and did little to mitigate the probability that future events would occur (Markell 2014). Such concern was echoed by the EPA when Deputy Administrator Johan Quarles argued that despite some authority by federal authorities to regulate substances such as with pesticides, food additives, and drugs, "most existing Federal authorities are designed to prevent harmful exposure only after the substances have been introduced into production" (Quarles 1975).

After their early comments in 1971, CEQ ultimately recommended to Congress and the President that the federal government should construct a comprehensive policy centered on the regulation and oversight of those chemicals produced, consumed, and disposed of within the United States (Schierow 2009). Specific recommendations by CEQ included the need to (i) establish premarket approval for those producers generating new chemicals or producing large quantities of existing ones, (ii) premarket approval should require producers to test proposed chemicals and report information related to the risks, hazard, and exposure properties of such materials to a relevant government body, and (iii) information related to health risks posed by such chemicals to human and environmental health should be disclosed to the public (Markell 2014). Within a backdrop of a rising incidence in cancer from exposure to industrial chemicals in consumer products (Markell 2014), Congress responded to CEQ's statements by issuing separate bills in 1972 and 1973 related to chemical regulation (Schierow 2009; Markell 2014). Congress' approach to designing formal regulation and oversight of potentially hazardous chemicals centered around three concepts, including (i) the need for robust premarket assessment of chemical risks along with a notation of available preventative measures to mitigate or manage such risks, (ii) the adopting of a holistic approach to risk assessment rather

than a fragmented one that considered only small portion of what causes such risks, and (iii) the promotion of data collection to guide risk assessments of existing and future chemical products (Markell et al 2014).

Even with widespread support within Congress, the codification of what eventually would become TSCA was stalled until 1976 due to disagreements of appropriate chemical screening and oversight measures enjoyed by the EPA under the new law (Schierow 2009; van Leeuwen and Vermeire 2007). However, growing environmental concerns such as the impact of chlorofluorocarbon (CFCs) to reduce global ozone as well as growing concerns of environmental contamination of industrial chemicals drove Congress to eventually pass the TSCA in 1976 (Engel 2015). This effectively empowered the EPA to review and regulate chemical health risks throughout the life cycle of a novel chemical, where such substances are defined in TSCA as *"any organic or inorganic substance of a particular molecular identity" as well as "any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature"* (15 U.S. Code § 2601).

Two important considerations to account for relative to the passage of TSCA. The first includes the issue of 'grandfathering', where all chemicals in existence prior to TSCA's passage in 1976 existing chemicals were considered to be safe for use (Ekey 2013; Lohmann et al 2013). This included approximately 62,000 chemicals, which were allowed to remain on the market without first assessing their toxic impacts (Wallinga 2008). The second issue includes concerns related to the burden of proof related to chemical safety, where EPA may regulate new chemicals that seek to enter the market under TSCA, it carries the burden of proof to test the safety of such chemicals (Wilson and Schwarzman 2011). Wilson and Schwarzman (2011) note that such a burden limits the EPA's ability to effectively gauge risk for the thousands of chemicals they are required to review.

Even after its successful passage, TSCA implementation was frequently disrupted and challenged in the late 1970s and 1980s due to several factors, including:

(i) the high cost of toxic impact assessments for thousands of proposed chemicals by the EPA (not including those already grandfathered),

(ii) limited available data by chemical manufacturers for various risk categories noted in TSCA (specifically a chemical's identities, molecular structures, categories of use, amount manufactured and processed for each category of use, descriptions of byproducts across the product's life cycle, environmental and health effects, number of individuals exposed, number of employees exposed and the duration of exposure, and manner or method of chemical disposal),

(iii) the sheer quantity of what data is available for hundreds of thousands of existing and new chemical compounds, and

(iv) uncertainty pertaining to environmental and human health outcomes associated with emerging chemical products (Markell 2014; Schierow 2009; van Leeuwen and Vermeire 2007).

Wilson and Schwarzman (2009) particularly note data deficiencies of pre-manufacture notices (PMNs) provided by companies as being particularly problematic, with 85% of PMNs containing deficient health effects data. To help rectify concerns of limited health risk data being available for PMN submission, Wagner et al (1995) assert that models and comparisons of the novel substance with analogous chemicals as being approaches frequently used to gauge the degree of risk posed throughout the life cycle of a novel chemical to human and environmental health.

Despite its promise, the regulatory scope of TSCA has been decried as containing several weaknesses that limit its ability to regulate chemicals with potential hazards to human and environmental health (Wilson et al 2009). For starters, Vogel et al (2011) argue that TSCA has not been substantially updated since its passage in 1976,. The EPA has also been accused of inconsistency with how it regulates hazardous chemicals, such as with their failure to subject formaldehyde to TSCA regulatory requirements in 1982 (Jasanoff 1986) or the Office of the Inspector General's statement regarding how trade secrets limit the ability of the EPA to conduct a thorough chemical risk assessment for proposed materials and otherwise have limited data by which to conduct a risk assessment with (Office of the Inspector General 2010).

Even in the midst of these limitations in addressing risk and conducting robust risk assessments of novel chemicals, TSCA has been noted as being one of the key legislative

instruments which capture the process of synthetic biology development. This is due to the ability of EPA under TSCA Section 5 to *"assess potential risks from genetically engineered microbes and to require appropriate risk mitigation measures",* particularly where synthetic biology research involves the manipulation of plant genetic information and/or the modification of plants altogether (Carter et al 2014; Mandel et al 2014; Paradise and Fitzpatrick 2014).

On June 7, 2016, the U.S. Senate passed the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Denison 2016). Known as the Frank R. Lautenberg Chemical Safety for the 21st Century Act, these reforms sought to change the EPA's responsibilities under TSCA via the following (Denison 2016):

1) Shift from cost-benefit risk assessment to human and environmental health-only risk assessment, where non-health risk factors like cost are used to review only *how* to regulate, not *whether* to regulate,

2) Identify vulnerable populations at risk to exposure via chemical development,

3) Establish risk reviews of existing chemicals in active commerce, including those that were previously grandfathered-in to approved use without such a review,

4) Remove EPA's previous Catch-22 requirement that EPA first have evidence of risk prior to testing, and

5) Establish a 'TSCA Implementation Fund', where companies directly pay EPA for their risk evaluation.

Such reforms were sought by Congress to resolve concerns of the EPA's difficulties via TSCA to review and regulate new chemical candidates (genetically modified organisms included) due to issues of chemical grandfathering, the evidence-based Catch-22 noted above, and implementation concerns about EPA's difficulties to execute their authority via TSCA (Denison 2016).

Aside from TSCA, several other laws have been referenced as capturing the process of synthetic biology development, including the Plant Protection Act (PPA) and the FDCA. For the former, the PPA was introduced in 2000 to consolidate several statutes such as the Plant Quarantine Act, the Federal Plant Pest Act and the Federal Noxious Weed Act of 1974

(McHughen and Smyth 2008). Specifically, the PPA empowered the Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) to review any genetically engineered plan pest research and production, and conduct an environmental impact statement (EIS) related to the risks of such materials to human and environmental health if environmental risk is possible or uncertain (McHughen and Smyth 2008; Carter et al 2014).

However, similar to TSCA, APHIS' authority via the PPA was criticized as containing loopholes that developers could exploit (Camacho et al 2014). Camacho et al (2014) and Pollack (2015) argue that APHIS' regulatory authority under the PPA's Sections 7414 and 7712 are only valid while the genetically-modified organism under discussion is genetically similar to an existing natural plant pest, where more artificially engineered plant pests would not qualify for oversight under the PPA. As such, the sections noted above would not enable APHIS to restrict or regulate the import and distribution of such genetically modified materials unless they had a clear effect upon plant pests. Likewise, Montgomery (2012) and Carter et al (2014) indicates that attempts to update the PPA to reduce oversight and tighten regulation for engineered plant pest organisms was discussed yet not implemented in 2008, with Quinn et al (2013) noting resistance by producers and certain government officials as strengthening such resistance to the implementation of the new rule. In this way, Carter et al (2014) notes the PPA as still containing regulatory loopholes that potentially harmful synthetic biology products may be able to exploit, although limited impetus exists for further regulatory development until synthetic biology products become more developed (see also PCSBI 2010).

For the Food, Drug, and Cosmetic Act of 1938, the Food and Drug Administration (FDA) is empowered with the capability of regulating, among other things, pharmaceutical development. The initial introduction of the law was driven by a reaction to dozens of patient deaths via sulfanilamide medication, and replaced the preexisting Pure Food and Drug Act of 1906 (Borchers et al 2007). The law has been amended several dozen times since its passage in 1938, including rules pertaining to the regulation of genetically-engineered material in FDA (1995) and soft law guidance in FDA (2002).

Carter et al (2014) and Bar-Yam et al (2012) have also described the FDCA and NEPA as having the greatest coverage over synthetic biology pharmaceutical health risks, although also

notes several loopholes that may reduce the law's efficacy as synthetic biology products begin to commercialize. One such loophole includes the inability of the FDA under the FDCA (Chapter 5) or NEPA (Section 351, discussed above) to conduct field trials and risk assessment exercises of engineered plants until its pharmaceutical material has been submitted as a "investigational new drug" – effectively limiting pre-clinical regulation of synthetic biology pharmaceutical products (Winter 2016; Paradise and Fitzpatrick 2012; Carter et al 2014). Instead, Draft Guidance by FDA in 2002 noted that such preclinical assessment of plant development intended for use in pharmaceutical products would fall under the assessment of APHIS (FDA 2002). Further, the FDA has limited authority via Section 102 (c) of NEPA to regulate solely based upon perceived environmental harms such as with concerns to biodiversity that a synthetic biology pharmaceutical has the probability to disrupt (Carter et al 2014).

Given the nature of federalism in the United States where power is shared between the national and state governments, state regulation must also be accounted for with respect to synthetic biology research and development. Generally speaking, each of the 50 state governments must meet the minimum standards indicated by national legislation and regulation. However, states may then pass legislation that strengthens such standards within their respective state borders (List and Gerking 2000; Warner and Shapiro 2013). Such state regulation may at times clash with national legislation, which may subsequently be contested in federal courts (Jones 2016). One subject pertinent to synthetic biology research includes state regulations on the labelling of genetically modified products (Reilly 2013). Specifically, Connecticut, Maine, and Hawaii have all passed regulation on the labelling of genetically modified products, with particular emphasis on food products or derivatives (Reilly 2013; Herling et al 2014). Further state regulation includes the importation and shipment of genetically modified organisms, where Idaho in the Idaho Plant Pest Act of 2002 sought to require permits and state regulatory approval for those who would seek to ship, import, or otherwise move genetically modified plant pest material within state boundaries (Hillson 2007).

Further, local governments within states (cities, counties, etc.) are also empowered with the ability to pass and implement regulations that do not seek to invalidate or reduce related state and federal jurisdiction. One example includes the respective regulations of Mendocino

County, Marin County, Trinity County, and the Arcata City Government, which banned the propagation, cultivation, and development of genetically modified organisms within the local jurisdictions (Hillson 2007). Such local regulations are limited in power, however, where their implementation is affected by limited financial resources and a general subservience to state and national regulatory authorities. One example includes Maui County in Hawaii. Specifically, one of Hawaii's county regulations (Maui) was invalidated by a federal court ruling in 2015, where the local government sought to introduce a "moratorium on the growing of genetically engineered crops until scientific studies are conducted on their safety and benefits" (Jones 2016). The federal judge noted that such a regulation exceeded the authority of the local state and country governments (Jones 2016).

Of these three pieces of national legislation (TSCA, PPA, and FDCA) and their corresponding regulatory agencies (EPA, APHIS, FDA), common themes emerge related to how existing legislative and regulatory instruments regulate risk associated with emerging products such as with products derived from or containing genetically modified organisms. Among others, these include the notion that US hard law generally does not change quickly – particularly in the midst of uncertainty (Paradise and Fitzpatrick 2012; Mandel et al 2014; Carter et al 2014). Occasionally, regulators are able to overcome such impediments by employing their legislative and regulatory authorities in creative ways to address risk challenges such as where the EPA required notification by manufacturers of chemical substances contained in Significant New Use Rules (SNURS) via TSCA Section 5(a)(2) (Monica 2009). For cases where agencies do not have such leeway or do not have known solutions to extend their regulatory authority, changes in hard law are generally initiated in the aftermath of a triggering event related to substantial negative health consequences rather than with preemptive discussion about how to improve existing regulation for future threats (Borchers et al 2007; Markell 2014).

4.3.2.2 Assessment of the risk culture influencing the regulation of novel compounds and scientific processes like synthetic biology

Discussion of the influences of the American regulatory system along with the political and institutional factors that sway regulatory change are important to better understand the

realities behind future regulatory change related to synthetic biology regulation. Below, this section centers on views of how the American risk culture related to the regulation of chemicals and genetically-engineered materials has come to be shaped by such political and institutional factors, which ultimately informs the lens by which American experts interviewed for this study understand the regulatory realities and possibilities by which synthetic biology risk may be perceived and governed.

Among the first points to consider based upon the history of relevant synthetic biology legislation above includes the slow progress of legal and regulatory change to better cover risks pertaining to novel chemicals and genetically engineered products. Authors such as Vogel and Lynch (2001) and Jasanoff (1986) describe American regulatory decision making and management of technological risks in the 1970s and 1980s as "more contentious, confrontational and adversarial than in Europe", with little incentive to engage with regulatory discussions in an informal and cooperative manner. Instead, Kelemen (2011) and Gouldson et al (2015) argue that the American regulatory system as being more 'adversarial', with various actors such as lawyers, courts, and combative politicians to resolve political disputes in a manner that removes incentive of policymakers to quickly resolve regulatory disputes or advocate for rapid change to the regulatory system. Instead, Volcansek (2014), Kagan's (2009), and Kelemen's (2011) discussion of adversarial legalism describes an American regulatory environment as containing:

1) "detailed, prescriptive rules often containing strict transparency and disclosure requirements",
2) "legalistic and adversarial approaches to regulatory enforcement and dispute resolution",
3) "costly legal contestation", and
4) "active judicial review of administrative decisions and practice".

In this way, Kelemen and Sibbitt (2004) and Kelemen (2011) envision adversarial legalism in the United States as being notable for "enforcing legal norms through transparent legal rules […], empowering private actors to assert their legal rights." Such a system is not just characterized by large volumes of litigation, but instead by an amalgam of growing judicial

power in the ability to resolve regulatory disputes as well as an adversarial rather than cooperative relationship between US government officials and their regulated entities (Kagan 2009; Kelemen 2011). For the former, the notion of regulated entities turning to lawyers to dispute legal and regulatory developments, which, even if government regulators are successful in their endeavor, would cause substantial delays in the regulation-building process (Kelemen 2011). For the latter, a lack of trust and inability for private, non-governmental, and governmental stakeholders to collaborate on the subject of regulation-building and best practices for product regulation can prevent the spread of information about risk across actors as well as limit the potential for a negotiated series of oversight that is neither excessively burdensome nor excessively limited – an outcome favorable to all parties (Farhang 2012; Kelemen 2011; Mandel et al 2014). Such instances related to genetically modified organisms and synthetic biology are described by Carter et al (2014) such as with the delay and lack of implementation to improve APHIS' regulatory coverage of genetically modified plant pests.

Relative to adversarial legalism, Volcansek (2014), Kelemen (2011), and Kagan (2009) argue that legal requirements for transparency alongside formal and combative regulatory disputes within the courtroom contribute to a regulatory environment that makes it difficult for legislation to be passed and implemented. Kagan (1994) notes one of the major causes of this adversarial legalism in the United States as the result of lawyers and legal disputes being common within the regulatory development process, with Farhang (2012) and Kelemen (2011) particularly noting the rise of 'mega-lawyering' techniques where large firms engage in costly legal battles related to the rights of developers. In this way, the United States' regulatory system is one of high transparency and high reliance on formal mechanisms for legal and regulatory disputes, (Farhang 2012; Kagan 2009).

Aside from considerations of transparency and adversarial approaches to regulatory enforcement via legal contestation, an equally concerning development that complicates American regulation of emerging technologies like synthetic biology includes the presence of multiple actors in the hard law policymaking process. Via a transparent policy process with multiple adversarial actors, such a process can stymie the passage of new law and discourage

legislators and regulators from attempting to develop and implement new regulation (Brady and Volden 1998; Cox and McCubbins 2007; Howell 2003).

In such scenarios, differing political agendas between members of the Legislative or Executive branches can contribute to situations where policy proposals are more subject to scrutiny and less likely to be passed into law (Howell 2003; Cox and McCubbins 2007). Such a situation feeds into the formal discourse and interactions in American regulatory reform noted in Farhang (2012), Volcansek (2014), and Kelemen (2011), where a rigid institutional framework and adversarial relationships between government officials contribute to situation where disputes are rarely resolved without financially and/or politically costly legal disputes.

Such institutional policy gridlock may be alleviated by a triggering event (Markell 2014) or by unilateral Presidential action (Howell 2003), although these options are not without their own limitations and concerns (Brady and Volden 1998). For the former, reliance upon a triggering event (or a crisis where the public demands political action) places regulatory reform in an inherently reactionary manner, and can contribute to significant health harms to humans and the environment (Markell 2014; Schierow 2009). Likewise for the latter, unilateral Presidential action via signing statements and executive orders can contribute to relatively swifter policy change than with traditional hard law passed via Congressional approval, yet this option can also be politically costly and breed resentment and distrust for the President and their political party as acting outside of the formal policymaking process (Howell 2003; Brady and Volden 1998). Further, Cooper (2002) and Bradley and Posner (2006) note that such executive orders and signing statements are limited in scope, where major policy initiatives such as the creation of new regulatory agencies require Congressional legislation to approve.

4.3.3 Applications to Interview Data

The values described within the risk culture of the American regulatory process described above (Section 4.2.2.2) are important factors to consider when reviewing comments left by American subject experts contacted for interview in this study on the subject of synthetic biology regulation. Keeping such institutional and political values in mind, several points of discussion were raised about the importance of dealing with such institutional and

political factors for synthetic biology regulation, including (i) preemptively avoiding the potential for policy gridlock, (ii) the adversarial nature of regulatory decision making for high uncertainty technologies, and (iii) working within a rigid yet transparent political system that limits options for regulatory reform on a federal level for any synthetic biology product. Inferred discussion on these points is indicative that US-based respondents are mindful of the political resources necessary to instill regulatory policy change within an adversarial environment as described in Volcansek (2014), Kagan (2009), or Kelemen (2011), and select comments are noted here to indicate an adherence to such risk culture.

The fear of regulatory reform getting caught in policy gridlock was a discussion point that framed several responses about the type of regulation needed to rectify perceived limitations of existing laws like TSCA or FDCA (a point of discussion also raised in Carter et al 2014). When asked to describe appropriate measures needed to improve synthetic biology regulation, US Respondent 1 (Social Scientist) argued that "a big concern that we have to keep in mind includes how easy new regulations would be adopted, and sweeping reform is unlikely without a lot of evidence to back it up." Further, US Respondent 2 (Social Scientist) discussed how "[American] regulatory reform moves slowly and can easily be held up in court. […] Governance for synthetic biology should navigate these issues by making use of existing regulations than fashioning brand new ones." More cynically, US Respondent 3 (Social Scientist) noted that "it's probably not a good time to advocate for significant regulatory change for synthetic biology, because it'll be difficult to prove to lawmakers that it's worth it to change existing laws like TSCA until there's a clear reason to make such changes happen." Given these and other comments noted throughout this Chapter, American interview respondents were generally mindful of the slow and complex timeline associated with regulatory evaluation in the United States – something that synthetic biology regulation would have to pass through if such regulation is found to be necessary in the future (Kelemen 2011; Carter et al 2014; Mandel et al 2014).

Additionally, concerns related to adverse legalism in American regulatory politics can be inferred into interviewee responses on the subject of dealing with uncertainty for synthetic biology regulation and the ability to pursue a more adaptive regulatory framework moving

forward. From the perspective of government regulation, US Respondent 4 (Social Scientist) argued that "synthetic biology governance reforms will have to account for what is required by law for technological risk management […] and anything outside of these requirements would be difficult to implement." Such concerns are noted by Kagan (2009), Kelemen (2011), and Vogel and Lynch (2001), which collectively argue of the importance of formal institutions and the ability of courts to resolve disputes – something that impedes efficient regulatory reform. US Respondent 5 (Social Scientist) may have described this point most explicitly when they stated "improvements to synthetic biology governance will probably be stepwise and incremental, because it'll probably be unrealistic to replace established regulation quickly."

These concerns overall led to comments by respondents about how best to improve existing legislative instruments and regulatory regimes given an adversarial culture around regulatory negotiation and reform as well as considerations of legal requirements that regulators must uphold when conducting regulatory assessments of synthetic biology products via TSCA (pre- and post-market environmental assessment of research involving modified plant microbes), FDCA, PPA, and others. American interview respondents generally advocated for improvements to *existing* regulatory frameworks, if any changes were described as being necessary and plausible to make within the current state of synthetic biology development. In sum, the risk culture of American regulatory discussion – one of adversarial relationships, reliance upon formal institutions, high transparency and multiple veto points in the policy process, and the high degree of political and financial resources needed in order to push forward regulatory change – shapes the debate regarding how synthetic biology should be governed now and in the future, with particular emphasis placed upon navigating a high visibility regulatory environment with combative players and incomplete information by which to advocate for regulatory change to a potentially skeptical audience (see Mandel et al 2014; Carter et al 2014; similar extensions for nanotechnology in Malloy 2012 and Marchant et al 2013).

4.4. Synthetic Biology Research in the United States

As noted within Chapter 3, some of the earliest scholarly discussion and research of modern synthetic biology began in the United States and Europe, with early research occurring in universities such as with the Massachusetts Institute of Technology, California Institute of Technology, the University of California, Berkeley, Carnegie Mellon University, and Stanford University (Endy 2005, Arkin 2008; Andrianantoandro et al 2006, Cameron et al 2014). As outlined within Chapter 3, the period between 2005 and 2010 included stepwise improvements to circuit and metabolic engineering, where biologists gained greater refinement and control of cellular inputs that are considered essential elements of synthetic biology research (Cameron et al 2014). This culminated in the 2010 announcement by the James Craig Venter Institute that the lab had fostered the creation of the world's first 'synthetic cell' (Gibson et al 2010). While Chapter 3 describes in detail the history of synthetic biology research through 2015, it is important for this case to note here that research laboratories within the United States have been active with synthetic biology research in general and pharmaceuticals in particular since the field began to take more concrete shape in the early 2000s (Cameron et al 2014; Paddon and Keasling 2014).

Since the James Craig Venter Institute's announcement in 2010, synthetic biology funding within the United States has been dominated by the Department of Defense, which accounts for approximately 67% of total research investment for US projects (Kuiken 2015) in agencies such as the Defense Advanced Research Projects Agency, US Army, US Navy, US Chemical and Biological Defense Program, and the Office of the Secretary of Defense (Kuiken 2015). While many projects funded under the auspices of the Department of Defense are classified, the Woodrow Wilson International Center for Scholars noted available funding and general scopes of work for several hundred projects (Woodrow Wilson Center 2015), which includes funding for projects ranging from biofuels to pharmaceuticals to projects related to environmental remediation. Funding from the US government for these varied projects eclipsed $200 million in 2014 (Kuiken 2015), up from less than $20 million in 2008 for a collective total of approximately $800 million between 2008 and 2014 (Woodrow Wilson Center 2015; Kuiken 2015). While it is difficult to estimate the degree of private funding invested into synthetic biology research, options for funding such research are likely to grow as companies come to

utilize synthetic biology for a variety of project development and proprietary innovation by 2020 (Kuiken 2015; Mandel and Marchant 2014).

From the perspective of pharmaceutical development, United States synthetic biology research efforts have generated several projects related to developing drugs and therapeutics for applications such as with malaria, influenza, and diarrheal disease, among others (Paddon and Keasling 2014; Neumann and Neumann-Staubitz 2010; Khalil and Collins 2010). These efforts are also further detailed in Chapter 3, although one particular case of note includes an effort led by Jay Keasling at the University of California, Berkeley, who developed a method of producing artemisinic acid in order to foster more efficient and less costly measures of developing therapeutics for malaria victims (Paddon and Keasling 2014).

4.5 Perceptions of Health Risk for Synthetic Biology Pharmaceutical Products

From an early stage, synthetic biology health risk within the United States centered around two primary concepts, including i) biosafety, and ii) biosecurity (Kelle 2009; White and Vemulpad 2015; Garfinkle and Knowles 2014). Within this dissertation's interviews as well as discourse within Kuzma et al's interview transcripts, these concepts were discussed as the primary considerations of the regulation of the processes associated with synthetic biology product development, and is consistent with such discussion within published literature (Kelle 2009; Schmidt 2008; Wright et al 2013; Mukunda et al 2009). This section explicitly discusses feedback received from such interviews conducted with American experts on the subject of such synthetic biology health risks. In this vein, this section is further subdivided into (i) general discussion of synthetic biology risks, and (ii) synthetic biology risks across a pharmaceutical product's life cycle.

4.5.1 Conventional and Novel Risks from Synthetic Biology Pharmaceuticals

This Chapter focuses on responses from 17 experts, practitioners, and decision makers related to synthetic biology from the United States. Information about the backgrounds of these groups are noted below in Table 5. Such experts include those engaged in synthetic

biology laboratory research (9), as well as published scholars and researchers related to social science and implications studies for the field (8).

Further, interview respondents in this chapter have a PhD-level education in biology, chemistry, or similar field in science, or have a PhD in a social science background pertinent to the risk analysis and regulation of emerging technologies. Such interviewees also had a formal position of employment at an American institution at the time of interview, such as with a post doctorate or research professorship at an American university or a position at an American company based within the US borders. As noted in Chapter 2, these respondents were selected based upon their history of publications or conference presentations on the subject of synthetic biology.

Table 5. Breakdown of Research Backgrounds of US-based Respondents			
	Lab Research	**Social Science/Implications**	**Total**
Academia	5	3	8
Government	2	2	4
Industry	2	1	3
NGO	0	2	2
Total	9	8	17

Table 5. Breakdown of Research Backgrounds of US Respondents. 'Lab Research' includes those respondents who work primarily in an experimental, laboratory-driven setting. 'Social Science/Implications' includes those respondents who work outside the lab and comment upon risk and regulatory needs for synthetic biology.

US-based respondents across all constituencies generally (16 of 17) noted that products derived from synthetic biology possess novel health risks that, while unlikely to occur in any individual case, are likely to occur in the aggregate as such technological development becomes more widely commercialized and used. Figure 6 below notes that aside from one respondent who argued that novel health risks from synthetic biology are so statistically unlikely that they should not be considered as plausible, the remaining 16 respondents did all state a belief that, with varying degrees of probabilistic occurrence, synthetic biology's biosafety and biosecurity risks produced within the process of synthetic biology development *were* plausible and required the consideration of regulators for various products that may soon be commercialized as with pharmaceuticals. Of these, 5 (scored as '1') respondents argued that such risks are implausible but are likely enough that it warrants regulatory review, while 9 argued that while

synthetic biology product risks are highly unlikely from a case-by-case perspective, it is very likely that they will occur throughout a given product's life cycle as the use of such technologies becomes more widely available (scored as '2'). Lastly, one respondent did argue that the novel risks of synthetic biology are almost certainly bound to materialize through the vehicle of horizontal gene transfer, although probabilistically this will only occur on a very small number of cases for a given pharmaceutical product, and only where the end-product itself actually contains novel genetic material (scored as '3').

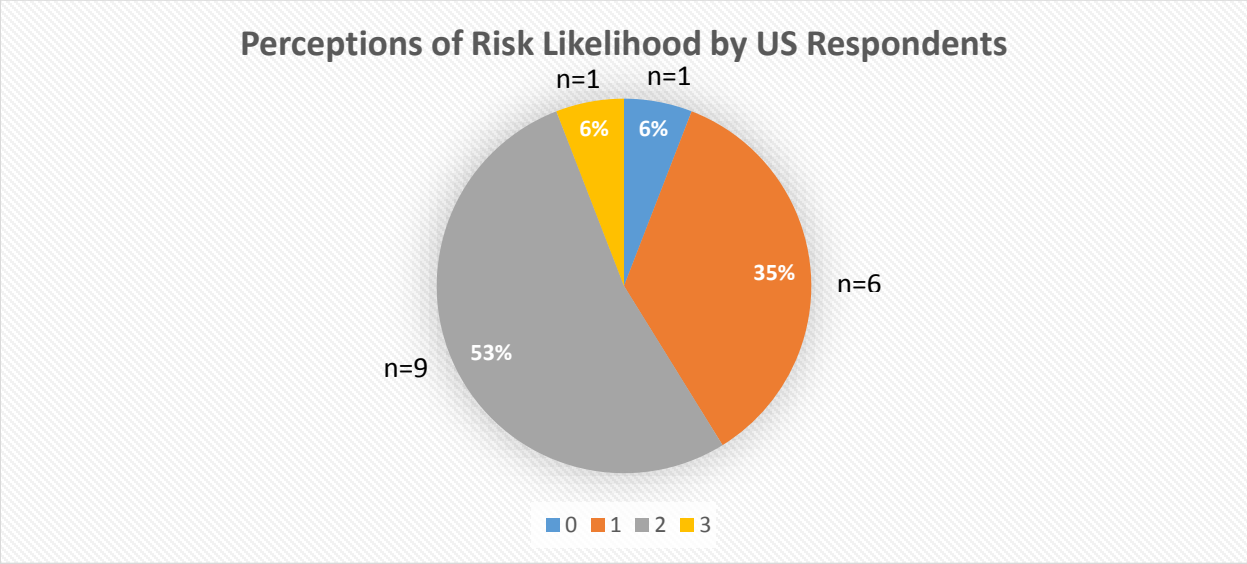

Figure 6. General Perceptions of Synthetic Biology Pharmaceutical Product Novel Risks by US Respondents. 0 = no novel health risk; 1 = possible but proportionally limited novel health risk; 2 = moderate chance of novel health risk across large populations; 3 = guaranteed novel health risk

Given these very general perceptions and beliefs regarding the probability of novel synthetic biology health risk, each interview respondent was asked to clarify (i) the type of risk that they describe as possibly occurring, (ii) the mechanism by which these risks generate negative health outcomes to humans or the environment, and (iii) where these risks occur along a given pharmaceutical product's life cycle (discussed in the section below). Looking at the first line of questioning, respondents were asked to offer their views on two general themes of synthetic biology risk that frequently arise within published literature, including biosafety and biosecurity (Kelle 2009; Schmidt 2008; Serrano 2007; Moe-Behrens et al 2014). Below,

Figure 7 indicates responses by interviewed US experts related to their perceptions of the probability that novel health risks to humans or the environment related to biosafety and biosecurity could respectively occur. Overall, the mean score of related to the respective probabilities of biosafety and biosecurity are 1.8 and 1.3, indicating that respondents considered novel biosafety risks as moderately likely while biosecurity risks were plausible but generally unlikely.

Unpacking this further, interview respondents described biosafety risks as moderately likely due to the widespread nature of such research and historical examples of accidental and unintended exposure, containment breaches, and releases of such biological material in the United States and worldwide (Della-Porta 2008; Schmidt 2008; Altieri and Rosset 2000). A small number (4 of 17) contended that such risks are plausible but highly unlikely, and are consistent with discussion levied by de Lorenzo (2010) that the potential for novel biological material to interact with humans and the natural environment and produce noticeable health harms is unlikely given the current state of the science. However, the majority of respondents (12) noted that the potential for accidental release of such materials or the unintended exposure of novel genetic material to the natural environment in the midst of a controlled release was plausible and likely if carried out for various product development tests, pharmaceutical or otherwise. US Respondent 1 (Social Scientist) noted that "history isn't on our side here […] we need to be very cautious about advancing [syn bio] research moving forward, because the potential for biosafety risks and the unique health consequences coming from such risks may negatively harm the lives of many."

Respondents were less certain of the exact consequences that may arise from such biosafety concerns, 8 mentioned the potential for "a potential rise in invasive species upon environmental contamination with [synthetic biology] material", and "acute, possibly painful, and potentially life-threatening health risks to humans within [synthetic biology] pharmaceutical clinical trials." Four academic respondents all stated that (specific to the case of pharmaceutical development), while the acute risks to individuals suffering from such side effects may be severe, the chances of this being a contagious phenomenon are highly improbable.

While respondents were moderately concerned with the potential of biosafety risks to arise within the research and development of synthetic biology pharmaceuticals, 11 of 17 were less concerned about the potential for a biosecurity incident to accrue due to the actions of a deliberate or nefarious actor to use the principles of synthetic biology to develop a harmful virus or pathogen to damage human and environmental health. This concern, noted as the potential for 'dual use' applications of synthetic biology where technological improvements could be used for harmful applications, is noted in literature as a challenge to the regulation of synthetic biology (Tucker and Zilinskas 2006; Kelle 2013; Schmidt et al 2008; Marris et al 2014).

However, 16 of 17 (94%) interview respondents argued that the potential for such events was highly unlikely due to the existing oversight structures in laboratories, the technological difficulty in fostering such a biological threat, and the degree of resources needed to produce such a harmful bacteria or virus. US Respondent 9 (Lab Researcher) noted that "I guess you can't totally rule such a scenario out because it's *possible,* but I can't imagine such a situation being likely to occur across globe's biological research capabilities, let alone within the United States." Likewise, US Respondent 10 (Lab Researcher) stated that "we can't ignore these threats on a policy level, but at the same time, truly malicious biosecurity threats via synthetic biology are a bit unlikely." When asked to explain why, US Respondent 10 (Lab Researcher) stated that "do-it-yourself synthetic biology has opened up the potential for anyone to get involved with biological experimentation, but the synthesis and programming of biological material into a harmful and virulent pathogen is more complex than simple experimentation."

Similarly, US Respondent 5 (Social Scientist) noted that "existing oversight capabilities are fairly thorough to prevent something like bioterrorism in the United States […] where all biological material acquired by a lab is screened to make sure you aren't weaponing smallpox, or something like that." Further, US Respondent 11 (Lab Researcher) noted that "you'd need extensive resources to accomplish something like that […] like an extensive lab, biological samples, and lots of human assistance that just would not be easy to come by for a deliberately harmful exercise."

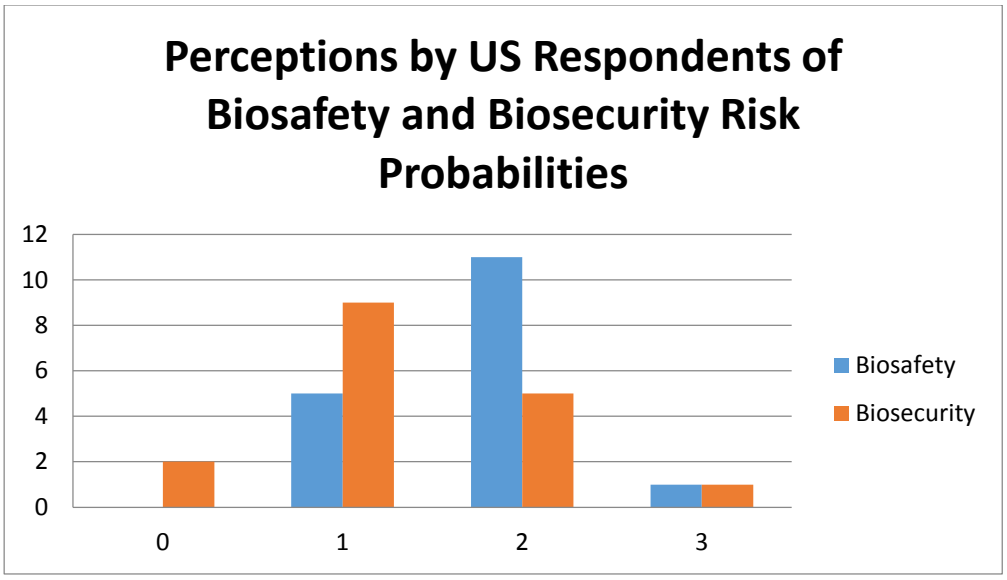

Figure 7. United States Perceptions of Synthetic Biology Pharmaceutical Risks Associated with Biosafety and Biosecurity. Responses are coded on a scale from 0-3, where increasing values indicate greater likelihood of novel health risk. 0 = no novel health risk; 1 = possible but proportionally limited novel health risk; 2 = moderate chance of novel health risk across large populations; 3 = guaranteed novel health risk. (n=17).

After discussing the general probability that novel risks could arise from the process of synthetic biology development and incur negative health consequences to humans or the environment, respondents were asked about their perceptions regarding the mechanisms that could drive such risks to occur. From a biosafety perspective, the most consequential threat indicated by respondents includes 'horizontal gene transfer' (discussed in Chapter 3), which refers to the transfer of genes between organisms in a manner other than traditional reproduction (Wright et al 2013; De Lorenzo and Danchin 2008; Mukherji and van Oudenaarden 2009).

Horizontal gene transfer has been discussed as a potential mechanism by which novel genetic material may gain exposure to unintended human or environmental targets and contribute to the exchange of genetic material in a manner that could yield health harms for the unintended target (Endy 2005; Wright et al 2013; Cardinale and Arkin 2012). Specific to this point, 11 (65%) of respondents generally viewed horizontal gene transfer as the primary mechanism by which biosafety threats to humans and the environment could arise, with US Respondent 6 (Lab Researcher) noting that "the horizontal exchange of genetic information is a

known concept that, however unlikely, we should be concerned with." When asked why, US Respondent 6 (Lab Researcher) replied that "the minute probability for artificial genetic material to interact with human or animal DNA is troubling, because the consequences of this *could* be troublesome […] because we would in effect be manipulating the natural environment and natural cellular interactions without an idea of what the harms could be."

The other two commonly discussed concerns include (i) the potential for novel genetic material to break containment and proliferate in the natural environment, and (ii) a potential lack of efficacy of synthetic biology products to accomplish medical/therapeutic functions *in vivo* for a predetermined purpose. For the former, interview respondents raised discussion such as within Wright et al (2013) and Moe-Behrens et al (2014), which stated that there exists a potential for artificial genetic material to escape containment and proliferate within the natural environment, all outside the intended fate of the novel genetic material in question. US Respondent 12 (Lab Researcher) noted that "even with secure labs, you can't rule out the human element […] and the potential for human error" – a concern noted by several US-Based respondents. US Respondent 13 (Lab Researcher) stated that, related to the process of synthetic biology development, "all it takes is one lapse of caution […] to generate a biosafety hazard event", while US Respondent 2 (Social Scientist) argued more specifically that "particularly in less secure or modern labs, it is almost guaranteed that novel genetic material will unintentionally reach the environment as more and more countries conduct such research for drugs and other applications." Further concerns here will be reviewed across a pharmaceutical product's life cycle in the section below.

For the latter, Wright et al (2013) and Cardinale and Arkin (2012) have raised concerns that due to current limitations and control over circuit and metabolic engineering within the context of synthetic biology research, many products (pharmaceutical or otherwise) may have a high failure rate in terms of accomplishing their intended goal. US Respondent 6 (Lab Researcher) claimed that "the big issue here is that engineered cells may not be as reliable as conventional pharmaceuticals, and would contribute to economic losses and maybe even health concerns." Other respondents noted similar concerns, although at least two respondents from academia, one from industry, and one from government all noted that issues with product

efficacy would likely be somewhat resolved as the technology further refines and develops. US Respondent 7 (Lab Researcher) stated that "once we are able to develop a more robust and reliable library of cellular inputs […] and gain greater control over cellular activity and behavior, we'll make engineered cells more robust and reliable for purposes like with pharmaceuticals." In the meantime, however, interview respondents described efficacy concerns associated with synthetic biology pharmaceutical products could yield financial and health harms, and reduce public confidence with such treatments due to the inability of such treatments to resolve or mitigate those conditions they are designed to treat.

Throughout interview discussion of biosafety risks and the mechanisms that may make such risks possible, all American interview respondents noted that an important distinction between novel and conventional health risks includes whether or not the pharmaceutical in question actually contains any novel genetic material within its final product. Specifically, respondents noted that for cases as with Keasling's antimalarial or Novartis' influenza vaccine, synthetic biology is used to foster the development and growth of pharmaceutical material that would be indistinguishable from their natural-occurring alternatives, leaving US Respondent 14 (Lab Researcher) to state that "aside from early stage research, it's unlikely that there are any serious novel biosafety threats from these products, […] conventional risk sure, like with adverse effects and side effects that you'd already see on labels of commercials, but probably no novel risks from exposure to genetically engineered cells." Similarly, US Respondent 12 (Lab Researcher) noted that "as pharmaceuticals become more 'synthetic' in nature, there may be a greater risk for novel health consequences in terms of exposure to genetic material like with horizontal gene transfer […] but not likely with existing pharmaceutical candidates."

Overall, US-based respondents did describe how biosecurity and biosafety risks in their various manifestations were plausible and should be addressed by regulatory authorities. However, they did indicate that biosafety concerns were far more plausible and consequential, due to the technological and oversight limitations that respondents described as making biosecurity risks highly unlikely to come to fruition. Instead, biosafety risks were viewed as less avoidable due to the potential for them to arise 'accidentally' or 'serve as the result of unintended and unforeseen exposure to the natural environment' – something that has been

discussed in literature for decades (Rhodes 2009; Zaki 2010; Kaufman et al 2007). Specific concerns here include the need to promote lab security and ensure that private organizations are following established requirements to protect against such biosafety concerns.

4.5.2 Pharmaceutical Product Risk Across Life Cycle

After describing general perceptions of synthetic biology pharmaceutical risk probabilities as well as the mechanisms which make such risks possible, each interview respondent was next asked to discuss their perceptions of where risk may occur throughout a generic pharmaceutical product's life cycle. This exercise was repeated for each of the three cases, where the life cycle stages discussed include Research, Manufacturing, Commercialization, and End-of-Life Disposal (consistent with considerations made by Bates et al 2015 and Mohan et al 2012, where emerging technology risk is considered via these life cycle stages). Results specific to United States respondents are described below. The purpose of reviewing perceptions of novel risk across a pharmaceutical product's life cycle is to gain a bit more insight into where such risk may be probabilistically likely. Further consideration includes where such risks might be more consequential, which in turn may indicate where improvements or extensions of existing regulation may be necessary relative to activities taking placing within those higher risk life cycle stages.

Figure 8 and Table 6 below indicate the collective perceptions of US-based respondents relative to the likelihood that a life cycle stage may experience a risky event (or those events where negative health consequences may possibly arise due to the use of engineered genetic material) within the development and use of a synthetic biology pharmaceutical. Generally speaking, respondents collectively argued that the 'End-of-Life' (16 of 17 respondents indicated high risk potential) and 'Research' (12 of 17 respondents) stages were those with the greatest potential for novel biosafety risk, while 'Manufacturing' (7 of 17 respondents indicated high risk potential) and 'Commercialization' (9 of 17 respondents) possessed lower perceived probabilities for such novel risk. Each life cycle stage is individually discussed below, yet it is important to note up front that responses within this life cycle exercise are coded based upon

the respondent's belief in how likely novel health risk may occur within a given life cycle stage, as well as some indication of how and/or why this risk event arises.

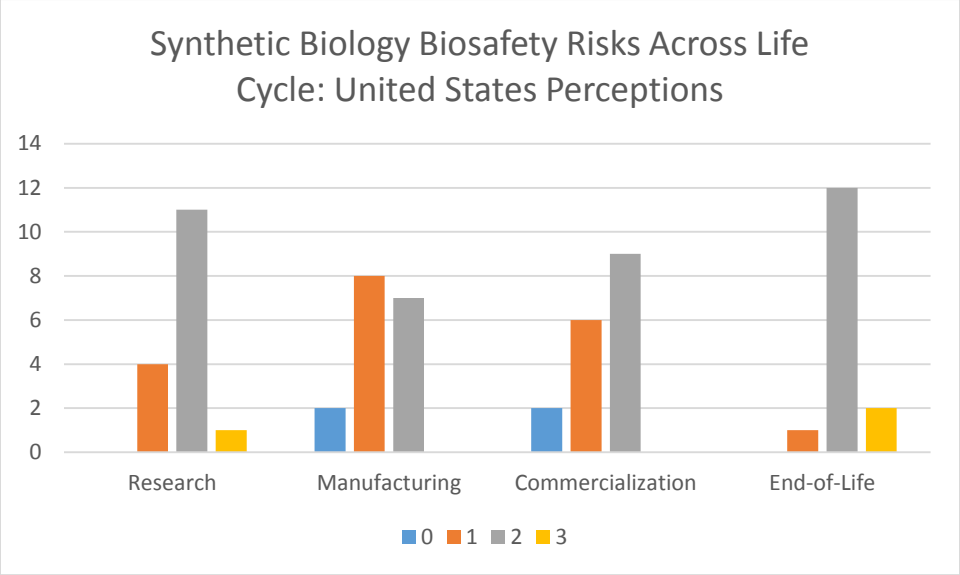

Figure 8. United States Perceptions of Synthetic Biology Pharmaceutical Biosafety Risks Across Product Life Cycle. Blue = No Risk; Orange = Unlikely yet Possible Risk; Gray = Moderately Possible Risk; Yellow = Likely Risk

Research	***Manufacturing***	***Commercialization***	***End-of-Life***
1.8	1.3	1.4	2.1

Table 6. US-based perceptions of risk likelihood scores for across a synthetic biology pharmaceutical's life cycle (0 = no risk likelihood, 3 = maximum risk likelihood)

Looking first at the life cycle stage with the greatest degree of perceived novel risk probability, the 'End-of-Life' life cycle stage was described by all US-based respondents as potentially containing some degree of risk to humans or the environment. This concern is not necessarily unique to synthetic biology, however, where Breggin and Pendergrass (2007) and Gottschalk and Nowack (2011) note similar concerns with nanomaterials and other emerging technologies. The primary concern raised by respondents here specifically centered on environmental health concerns, where all 17 respondents described that there exists a varying degree of potential for novel health risk to occur upon the disposal of synthetic biology pharmaceuticals, with particular worry placed upon the unlikely potential for horizontal gene transfer to allow for the transmission of novel genetic material to the natural environment as well as the potential for engineered cells to act like an invasive species and proliferate in the environment. "There are a few avenues for these products to generate risk upon disposal" said

US Respondent 6 (Lab Researcher), “with the two most likely including aqueous disposal […] or the typical disposal of these products into a landfill.” US Respondent 15 (Social Scientist) argued that “we already have concerns of certain drugs proliferating within the water table by being flushed down the toilet or excreted […], and I think it’s premature to rule out the possibility that there isn’t a risk of this happening for synthetic biology drugs.”

When asked to describe what types of health risks may occur should this scenario arise, US Respondent 12 (Lab Researcher) stated that “you’d be exposing living organisms (human, plant, and animal) to novel genetic material that, through horizontal gene transfer, has a tiny probability of allowing synthetic DNA to spread into their natural host.” Later in the interview, US Respondent 12 (Lab Researcher) continued by saying “while the risk to any one person, plant, or animal is fairly unlikely, when you commercialize these drugs and make them available in millions of doses, side effects and exposure hazards are going to arise.” US Respondent 7 (Lab Researcher) further argued that “risks occurring post-disposal are those we’ll have the greatest difficult monitoring, and while it is unclear the consequences these risks may have, we have to bank on harmful scenarios happening fairly soon after some of these drugs reach the market.” Overall, 14 of 17 respondents stated that end-of-life risks have a moderate to likely probability of occurrence, which, depending on the type of drug and its degree of commercialization, would be exacerbated by “public dissemination of these drugs and vaccines rather than their controlled distribution and use by a physician or nurse.”

Similar to the ‘End-of-Life’ life cycle stage, the ‘Research’ stage was noted by all respondents as possessing some probability of novel biosafety risk to humans or the environment. The main point of discussion raised by all respondents with varying degrees of severity centered on laboratory safety and the ability to effectively contain novel biological material. For 12 respondents who described such risks as moderately or very likely to occur, the general consensus was that due to the potential for synthetic biology research to be widespread outside of modern laboratories and strict experimental protocols, the potential for novel genetic material to either gain accidental exposure to researchers or escape containment and proliferate in the environment was a strong possibility that cannot be ignored from a regulatory perspective. “We can impose rigorous biosafety protocols” US Respondent 1 (Social

Scientist) noted “yet there’s always going to be a chance for mistakes or downright failures in safety to prevent some of these synthetic organisms from breaking containment.” When asked to explain why such a scenario was likely to occur, US Respondent 1 (Social Scientist) further argued that “this [synthetic biology] research is going to go global, and won’t be conducted only at BSL-4 (Biosafety Level 4) facilities. Carelessness, ineffective containment measures, simple accidents that occur one out of a thousand times a veteran bench scientist conducts research […], these biosafety risk incidents are bound to occur.”

While each of the 17 respondents did note some agreement with this statement, 4 respondents specifically noted that the consequences of such incidents were questionable, such as where US Respondent 16 (Lab Researcher) stated that “honestly, while I think biosafety risks may arise within the Research phase of product development, it’s far more likely that the synthetic organism would die off fairly quickly.” US Respondent 10 (Lab Researcher) went further for this line of discussion, stating that “as cells become increasingly synthetic, they’ll likely be less able to proliferate outside of ideal circumstances and without supervision […], meaning the consequences of biosafety incidents may be minimal in the rare event that they occur.” Overall, the collective respondents gave varying responses relative to the consequences of biosafety risk events at the Research life cycle stage, although most noted that risks of severe injury or death to humans or the extensive proliferation of an invasive engineered organism would be highly unlikely given the present state of science. Further, 12 of 17 respondents noted that the relative consequences of such risks varied based upon the material that researchers engineered, where “engineered vaccine material could be risky to human health on one hand, but in other cases less so due to the nature of the virus.” The majority opinion was that, particularly for emerging products as with artemisinic acid or an influenza vaccine, there exists a nonzero likelihood that biosafety events may occur at the Research phase, yet the novel health risks associated with these events would generally be minimal and short-lived (however, conventional health risks due to exposure with harmful biological materials would still pose risks to researchers).

While most interview respondents did note that the ‘Commercialization’ life cycle stage had the potential to produce novel biosafety risk, the collective general perception by

respondents was that the likelihood of such events occurring was highly unlikely. As with the other life cycle stages, the potential for such novel risk hedged on the need for novel genetic material to actually reside within the end-product pharmaceutical, where several respondents argued that existing applications and proposed products for synthetic biology pharmaceuticals do not. US Respondent 11 (Lab Researcher) stated that "right now, synthetic biology is more of a production process, meaning that it allows us to better produce drugs, rather than make entirely synthetic ones. This will come later, but with no novel gene sequences in a drug candidate, it's hard to argue that something like horizontal gene transfer or novel health risks could occur." US Respondent 10 (Lab Researcher) argued that "without novel genetic material, novel health risk is essentially impossible", where "at that point, we're only concerned with conventional risks that are well covered by the FDA." Futuristically, several respondents noted that "the potential for novel health risk could change at the Commercialization life cycle stage", with the primary reason being that vaccines and drugs containing increasingly synthetic pharmaceutical products will be available for public consumption. US Respondent 1 (Social Scientist) noted that "when these engineered products become available, we'll have to consider whether our governance capabilities are adequate to cover the potential for gene transfer or harmful side effects *in vivo*." For the foreseeable future, however, the general consensus by respondents is that novel health risks are possible but unlikely, and the consequences of such risks are likely to be minimal and short-lived.

Last, the 'Manufacturing' life cycle stage was generally described by most respondents as having the least probability of novel biosafety risk to humans or the environment (where only 7 of 17 respondents noted concern over the potential for risk events at this stage). This is not to say that this life cycle stage is entirely devoid of health risk – respondents noted that there exists significant potential conventional risks to those employed with the task of producing synthetic biology materials – yet the general perception amongst those interviewed centered on the notion that *novel* biosafety risks here were plausible yet highly unlikely to occur. US Respondent 7 (Lab Researcher) stated that "in the United States and Europe, facilities are generally well equipped to protect workers during the pharmaceutical production process, and I don't think that synthetic biology products will be much different."

This sentiment was shared by US Respondent 10 (Lab Researcher), who argued that "the exposure scenarios are possible, but biosafety protocols are fairly robust here and various pieces of automation and redundancy limit the potential for human error in the manufacturing process for drugs." When asked to explain their opinion, US Respondent 10 (Lab Researcher) further articulated that "generally speaking, biosafety is taken very seriously, but I think there might be more potential for human error at the Research phase than in Manufacturing, because there's less direct human interaction with novel and potentially unstable and harmful biological material", and "by the Manufacturing stage, a lot of uncertainty related to novel risk of these products will be reduced by testing and trials […], which would allow for more redundancy and safety precautions to be taken prior to production." While 7 respondent did state that novel risks are possible at the Manufacturing stage, the general belief across the field and explicitly argued by 8 respondents is that these exposure pathways are controlled through well-established safety protocols and machines, as well as the general notion that potentially harmful phenotypic expression by engineered cells or vaccines would be mitigated or eliminated prior to mass production.

As with the general discussion of biosafety and biosecurity risks noted in the previous section, respondents noted that the potential for novel biosafety risk to occur within any life cycle stage depends significantly upon whether or not a pharmaceutical product actually contains any artificial genetic material. Specifically referring to the particular examples of Keasling's antimalarial and Novartis' influenza vaccine candidate, various respondents stated that "the potential for novel risk heavily differs based upon whether the synthetic biology product contains novel genetic material, or is produced via novel manufacturing techniques."

For these and other early cases of synthetic biology research and development, novel risk may not be a significant factor of concern due to the lack of such novel genetic material in the end-product (Tait 2012; Kuzma and Tanji 2010). Ultimately, US Respondent 8 (Social Scientist) noted that "the inclusion of novel genetic material within end-product pharmaceuticals is what would trigger the need for stronger governance – otherwise it probably isn't necessary." Specific concerns noted by the respondent centered on the need for stronger pre-clinical trial regulation and approval of potential pharmaceutical candidates,

particularly in relation to environmental impacts. Below, the next section discusses (i) existing hard and soft law regulation to capture synthetic biology research as well as (ii) perceptions by interview respondents regarding perceived weaknesses within such frameworks.

4.6 Regulatory Mechanisms Related to Synthetic Biology in the United States

Synthetic biology regulation within the United States has been widely discussed within published literature, including subjects of (i) the regulatory bodies currently able to govern synthetic biology product development, and (ii) the specific regulatory mechanisms that may or may not be capable of regulating various facets of such products. (Mandel et al 2014; Carter et al 2014; Kelle 2009). This section discusses both the actors responsible for executing such regulation alongside the regulatory and/or legal authority that empowers such organizations to engage in such activity, where such an understanding of the regulatory frameworks currently utilized within the United States is important in order to review where, if at all, potential limitations or gaps within such regulation exists relative to synthetic biology products such as with pharmaceuticals.

4.6.1 Evaluating Existing Regulatory Capabilities within the United States

After discussing the various governmental agencies and hard/soft law pertaining to synthetic biology, interview respondents were next asked to offer their impression of (i) how capable existing hard/soft law are with respect to adequately regulating synthetic biology pharmaceutical products, and (ii) indicate what changes, if any, may be helpful to bolster or improve such regulation in order to better provide guidance for synthetic biology research companies and similar groups. Nearly all (16 of 17) respondents indicated that, while existing regulation captures some of the risks associated with synthetic biology pharmaceutical development, certain reforms to formal regulation or at least some guidance/best practices would be needed in order to adequately protect against potential risks (this stream of logic is further described in Mandel et al 2014). Figure 9 below reflects such discussion, where each respondent was asked whether they felt that new legislation/regulations were needed to meet

such challenges, whether improvements of self-regulation would be adequate, or whether existing regulation was appropriate and that no further regulation would be needed.

The largest group of respondents (n=11, 65%) argued that formal legislative instruments and agency power could be required in order to mitigate and control potential activities that have the potential to produce novel risks where artificial genetic material comes into contact with humans, animals, or the environment. Several respondents echoed concerns raised by Carter et al (2014), which articulated that the FDA may not retain the capability to regulate engineered pharmaceutical products within early trials that are derived from plant products. These respondents argued that, given the limitations of the FDA's ability under Section 351 of the PHSA and Chapter 5 of the FDCA to prevent the entry of pharmaceutical products with potential risks to environmental health (which Carter et al 2014 indicates as being a significant precursor for many drug prototypes), extensions of pre-market approval by the FDA are necessary to mitigate potential risk. US Respondent 3 (Social Scientist) argued that "The FDA is going to be the organization in power to regulate syn-bio pharmaceuticals […] and they'll need the capability to adapt to technological capabilities as we're better able to engineer cells and viruses for medical purposes." US Respondent 4 (Social Scientist) stated that "The FDA is currently the major pre-market approval authority for synthetic biology-derived drugs, and regulatory guidance is needed to close loopholes about what types of trials they can and cannot review […] because they should be involved in all early stage medical trials." These comments correspond to the need for regulatory reform to bolster the FDA's ability to engage within pre-market approval of early stage synthetic biology pharmaceutical research (Mandel et al 2014).

Likewise for the EPA and APHIS, respondents argued that these regulatory agencies must have clear extensions of their existing capabilities to conduct post-market assessment of the effect that pharmaceuticals with artificial genetic material have upon the environment. US Respondent 1 (Social Scientist) argued that "While EPA under TSCA and APHIS under the PPA [Plant Pest Act] have post-market review capabilities for some synthetic biology products […], their ability to conduct post-market assessment and approval of pharmaceuticals over environmental risk concerns remains uncertain and potentially nonexistent with current governance." While FDA maintains rigorous pre-market assessment via clinical trials with only

some lapses in coverage discussed in the paragraph above (Carter et al 2014), US Respondent 2 (Social Scientist) stated that "post-market assessments for environmental health are absolutely necessary for syn-bio pharmaceuticals, but aren't rigorously defined." When asked to explain why this is a concern for regulators, US Respondent 2 (Social Scientist) continued by stating that "we [government regulators] need to be able to monitor for potential environmental risks such as environmental gene transfer, however unlikely these risks are, […] because we just don't know enough about how these risks could impact environmental health." In this way, several respondents noted that clearly outlining the ability of APHIS, EPA, or some other agency to conduct a post-market environmental risk assessment and evaluation process would help further protect the natural environment from long-term exposure to novel genetic material and the consequences thereof, where current authorities geared towards the post-market assessment of genetically-engineered pharmaceutical products are limited from the perspective of environmental risk assessment.

Frequent discussion centered on the need to establish a common series of terms and definitions that could be clearly included in future regulation of genetically-modified materials. US Respondent 1 (Social Scientist) noted that "without a regulation or law clearly referencing 'synthetic biology', there exists potential loopholes or gaps in coverage where best practices aren't enforced and these novel risks could arise." Such concerns are not unique to synthetic biology, where Azoulay and Buonsante (2014) described similar concerns with nanotechnology. However, Carter et al (2014) and Mandel et al (2014) note that potential loopholes and gaps in coverage are important for synthetic biology regulation as they could potentially enable the release, without thorough regulatory reviews, of artificial genetic information that could harm human and environmental health. Most did not describe this as being a complicated action, but an important one where it would "clearly outline exactly what authority synthetic biology falls under, and the expectations of governance that producers would expect to operate under."

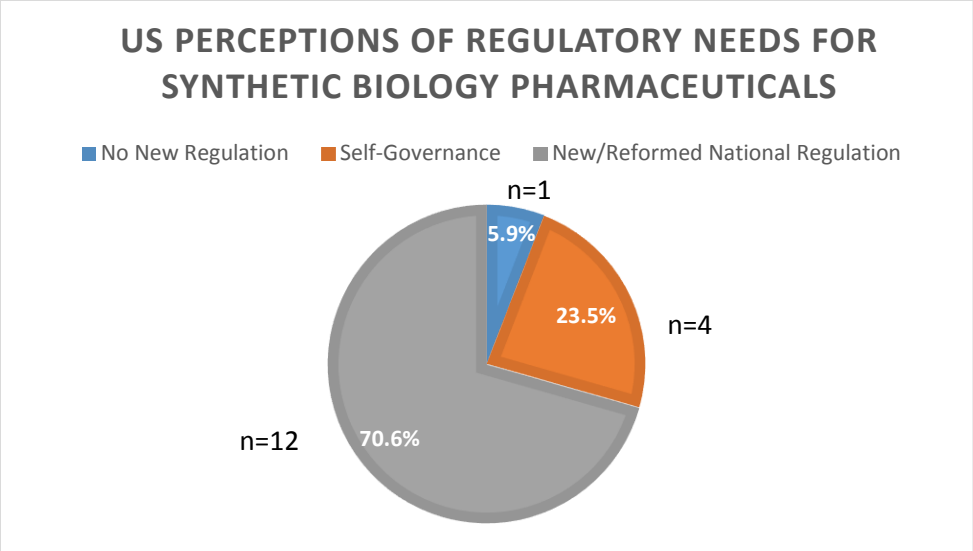

Figure 9. Perceptions Amongst US-based Respondents Regarding the Regulatory Needs for Synthetic Biology Research and Development

A concern raised by 11 of 17 interview respondents related to the ability of regulatory authorities to cover synthetic biology research includes the lack of quantitative information to drive regulatory decision making in a manner consistent with the regulation of chemical products. Such concerns are similar to other technologies like nanotechnology (Breggin and Carothers 2006), where limited information on nanoparticle hazard, exposure, and health consequences complicates regulatory decision making. US Respondent 5 (Social Scientist) argued that "The President's Commission of the Study of Bioethics in 2010 (PCSB 2010) was quite clear that preemptive regulation may be unnecessary and unhelpful, and I personally believe that working with scientists in the field to establish best practices may be a better path forward than new regulation or law." US Respondent 15 (Social Scientist) stated that "conventional authorities seem to be working thus far, and self-governance activities like IRBs [internal review boards] and other non-governmental groups would be able to adequately review technological risk and understand the actual implications of such risk."

These statements reflect the general attitude of these respondents, where they all articulated a belief that conventional regulatory authority outlined by the FDA, APHIS, and EPA alongside formal additions of IRBs and similar self-governance review boards are all that is needed for synthetic biology research to be conducted responsibly unless a realistic risk scenario is proven plausible. This mentality was rejected by the 69% of respondents who

argued for enhanced national regulation, US Respondent 8 (Social Scientist) stated that "the precautionary principle likely applies to synthetic biology […], particularly given all of the unknowns surrounding how it may affect humans, animals, and nature."

Only one respondent (US Respondent 5 – Social Scientist) argued that no new regulation of any kind was necessary to assess and govern synthetic biology health risks. Discussion raised within that interview centered on a belief that "the more synthetic a cell is, the less likely that it will propagate in nature and incur health harms", and "the probability as we currently understand things of horizontal gene transfer occurring […] is essentially zero – basically a rounding error." Rather than institute new regulation, the respondent argued instead that existing legislative instruments and regulatory authority dedicated to the review and management of genetically engineered organisms effectively captured much of the process of synthetic biology development, and that any new regulation would unnecessary impinge upon technological development moving forward. Specific to pharmaceuticals, the Respondent 5 stated that "the FDA's regulations for clinical trials are capable of reviewing health risks of synthetic biology drugs […], although greater stress will need to be placed upon early stage pre-assessment of such drugs prior to Stage 1 Clinical Trials."

Overall, however, most US-based subject experts argued that some improvements to synthetic biology regulation are required to monitor and assess novel health risks associated with the potential risk, hazard, and exposure effects related to synthetic biology pharmaceutical products. The reasons for this are varied, but as articulated above, generally center on concerns that the exposure of humans, animals, or the natural environment to artificial genetic material could yield novel health risks at various stages of a given pharmaceutical's life cycle. Frequently referenced include the need to improve pre- and post-market assessment of such products to review the potential and health consequences of such risks occurring, as well as the need to reduce confusion and uncertainty related to which regulations apply to synthetic biology by clearly adding the term to various regulations' list of defined terms and included processes which are regulated by the FDA, APHIS, EPA, or others. Given the discussion of risk probability above, the respondents further noted that additional scrutiny be placed at the Research and End-of-Life life cycle stages of pharmaceutical product

development, which corresponds with the need to improve and clarify pre- and post-market regulatory reviews and approval.

Aside from formal government regulation, industry stakeholders in the United States also have an important role relative to the governance of synthetic biology. Via discussion noted in Section 1.4.2, options here include, among other things (Mandel et al 2014):

i) NGO-Industry rule-setting partnerships,

ii) An 'issue manager' via a multi-stakeholder coordinating body amongst key industry stakeholders,

iii) An international science advisory board on synthetic biology, and

iv) Public-Private partnerships between government agencies and industry stakeholders.

Relative to NGO-Industry partnerships, Mandel et al (2014) state that such soft law partnerships have arisen in the United States such as with the case of nanotechnology. One example here includes the partnership of the Environmental Defense Fund and the DuPont Corporation (Environmental Defense Fund-DuPont Partnership 2007). Specifically, the partnership sought to provide a framework available publically to nanomaterial developers that included evaluation procedures and metrics for products composed of or produced via nanoparticles (Environmental Defense Fund-DuPont Partnership 2007). Mandel et al (2014) noted that such a framework may be extended to synthetic biology, where the balanced assessment of industry and NGO risk perception and analysis would be seen as appropriately accounting for both risk *and* benefit for synthetic biology product development.

A further approach with previous use in the United States includes public-private partnerships. As with above, an example of this includes nanotechnology, where the NanoSafety Consortium for Carbon was formed to generate knowledge and safety data (Monica 2010b). Such data is intended to facilitate EPA guidance and best practices for carbon nanotechnology products (Mandel et al 2014).

Four interview respondents directly advocated for self-governance for synthetic biology product development – all of which referred to public-private partnerships. Such partnerships would include voluntary membership from key stakeholders in industry alongside agencies like the EPA, APHIS, or FDA. Such partnerships would directly facilitate information-sharing and best

practices to mitigate risk as described by Abbott et al (2012), which Respondent 15 (Social Scientist) referred to as “an avenue to help govern synthetic biology quickly and efficiently without waiting for new law to be created.”

4.7 Discussion

Over the course of interviews with US-based respondents, several important themes emerged related to synthetic biology and pharmaceutical regulation. First included a belief that biosafety risks are possible yet checked by existing regulation pertinent to synthetic biology biosafety and biosecurity concerns as with Chapter 5 of the FDCA, particularly “when synthetic biology research becomes more and more common across the globe, and labs with dubious safety records become engaged with such research.” These risks are noted by US-based respondents as being somewhat likely to occur, yet their consequences may be minimal and more problematic from the perspective of environmental health than risks to human health. Likewise, biosecurity risks, or deliberate attempts to utilize synthetic biology to incur harm to humans or the environment, are perceived as being plausible but unlikely, with various existing oversight mechanisms and resource requirements preventing such behavior from arising. Looking across the life cycle of a pharmaceutical product, the probability that such novel biosafety risks may occur was viewed as greatest in the Research and End-of-Life stages.

Looking next at discussion of regulation, US-based respondents generally sided with the notion that improvements and additions to existing regulation is necessary to both clarify how synthetic biology pharmaceutical production will be governed, while also strengthening pre- and post-market assessment capabilities by agencies such as the FDA and APHIS. Such improvements would correspond with perceived risks at the Research and End-of-Life life cycle stages, and would help reduce potential harms to human and environmental health while promoting best practices to help the technology continue to innovate for emerging applications in medicine. A small number of respondents (4) did argue that self-governance promotion and industry compliance with existing regulations may be the best option forward to prevent the imposition of exceedingly burdensome national regulation on a growing field, particularly given that existing regulatory regimes already capture synthetic biology biosafety and biosecurity

concerns. However, 11 of 17 respondents argued that at least some changes were needed based upon perceived loopholes and gaps in coverage as discussed within scholarly literature or described via the personal opinions of the respondents individually.

Synthetic biology research and development will continue to grow within the United States, with research eclipsing $120 million annually as of 2014 with indications that such growth will only continue for the near future (Kuiken 2015). Given this drive to innovate, establishing regulation to cover the process of synthetic biology development will be important in order to protect against novel risks associated with the exposure of novel genetic material to humans and the environment. This case demonstrates how the collective opinion of subject experts may help to better understand (i) the relative probability and consequences of novel health risks occurring, (ii) the mechanism or method by which such risks will propagate, (iii) the hard and soft law regulatory mechanisms applicable to synthetic biology, and (iv) perceived limitations and suggestions to improve such regulation moving forward.

Chapter 5:

Synthetic Biology and Risk Regulation – The Case of the European Union

5.1 Introduction

Synthetic biology is a research topic that has been widely discussed by European scholars with respect to the technology's benefits alongside the risks that may accrue within the process of development (Kelle 2007; Torgersen 2009; Molyneux-Hodgson and Meyer 2009; Bhutkar 2005; Pei et al 2011; Oldham et al 2012; Konig et al 2016). However, while the United States and Europe are both confronted by shared exposure to emerging concepts and scientific process behind synthetic biology, the responses with respect to synthetic biology regulation have differed in terms of how stringently regulators and policymakers within each area believe the technology should be regulated and governed within the immediate term (Carter et al 2014; Bar-Yam et al 2012). To better understand the perceptions and beliefs of synthetic biology risk and regulation for the European Union, this chapter discusses (i) the current state of European research and investment within synthetic biology innovation, (ii) the perceptions of synthetic biology risks by European experts within academia, government, industry, and non-governmental organizations, and (iii) discussion of the legislative and regulatory mechanisms within the European Union covering synthetic biology research and development.

Similar to Chapter 4, the goal of this chapter is to review those elements of risk culture that may influence the regulation of synthetic biology within the European Union. To accomplish this goal, Sections 5.2 and 5.3 outline the regulatory history and political and institutional risk culture that shape regulatory decision making in the European Union. Specifically, this includes the need to account for how a historically cooperational, informal, yet democratic and transparent risk culture has come to influence regulatory decision making, along with considerations of how such a risk culture may or may not be moving towards a more adversarial nature for emerging technology regulation (Kelemen 2011; Volcansek 2014; Kagan

2009). Later sections build on this discussion by reviewing European Union-based subject expert opinion regarding the risk perception and regulation of synthetic biology within the EU – something that has been directly shaped by existing sui generis regulatory frameworks utilized for biotechnology and genetic engineering alongside the political and institutional risk culture that is prevalent for EU technology regulation.

5.2 Regulatory Culture and Regulatory Decision Making in the European Union

This section reviews several general considerations of the risk culture of European technology regulation, including (i) how existing synthetic biology hard and soft law formed in the manner that they did, (ii) how different legal and institutional authorities influence behavior and regulatory change for synthetic biology, and (iii) considerations of what regulatory actions are probable or improbable based upon such regulatory history and institutional structure.

5.2.1 History and Background of the Political and Institutional Structure of Regulation in the European Union

The European Union is a conglomerate of 28 member states (as of March 2016) that was gradually formed in the aftermath of the Second World War (Dinan 1999). An early precursor to the modern European Union began formally in 1958 with the Treaty of Rome, which created the European Economic Community (EEC) (Dinan 1999). The EEC grew to include many West and Central European states until the adoption of the Maastricht Treaty in 1993, which formally created the European Union (Craig and De Burca 2011). By 2009, the Lisbon Treaty further changed the structure and operations of the modern European Union, where it (i) merged the 'Three Pillars of the European Union' (The European Communities, The Common Foreign and Security Policy, and the Police and Judicial Co-operation in Criminal Matters) into a single legal entity, and (ii) established the permanent position of 'President of the European Council' (Cini and Borragán 2016).

Several institutions shape formal European Union regulation in its current state. Legislatively, this includes the European Parliament as well as the Council of the European Union. These bodies collectively administer European Union budgetary policy and develop hard

law policy to be carried out by executive bodies. The primary body here includes the European Commission, which is responsible for implementing policy decisions and managing daily business for the European Union. The Commission is comprised of 28 members (one per Union member state), with a Commission President chosen by the European Parliament to head the Commission (Schütze 2012). Lastly, the Court of Justice of the European Union represents the judicial branch of European Union regulation, and oversees the application and interpretation of European Union law and also resolves legal disputes between member state governments and EU institutions (Schütze 2012).

Legislation passed by the European Parliament or the Council of the European Union takes on many forms, including those that are legally binding for member states (Regulations, Directives, and Decisions) and those that are not legally binding but are recommended to follow (Recommendations and Opinions) (European Union 2016; Hix and Høyland 2011). For the former, Regulations are those pieces of legislation that are legally binding across all member states and upheld by Commission agencies. Likewise, Directives are also legally binding, yet allow each member state to determine how to achieve the given policy goals and guidelines laid out in the Directive text. Lastly, Decisions are more limited in scope and are not generally applied across all member states, but remain binding for the member state or organization targeted within Decision discussion. For the latter, Recommendations and Opinions allow the European Union government to opine on certain issues and make statements for particular policy goals that are non-binding yet still signal the desires of government agencies.

From an organizational perspective, while each member state participates within the Union's legislative process and is bound by relevant hard law on various policy issues, member states retain autonomy relative to Directives, Recommendations, and Opinions issued by Union legislative authorities. Recommendation and Opinions serve further mechanisms by which regulators within the European Union may express their opinions on best practices and guidance on specific issues, yet generally lack a legal requirement for Member States to formally adopt such guidance into their own national regulatory frameworks (Hix and Høyland 2011; Wallace et al 2015). On the other hand, Directives (such as 90/219/EEC on Contained Use of Genetically Modified Materials or 2001/18/EC on Deliberate Release into the Environment of

Genetically Modified Materials) have served as a common approach to govern genetically-modified organisms , where each member state is required to achieve identified Directive policy goals via their own means. For genetically-modified organisms, this often includes the use of existing member state regulatory agencies to cover related research within the respective state's political borders.

Bar-Yam et al (2012) and Konig et al (2016) described specific Directives and Regulations that have been applied to cover the process of synthetic biology development. This is driven by the sui generis framework for regulating biotechnology and genetically engineered organisms, which is comprised of the collection of Directives and Regulations that explicit address requirements that govern the process and products of genetic engineering exercises. Specifically, Directives concerning the transfer of genes 2001/18/EC), the deliberate release of genetically modified microorganisms (90/220/EEC), the mutation and potential proliferation of genetically modified microorganisms and biodiversity impacts (2001/18/EC), laboratory and workplace safety with experiments conducting genetic modification (2009/41/EC and 2000/54/EC), general consumer health regulation for products with artificial genetic information (1829/2003), and specific Directives of pharmaceutical products containing artificial genetic material (726/2004) were viewed both in literature as well as amongst interview subjects as being sufficient and capable of capturing synthetic biology risks in general and pharmaceutical development in particular via pre and postmarket approval and review of a given product's risks (Bar-Yam et al 2012; Konig et al 2016; Buhk 2014). These legislative instruments are discussed in further detail below.

Where the United States relies upon existing chemical regulatory instruments like the Toxic Substances Control Act to cover synthetic biology development, Bar-Yam et al (2012), Konig et al (2016), and Buhk (2014) have all noted that the European Union has instead applied legislative instruments pertaining to genetically-modified organisms as well as product-specific legislation for the same purpose. An early example of this includes 90/220/EEC, which sought to offer a definition and regulatory requirements for how GMOs should be covered. Specifically, the definitions in Article 2 have been used by future legislative instruments to discuss genetic modification, including:

i) "(2) 'genetically modified organism (GMO)' means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.", and

ii) "(3) 'deliberate release' means any intentional introduction into the environment of a GMO or a combination of GMOs without provisions for containment such as physical barriers or a combination of physical barriers together with chemical and/or biological barriers used to limit their contact with the general population and the environment."

Directive 2001/18/EC built upon the definitions and framework of 90/220/EEC to further regulate the transfer of genes. Specifically, the Directive calls for Member State regulatory agencies to engage with premarket assessment and approval of genetically-modified materials intended for release in Provision 25, where:

"*(25) No GMOs, as or in products, intended for deliberate release are to be considered for placing on the market without first having been subjected to satisfactory field testing at the research and development stage in ecosystems which could be affected by their use."*

Given that such Directives require Member States to execute such regulations using their own national regulatory instruments, it is necessary to consider how these Directives are explicitly applied to individual Member States. For example, requirements under 2001/18/EC have been applied to Part 6 of Environmental Protection Act 1990 and executed by the Department for Environment, Food and Rural Affairs in the United Kingdom (Environmental Protection Act 2002).

Further regulatory concerns include laboratory and workplace safety, which is covered in 2009/41/EC and 2000/54/EC. For 2009/41/EC, the Directive builds upon previous legislation (90/220/EEC and 2001/18/EC) to further outline best practices in laboratory and workplace safety for research involving genetic modification. Specific guidance includes Table 1A in Annex IV, which outlines proper laboratory safety for such experimentation. Further, the Directive states that:

"Save to the extent that point 2 of Annex IV allows other measures to be applied, the user shall apply the general principles and the appropriate containment and other protective measures set out in Annex IV corresponding to the class of the contained use, so as to keep workplace and environmental exposure to any GMMs to the lowest reasonably practicable level, and so that a high level of safety is ensured."

Laboratory and workplace safety concerns noted in 2009/41/EC is amplified by 2000/54/EC, which was set out earlier in 2000 to establish regulatory requirements for Member States related to biological agents in the workplace. Specifically, Objective 1 notes that:

> *"1. This Directive has as its aim the protection of workers against risks to their health and safety, including the prevention of such risks, arising or likely to arise from exposure to biological agents at work."*

Given this overall objective, 2000/54/EC requires employers to avoid using harmful biological agents where a less harmful agent may be used instead. Further requirements include providing safe facilities and equipment to mitigate and alleviate hazardous events, as well as requiring employers to acquire permissions to work with virulent or particularly hazardous biological substances prior to their use. This is noted in the Directive's text where:

> *"The employer shall avoid the use of a harmful biological agent if the nature of the activity so permits, by replacing it with a biological agent which, under its conditions of use, is not dangerous or is less dangerous to workers' health, as the case may be, in the present state of knowledge."* (Article 5), and
>
> *"Where the results of the assessment referred to in Article 3 reveal risk to workers' health or safety, employers shall, when requested, make available to the competent authority appropriate information on: (a) the results of the assessment; (b) the activities in which workers have been exposed or may have been exposed to biological agents; (c) the number of workers exposed; (d) the name and capabilities of the person responsible for safety and health at work; (e) the protective and preventive measures taken, including working procedures and methods; (f) an emergency plan for the protection of workers from exposure to group 3 or a group 4 biological agent which might result from a loss of physical containment."* (Article 7).

Related to import and biosecurity control, Regulation 1946/2003 outlines requirements pertaining to the import and movement of genetically modified materials. The overall objective of this Regulation is noted in Article 1, where:

"the objectives of this Regulation are to establish a common system of notification and information for transboundary movements of genetically modified organisms (GMOs) and to ensure coherent implementation of the provisions of the Protocol on behalf of the Community in order to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of GMOs that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health."

Further, 1946/2003 includes provision on intended shipment and use (Chapter 2) and unintended distribution (Chapter 3), where each Member State is obligated to strictly control the transfer of genetically modified organisms and take necessary steps to prevent against unintended release scenarios. Further, Section 4, Article 12 of Chapter 2 outlines requirements for transferors to submit appropriate documentation to gain approval for any such shipments.

Collectively, these Directives and Regulations are viewed in literature as capable of covering existing iterations of 'semi-synthetic' synthetic biology products, although may be challenged in the future as synthetic biologists are able to foster increasingly artificial synthetic biology -products such as with synthesized vaccines or other therapeutics (Konig et al 2016; Bar-Yam et al 2012). While their implementation occurs differently within each member state, general interpretation and guidance of risk is derived from the Scientific Committees within the Directorate-General for Health and Food Safety (Bar-Yam et al 2012). Specifically, these Committees include the Scientific Committee on Consumer Safety, the Scientific Committee on Health and Environmental Risks, and Scientific Committee on Emerging and Newly Identified Health Risks. Ultimately, Member States must comply with Directives such as those noted above within a predetermined timeframe, the European Commission may initiate legal action against the specific Member State in the European Court of Justice for monetary damages and legal requirements for the State to adopt the Directive as soon as possible (Falkner et al 2004; Zhelyazkova and Yordanova 2015).

5.2.1 Risk Culture in the European Union

As with Chapter 4, this section describes how political and institutional values that comprise the European Union's regulatory risk culture affect its regulatory policies. Within the spirit of this notion, the following two subsections discuss (i) the historical path taken by European Union regulators to cover synthetic biology research, and (ii) the characteristics of the European Union's risk culture which will ultimately influence how future synthetic biology regulation will be affected by such political and institutional factors.

5.2.1.1 Historical path of synthetic biology regulation and its related regulatory instruments

Looking at earlier influences of synthetic biology regulation in Europe, pan-European chemical regulation during the 1970s and early 1980s was relatively decentralized, where individual countries held jurisdiction over chemical regulation. Vogel and Lynch (2001) argue that early debates of European regulatory policy related to chemical risk assessment and regulation in the 1970s and early 1980s remained "closed to the public", with non-governmental organizations having limited access to policymakers and influence over the regulatory building process such as within the Directorate General on the Environment, Consumer Protection, and Nuclear Safety (Vogel and Lynch 2001; Jasanoff 1993). This was in direct contrast to American regulatory policy during that time, which Vogel (1986), Lofstedt and Vogel (2001), Wiener and Rogers (2002), and Kelemen and Vogel (2010) note as where American regulatory agencies were likely to ban products that were open to commercialization in the European Union.

By 2006, pan-European regulation of chemicals became more centralized with the passage of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations (Williams 2009; Bergkamp 2013; Gergely and Gayral 2015). Managed by the European Chemicals Agency (ECHA), the REACH regulations provided clearer requirements on information-sharing by manufacturers, importers, and consumers on various chemical products produced, sold, and disposed of within the European Union (Williams et al 2009). Further, REACH involves the registration of hazardous properties of chemicals, as well as the premarket authorization requirements for those producers that seek to potentially utilize such substances (Williams et al 2009; Bergkamp 2013). Overall, REACH represents an increase in centralized authority within the European Union, where Member States are required to implement and uphold standards established by the European Commission. Further, while chemical regulations have not been used to capture the process of synthetic biology development as with TSCA in the United States, the path of regulatory development here offers background insight into how the regulatory risk culture in the European Union unfolded in the second half of the 20th and early 21st Centuries (Guehlstorf and Hallstrom 2005; Kurzer 2001; Vogel 2003). This culture has affected the development of regulation pertaining to genetic modification (discussed below), which *has* been used to cover synthetic biology development.

European regulatory attitudes within chemical regulation came to influence biotechnology and genetic modification by fostering an increasingly centralized approach to premarket approval and information sharing by various relevant stakeholders (Vogel and Lynch 2001). Specifically, the Directorate General on the Environment, Consumer Protection, and Nuclear Safety's Biotechnology Steering Committee established in 1985 the Biotechnology Regulations Interservice Committee (BRIC), which served as a composite committee with representation from various European regulatory bodies tasked with the responsibility to develop biotechnology regulatory policy for the European Commission (Vogel and Lynch 2001). The policy recommendations related to the premarket approval of biotechnologies was far more precautionary than with previous regulatory discussions in Europe (Vogel and Lynch 2001; Vogel 1986), and eventually fostered Directive 90/220/EEC (discussed above in Section 5.2.2) on the Deliberate Release of Genetically Modified Organisms (Buhk 2014).

This Directive was inherently driven by the precautionary principle, which had been discussed as a regulatory concept since at least the World Charter on Nature in 1982 (see the history and adoption of the precautionary principle in the European Union in Section 5.2.2.2 below). Specifically, the Directive required biotechnology researchers to submit environmental reports and premarket risk assessment documents to the relevant regulatory authorities in the given country or countries where testing was to take place – where this approval process for product commercialization was eventually extended to genetically modified organisms, and granted each country the ability of a European Member State to prohibit such products from entering the market due to perceptions of risk to human and environmental health (Adler 2000; Vogel and Lynch 2001).

The first major tests of Directive 90/220/EEC included the regulatory review of genetically modified soybeans and corn in 1996-1998 (Vogel and Lynch 2001). Challenges by the trade association EuroCommerce and companies like Unilever included demands that genetically-modified soybeans imported from the United States be fully separated from naturally-occurring beans. These growing demands spurred the European Parliament and the Council of Ministers to argue that genetically modified foods should be labeled if the modified crops contain any changes to their phenotypic characteristics or food properties as with those

crops produced naturally (Skogstad 2003; Haslberger 2000). By 2000, the European Union constructed a new standard using an interpretation of the Cartagena Protocol on the need to protect biodiversity and human health from unknown risks from emerging biotechnologies (Strauss 2008). Specifically, the standard included where any food products containing at least 1% of their composite materials with genetic modification must be labelled as such (Vogel and Lynch 2001). Further, Member States were empowered with the ability to ban certain genetically modified organisms if there were 'justifiable reasons' that the organism could cause harms to humans or the environment (Strauss 2008).

In 2003, the United States and 12 other countries filed a complaint with the World Trade Organization (WTO) that the European Union, via its actions on imported genetically modified products, was violating international trade agreements (Isaac and Kerr 2003; Pollack 2013). In 2006, the WTO ruled that Europe's de facto ban of genetically modified agricultural products violated international trade agreements, yet Wirth (2013) and Young (2012) note that the ruling had little effect on the ability of individual member states to refuse the importation of such products.

Carter et al (2014), Buhk (2014), and Bar-Yam et al (2012) all contend that the growing calls for precaution driven by the regulation of genetically modified organisms fed into a similar attitude of precaution for synthetic biology products in the 2000s-2010s. In particular, Buhk (2014) argues that regulations related to genetically modified organisms 90/219/EEC (the contained use of genetically modified microorganisms) and 90/220/EEC (the intentional release of such products) set the stage for the eventual regulation of synthetic biology. Bar-Yam et al (2012) notes that 90/219/EEC has been explicitly used to drive regulation of synthetic biology in the late 2000s, where the regulation has been amended several times to keep pace with evolutions in genetic modification research. Specifically, the 90/219/EEC regulation contains four components that drive the regulation of covered biological materials, including (i) the identification of potential harmful effects posed by the modified genetic material, (ii) the characteristics by which the modified genetic material will be used for, (iii) the severity of consequences of identified harmful effects, and (iv) the general probability that such risks could occur. Bukh (2014) argues that these early directives served as a focus for the debate of

synthetic biology regulation, where in 2008 the European Commission chartered a Working Group to review new biological research techniques and offer insight into how they should be covered by existing regulation. These techniques include (Buhk 2014; Bar-Yam et al 2012):

1) Synthetic Biology
2) Zinc Finger Nuclease Technology
3) Olignonucleotide Directed Mutagenesis
4) Cisgenesis
5) RNA-dependent DNA methylation
6) Grafting
7) Reverse Breeding, and
8) Agro-infiltration.

The findings of this meeting were used to inform the development of several directives related to emerging biological technologies in general, and synthetic biology in particular. For the former, this included Directive 2001/18/EC on the Deliberate Release into the Environment of Genetically-Modified Microorganisms (see more info in Section 5.2.2 above), where researchers engaging with genetic modification were required to conduct a risk assessment and gain a Member State's approval prior to bring goods to market (with particular emphasis on effects on ecosystem health, biodiversity, mutative/evolutionary impacts, and considerations of gene transfer – Bar-Yam et al 2012). Another general regulation included Regulation 428/2009, which laid out regulatory practices for dual-use goods and placed oversight mechanisms which granted Member State authorization over the export of such goods (including considerations of laboratory and worker safety – Bar-Yam et al 2012). Further, the European Commission laid out in 726/2004 the explicit regulation of pharmaceuticals and medicinal practices the approval procedures for those medicines which include novel genetic material, overseen by the newly established European Medicines Agency of the European Parliament (European Commission Scientific Committees 2014).

Overall, while certain European Union-wide agencies such as the European Medicines Agency offer guidance for all European Union Member States, the execution of synthetic biology regulation and laws is carried out by domestic Member State regulatory bodies such as with Health and Safety Executive or the Department of Environment, Food and Rural Affairs in

the UK (Parliamentary Office of Science and Technology 2015; Bar-Yam et al 2012). General guidance and general best practice, however, is issued by the European Union to Member States, and includes such calls to action as implementing guidelines for genetically modified organism and synthetic biology biosafety through the promotion of adequately robust physical barriers in Directives 2009/41/EC and 2000/54/EC.

These legislative instruments compel premarket approval of various genetic modification efforts by a European Member State's regulatory authority as well as European Union agencies such as with the European Medicines Agency of the European Parliament, and were applied to synthetic biology regulation through a series of meetings known as the 'Final Opinion on Synthetic Biology', where three meetings (June 2014, June 2015, and December 2015) were conducted related to formally defining the field, identifying potential risks that synthetic biology as a field may pose to humans, and specific discussion on risks to biodiversity and the environment (European Union Health and Food Safety Scientific Committees 2014, 2015a, 2015b). This guidance signaled to Member States the risk assessment protocols needed for innovators to use for preassessment approval as well as indicating how synthetic biology products should be regulated using extensions of existing hard and soft law (European Union Health and Food Safety Scientific Committees 2014; 2015a; 2015b).

Within the European Union, the sui generis framework on the regulation of biotechnology has influenced the regulation and governance of synthetic biology, where the Directives and Regulations within this framework have captured the process and products of synthetic biology development. Hard law regulation, specifically Directive 2001/18/EC (on the Deliberate Release into the Environment of Genetically-Modified Microorganisms), 726/2004 (the regulation of pharmaceuticals containing artificial genetic material, 2009/41/EC (contained genetic modification experiments in laboratories) have all been built upon the legacy of previous regulatory efforts on genetic modification such as with 90/220/EEC (the deliberate release of engineered microorganisms), and within the spirit of the precautionary principle (Parliamentary Office of Science and Technology 2015; Bar-Yam et al 2012; Buhk 2014). Similarly, soft law regulation as with the pronouncements of the European Union Scientific

Committees (2014; 2015a; 2015b) also signals to European Member States certain best practices and general guidance that each Member should follow.

5.2.1.2 Assessment of the Risk Culture influencing regulation of novel compounds and scientific processes like synthetic biology

One of the more common considerations noted about European Union risk culture centers on its 'cooperative' approach to resolve regulatory disputes (Kelemen 2011; Kagan 1997; Guehlstorf and Hallstrom 2005). By this, Kelemen (2011) and Kagan (1997) generally describe European cooperativism as being "more informal, […] and relied less on the involvement of lawyers, courts, and private enforcement actions." Relative to the reliance upon informal measures to build technology regulation, Wallace et al (2015) and Luedtke et al (2010) argue that technology regulation is an informal process where government stakeholders seek to include stakeholders within industry and non-governmental organizations in the regulation-building process. This differs from the American risk culture described in Chapter 4, which is more adversarial in nature and where such collaboration between government and lay stakeholders is less common (Kelemen 2011).

Specific to the inclusion of judicial dispute resolution in the regulation-building process, Kelemen (2011), Luedtke et al (2010), and Kagan (2008) note that European technology regulation relies less upon formal dispute resolution via court decisions, and instead seeks to resolve disagreements via guidelines, best practices, and collaborative agreements with various stakeholders before disputes become irreconcilable. Kagan (2008) and Lindseth (2011) argue that this is due to the institutional nature of the European Union – particularly via the use of Directives that allow for member states to meet Union-derived regulatory goals using their own domestic regulatory agencies and frameworks. Such an approach is particularly applicable to the various Directives used to regulate genetically-modified organisms (Guehlstorf and Hallstrom 2005), although growing pressures by technology developers, the lay public, and academic researchers are beginning to push European dispute resolution towards a more judicial model similar to the United States (Pollack and Shaffer; Kelemen 2011; Kagan 2008). Specifically, the European Scientific Committees have served as an avenue where independent

advice from bodies of experts on various topics of health and safety have been used to drive formal regulation of potentially hazardous substances by the European Commission and its Member States (Walker 2012; Rocks et al 2014).

Garben (2013, Lindseth (2011), and Kelemen (2011) argue that this growing contention and pressure towards incorporating legal institutions within dispute resolution for technology regulation is driven by growing calls for full transparency in the regulatory process as well as the creation of a 'level playing field' with more active enforcement and adjudication of regulatory law. This is not to say that European technology regulation is not transparent – the political system is one that is responsive to public demand and clearly indicates how policy is created and upheld – but instead that the technology regulatory deliberation process should be 'fair' for all players and rely less on informal conventions and meetings to resolve differences (Kelemen 2011; Kagan 2008).

Given this and in spite of a generally cooperative nature in the technology regulatory process, Kelemen (2011), Pollack and Shaffer (2009), Kelemen (2006), and Kagan (1997) all describe the slow yet noticeable movement towards more adversarial legalism more commonly found in the United States. Kelemen (2011) describes this development as 'Eurolegalism', where a fragmented institutional structure within the European Commission and European Parliament along with the relative strength in retained powers by member states drives new Union-level attempts at technology regulation to be more transparent, formally defined, and applicable to a diversity of players across the 28-member Union. Kagan (1997) and Lindseth (2011) agree with this sentiment by noting that the need to resolve differences in opinion related to the appropriate level of technology regulation as well as the relative fragmentation of vertical regulation between the European Union proper and its member states individually all produce an environment that encourages private litigants to bring their complaints and disputes to formal courts. Pollack and Shaffer (2009) note that this may be particularly applied to genetically-modified organisms (with applicability to synthetic biology as described in Bar-Yam et al 2012), where cooperative regulation is 'failing' to resolve various disputes and concerns held by various players in the European Union government related to the domestic research and development of genetic research as well as the importation of genetically

modified foods and materials. While Kelemen (2011) and Lindseth (2011) do not yet contend that the European Union has fully moved to an adversarial model of legalism identical to the United States, they do note that such a change from cooperative regulation is noticeable and may continue to grow with more calls for increasingly transparent dispute resolution via formal court decisions on technology regulation.

An additional consideration within technology regulation of the European Union includes a general reliance upon the precautionary principle, which had been discussed since 1982 and subsequently applied to European Union policy and law by 2007 (Carter et al 2014; Levidow et al 2000). An important precursor to the precautionary principle in Europe included the Rio Declaration of 1992. Building from discussion in Chapter 1, Principle #15 of the Rio Declaration stated that:

> *"In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."*

The Rio Declaration was subsequently enacted in June 1992, and included follow-up meetings in 1997 and 2002 to assess the Declaration's application within its signatories. Such discussion was further applied in the 2000 Cartagena Protocol on Biosafety to the Convention on Biological Diversity, which was an international agreement that sought to protect biological diversity from the potential risks posed by genetically modified organisms. Discussed in January 2000, passed in May 2000, and enacted in September 2003, the Cartagena Protocol sought to reaffirm in its Preamble:

> *"the precautionary approach contained in Principle 15 of the Rio Declaration on environment and Development."*

More specifically, Article 10 of the Cartagena Protocol further specified the application of the precautionary principle to genetic modification and emerging biotechnologies, where it states that:

> *"Lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of an LMO on biodiversity, taking into account risks to human health, shall not prevent a Party of*

import from taking a decision, as appropriate, with regard to the import of the LMO in question, in order to avoid or minimize such potential adverse effects."

Such international discussion was adopted in by the European Commission, which in a February 2000 Communication called for the application of the precautionary principle in its regulatory activities (European Commission 2000). Specifically, Sections 4 – 6 of this Communication sought to outline the required use and deployment of the principle by noting:

"4. The precautionary principle should be considered within a structured approach to the analysis of risk which comprises three elements: risk assessment, risk management, risk communication. The precautionary principle is particularly relevant to the management of risk.
The precautionary principle, which is essentially used by decision-makers in the management of risk, should not be confused with the element of caution that scientists apply in their assessment of scientific data.

Recourse to the precautionary principle presupposes that potentially dangerous effects deriving from a phenomenon, product or process have been identified, and that scientific evaluation does not allow the risk to be determined with sufficient certainty.
The implementation of an approach based on the precautionary principle should start with a scientific evaluation, as complete as possible, and where possible, identifying at each stage the degree of scientific uncertainty.

5. Decision-makers need to be aware of the degree of uncertainty attached to the results of the evaluation of the available scientific information. Judging what is an "acceptable" level of risk for society is an eminently political responsibility. Decision-makers faced with an unacceptable risk, scientific uncertainty and public concerns have a duty to find answers. Therefore, all these factors have to be taken into consideration.

In some cases, the right answer may be not to act or at least not to introduce a binding legal measure. A wide range of initiatives is available in the case of action, going from a legally binding measure to a research project or a recommendation.
The decision-making procedure should be transparent and should involve as early as possible and to the extent reasonably possible all interested parties.

6. Where action is deemed necessary, measures based on the precautionary principle should be, inter alia:

- *proportional to the chosen level of protection,*
- *non-discriminatory in their application,*
- *consistent with similar measures already taken,*

- *based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis),*
- *subject to review, in the light of new scientific data, and*
- *capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment."*

Eventually, the lessons learned within international conventions and the 2000 Communication were adopted in the 2007 Lisbon Treaty. This formally entrenched the precautionary principle in regulatory decisions and policymaking within the European Union and its Member States. Specifically, Article 191 of the Treaty notes that:

> *"Union policy on the environment shall aim at a high level of protection taking into account the diversity of situations in the various regions of the Union. It shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay."*

With this history in mind, Carter et al (2014) notes that European regulation of genetic engineering in general and synthetic biology in particular has taken a precautionary angle, where oversight is required to review the potentially novel risk characteristics of synthetic biology products and made assessments related to whether such risks are likely or worrisome enough to prevent their expanded research or entrance into the market. This is not to say that a precautionary approach to synthetic biology regulation completely prohibits innovation, but instead slows the pace of innovation in order to gain more information related to novel health risks and approve those products that are demonstrated to contain minimal harms (Antonopoulou and van Meurs 2003; Kelle 2013; Kaiser 2012). Overall, however, general adherence to the precautionary principle serves as a central, codified principle in approaching and working through regulation and decision-making in the European Union and will likely shape the types of regulatory activity that European policymakers are willing to entertain over the course of synthetic biology regulation in the near future.

5.2.2 Applications to Interview Data

The risk culture and regulatory history surrounding technology regulation in the European Union are crucial factors to consider when reviewing European interviewee

comments for synthetic biology regulation below. European interviewees noted several comments on the importance of working within the European regulatory environment and cooperative culture by noting (i) the cooperative nature of regulation-building process within the European Union, and (ii) an adherence to the precautionary principle for research related to synthetic biology (see also Carter et al 2014; Bar-Yam et al 2012). Such concerns are in line with discussion raised by Kelemen (2011), Kelemen (2012), Kagan (1997), and Lindseth (2011), which collective argue that the cooperative, informal, and devolutionary nature of European technology policy and regulation are intrinsic values that shape such regulation-building activities in the European Union in a unique manner that differs from other developed political entities such as with the United States.

A recurring theme implied within European interviews is that European regulatory policy is a process that is cooperative in nature, where regulators, private researchers, academics, and other stakeholders often engage informally to collectively establish best practice and guidance for regulatory policy of genetically modified organisms (see Kelemen 2011 or Pollack and Shaffer 2009 for similar discussion). One such example of such sentiment includes comments made by EU Respondent 1 (Social Scientist), who argued that "New governance for synthetic biology should include inputs from industry and academics, who have also been active in discussion for GMOs for decades." Further, EU Respondent 2 (Lab Researcher) stated that "gaining input from stakeholders outside of government in a top-down manner would be important for future synthetic biology regulation […] and will help balance the technology's risks and benefits." These sentiments reflect a historical and current ability to cooperatively work with various private and academic stakeholders to identify guidance and best practices to shape regulation for genetically-modified organisms in the European Union – something that has been discussed as a precursor to contemporary regulation of synthetic biology in Europe (Bar-Yam et al 2012). Further, the need for government stakeholders to operate outside of a "top-down" manner and instead take into account the views of various researchers in the field is a further point consistent with Kelemen (2011), where such decision making is difficult to occur outside of a cooperative environment.

Despite this general perception that technology regulation in the European Union is a collaborative and cooperative affair, respondents did note some apprehension regarding the ability of genetic engineering (and synthetic biology by relation) to complicate regulatory decision making and reduce the potential for collaborative decision making (consistent with Pollack and Shaffer 2009, and Kelemen's discussion of the European Union's movement towards 'Eurolegalism'). EU Respondent 3 (Social Scientist) stated that "[the technology's] uncertainty complicates the regulatory environment, and will likely hinder the government's ability to allow products to enter the market without judicial support." Such sentiments raise concerns that, at least for the case of synthetic biology and genetically-modified organisms, there may be an increased desire to adopt formal dispute resolution via lawyers and courts within and across the European Union member states (see Kelemen 2011; Kagan 1997). However, the European regulatory environment cannot be deemed entirely adversarial, with EU Respondent 4 (Social Scientist) noting that "academics and industry professionals will play a significant role with synthetic biology governance" – indicating at least some appetite for cooperationalism amidst the technological uncertainty.

Lastly, EU-based respondents noted the importance of the precautionary principle as applied within European technology regulation via the Treaty of Lisbon in developing regulatory guidance for synthetic biology products (see also Kelle 2013; Carter et al 2014). This ideal is reinforced by Bubela et al (2012), Bar-Yam et al (2012), and Kaebnick et al (2014), which argue that the European regulatory environment favors an approach that allows synthetic biology products to move towards commercialization only when they have been demonstrated to have minimal hazardous effects and established safe use best practices. Such a framework would mimic the process of conventional chemical regulation laid out by REACH, yet contains the further complication of greater uncertainty pertaining to threats to biodiversity and human health related to the exposure of novel genetic information into the natural environment (Wareham and Nardini 2015; Moe-Behrens et al 2014). EU Respondent 3 (Social Scientist) noted the importance of precaution in Europe where they argued that "a recent history of GMO regulation will keep Europe on a path to entrench the precautionary principle for synthetic biology research." Where the precautionary principle has already been established into law

even before the rise of genetically modified organisms, White and Vemulpad (2015) and Oldham et al (2012) would agree with the above respondent by noting that future European discussion of synthetic biology will be squarely framed within the lens of the precautionary principle. Further, EU Respondent 1 (Social Scientist) stated that "the appetite for uncertainty and risk for synthetic biology is likely lower than the US or other areas of the world", indicating a tendency by European regulators to favor a more cautious approach to relevant product regulation where such products' risks remain uncertain in nature (see Bubela et al 2012; Vogel and Lynch 2001; Bar-Yam et al 2012).

Overall, interview data suggests some consistency with discussion in published literature that the European approach to technology regulation remains cooperative, informal, and precautionary in nature (consistent with Kelemen 2011; Kagan 1997; Kelemen 2012). Such an environment would enable collaboration between government regulators along with industry professionals and academic researchers to fashion policy and adapt regulations in a manner that both limits the potential for adversarial legalism while also constructing soft law to guide synthetic biology regulation in an anticipatory and adaptive manner (see Allan 2015; Howlett and Migone 2013; and Douglas and Stemerding 2014). However, the interviewers did suggest that this environment could change in the future, where challenges related to limitations of synthetic biology research and commercialization may be legally contested as with genetically modified organisms at the WTO (see also Garben 2013, Volcansek 2014, and Kelemen 2011). Volcansek (2014), Garben (2013), Sabino (2014) describe this change in European regulatory attitudes through the lens of Kelemen's (2011) concept of 'Eurolegalism', where European technology regulation may become more legally and formally derived and adversarial as with the case of the United States.

5.3 Synthetic Biology Research in the European Union

Looking next at synthetic biology research within the European Union, European companies have spent over $900 million on synthetic biology research from 2009-2015 on fields ranging from biofuels to pest control to pharmaceuticals (SynBioBeta 2016; Serrano 2007; Peralta-Yahya et al 2012; Weber and Fussenegger 2012; Oldham et al 2012). International

research consortiums such as the European Research Area Network in Synthetic Biology (ERASynBio) have formed to particularly coordinate and fund research related to synthetic biology innovation within the European Union (up to over $100 million annually as of 2014), while international meetings such as with the BioBricks Foundation and SynBioBeta have brought together an international collection of synthetic biology scholars and researchers to discuss the risks and benefits of various iterations of synthetic biology products now and moving forward.

From a research perspective, funding for synthetic biology research has grown each year since 2005. Kuiken (2010) and Kuiken (2015) discuss that where synthetic biology research had been funded less than $20 million each year up until 2010, by 2015 total funding across the Commission had eclipsed $100 million in 2014 alone. Important players within such research include the United Kingdom ($175 million from 2005-2014), Germany, and the Netherlands ($90 million from 2008 to roughly 2013), although every country within the European Union is eligible for funding and universities within each of the member states receive funding for various projects (Kuiken 2015). The primary funding mechanism by the European Commission for synthetic biology projects includes the Framework Programmes for Research and Technological Development, where synthetic biology was names a targeted area for such research in 2003 by the Sixth Framework. Likewise, the United Kingdom's funding bodies include the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, and the Wellcome Trust (Kuiken 2010). While Kuiken (2015) does note that gaining specific details of the specific projects funded by these bodies is a difficult task due to proprietary and/or confidentiality agreements with research companies engaged with synthetic biology innovation, he does note that the European Commission began funding inquiries into synthetic biology implications research as early as 2007, when $2 million was explicitly earmarked for ethical and social discussion of the risks and benefits of synthetic biology research.

Where European universities, government agencies, and research companies have begun to conduct synthetic biology research for a variety of topics, regulators and policymakers have also begun to engage with the task of how synthetic biology should be defined and

regulated from the perspective of hard and/or soft law (European Union Health and Food Safety Scientific Committees 2014). According to Carter et al (2014), Europe's approach to synthetic biology regulation since the early 1990s has taken on a precautionary approach, a notion further asserted by Kelle (2013) and Oldham et al (2012). European regulators have directly discussed synthetic biology in emerging hard and soft law regulation (Buhk 2014; Konig et al 2016) – the results of which will be discussed below in 'Regulation Mechanisms of the European Union'. For now, however, it is important to note that synthetic biology is a research topic that has been discussed by regulators and policymakers within Europe as a technology that incurs both potential benefits as well as possible risks to human and environmental health – including for pharmaceutical research (Buhk 2014; Kelle 2013).

For the remainder of this chapter, discussion will center on findings from the collective literature review and interview discourse analysis for the topics of synthetic biology risk and regulation, respectively. As with Chapters 4 and 6, discourse findings will be elicited solely from experts within the specific case identified here, with this particular case focusing on the European Union.

5.4 Perceptions of Health Risk for Synthetic Biology Pharmaceutical Products by European Respondents

Like their counterparts in the United States, respondents (n=9) from the European Union were asked to provide their perceptions and beliefs about whether they believed that novel risks related to the exposure of synthetic DNA to humans and the environment, the mechanisms that drive such novel risks to occur, and where along the life cycle of a synthetic biology pharmaceutical such risks might materialize. Likewise, discussion within literature was used to derive interview questions and guide discussion in a manner that reflects (i) expert perception of synthetic biology biosafety and biosecurity risks, (ii) how and where do such risks occur along a pharmaceutical's life cycle, (iii) what hard and soft law regulatory structures currently cover these products and their development, and (iv) what limitations and weaknesses, if any, exist within these existing structures? A breakdown of respondent types is noted below in Table 7.

As with Chapter 4, interview respondents in this chapter have a PhD-level education in biology, chemistry, or similar field in science, or have a PhD in a social science background pertinent to the risk analysis and regulation of emerging technologies. Such interviewees also had a formal position of employment at a European Union institution at the time of interview, such as with a post doctorate or research professorship at a European Union university or a position at a European Union company.

Table 7. Breakdown of Research Backgrounds of Europe Respondents			
	Lab Research	Social Science/Implications	Total
Academia	1	1	2
Government	1	1	2
Industry	2	1	3
NGO	1	1	2
Total	5	4	9

Table 7. Breakdown of Research Backgrounds of Europe Respondents. 'Lab Research' includes those respondents who work primarily in an experimental, laboratory-driven setting. 'Social Science/Implications' includes those respondents who work outside the lab and comment upon risk and regulatory needs for synthetic biology.

5.4.1 *General Perceptions of Novel Health Risk*

Looking first at general opinions of the likelihood of novel health risk to occur, EU-based respondents all indicated that such risks were possible, albeit with varying degrees of probability. The largest contingent of responses included those experts who argued that there exists more than a limited possibility that novel health risk could occur, yet such events may not be common or occur frequently outside of uncommon events. EU Respondent 5 (Social Scientist) argued that "while it's hard to say definitively that there will be novel concerns, it's pretty plausible that human, animal, and environmental organisms […] could be at risk of acute health harms." EU Respondent 6 (Lab Researcher) stated that "There are a variety of scenarios where these genetically engineered compounds could create risky exposure scenarios […] although the consequences of these events may not be as severe as one could imagine at present." When asked why they held such an opinion, the EU Respondent 6 (Lab Researcher)

replied by saying “we just can’t rule these risks out yet, either in the form of accidents or deliberate attempts to use the technology in a harmful manner […]. If synthetic biology takes off and becomes widespread in use, so too do the chances that we’ll see reports of risky events with exposure pathways and health consequences that we haven’t really seen before.”

One respondent expressed a similar view, yet generally noted how the chances of such risky events to occur would become far more common due to concerns of containing novel biological material inside an area that it will not proliferate unintentionally within the natural environment. EU Respondent 7 (Lab Researcher) stated that “particularly within the environment, there’s a strong chance we’ll see these organisms multiplying in various environments unless oversight is particularly strict with controlling their release and disposing of waste materials.” While the EU Respondent 7 (Lab Researcher) did argue that “there are technological improvements that could limit or eliminate the potential for such risks to occur” for the technology’s current development, “these control technologies are in their early stages and aren’t too useful yet.”

Respondents who scored ‘2’ and ‘3’ were less certain about the potential consequences of such risks should they arise, with some arguing that “the consequences could be environmentally significant or damaging on a cellular level”, while others noted that “highly consequential events may be rare […] and depend highly on the type of pharmaceutical you’re proposing.” This degree of uncertainty is consistent with discussion in Bates et al (2015), which found that respondents were generally uncertain of the health consequences of such risk events, with respondents noting a wide range of possibilities. Further, respondents in this and the other two cases discussed in this dissertation noted the importance of the type of pharmaceutical proposed relative to the degree of risk consequences that may be observed, where pharmaceuticals with novel genetic material in the commercial product (as with an engineered probiotic) or an engineered vaccine with live and genetically altered virus material would be significantly riskier than products undergoing research today (the production of artificial artemisinic acid or using yeast to facilitate the growth of influenza vaccine material).

A third contingent of respondents (3) did differ slightly from other interviewees by arguing that while such novel risk is possible, such events will be rare and may be eliminated

through various improvements to circuit and metabolic engineering in the years to come. EU Respondent 8 (Lab Researcher) likened such a scenario to "a red herring in the midst of valuable research", where although it is impossible to entirely rule out the potential for such risks to arise, "the odds are implausibly small that novel risk events should happen." EU Respondent 9 (Lab Researcher) articulated their belief from a different angle, arguing that "we have not really experienced any serious and recurring [novel] risk to human health from similar research related to GMO, and it would be unfair to negatively hype up such risks until there's a proven scientific reason to be worried about them." However, EU Respondent 9 (Lab Researcher) did note that such hype "is likely to develop, and somewhat already has on elements of the blogosphere." The collective opinion amongst respondents here is that, while such risks are *plausible,* there are no good reasons to think that their probability is likely. Similarly, respondents here were skeptical of the potential consequences of such risk events, where "those exposed to such materials may not even experience noticeable side effects […] and the engineered cells may die off too quickly for something like gene transfer to occur."

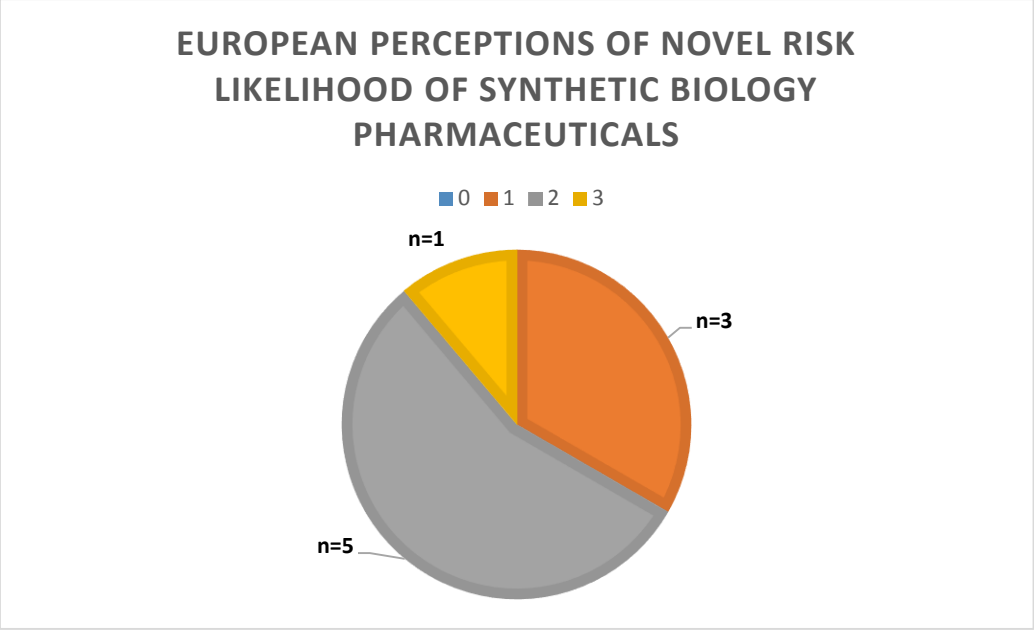

Figure 10. European Perceptions of Synthetic Biology Pharmaceutical Health Risks. Responses are coded on a scale from 0-3, where increasing values indicate greater likelihood of novel health risk. 0 = no novel health risk; 1 = possible but proportionally limited novel health risk; 2 = moderate chance of novel health risk across large populations; 3 = guaranteed novel health risk (n=9)

After offering their general perceptions of the probability that novel risk events would occur within the scope of synthetic biology pharmaceutical development, respondents were next asked to describe the mechanisms by which such novel risks could arise and cause potential harms to human and environmental health. A recurring mode of discussion included horizontal gene transfer, with respondents noting various opinions on the probability that such an event could occur where artificial genetic material from the engineered pharmaceutical could transfer artificial DNA into human, animal, or natural environmental cells (described in Keese 2008; Dröge et al 1998).

While all respondents did note that the probabilities of such an event occurring are difficult to track and generally rare events (also described in Heinemann and Traavik 2004), seven of nine respondents noted that these risks cannot be dismissed just because they are unlikely to occur. EU Respondent 5 (Social Scientist) argued that "the probabilities may be small, but horizontal gene transfer could produce dramatic effects to humans and the environment, […] and should be considered for mass produced products like pharmaceuticals." On the other side of the argument, EU Respondent 9 (Lab Researcher) stated that "the risks of a horizontal gene transfer event happening are quite low, and made essentially improbable by certain genetic controls within engineered cells."

Other respondents noted that engineering capabilities to prevent the potential of horizontal gene transfer by (a) preventing engineered cell colonies from growing beyond certain population counts, or (b) self-destructing if the cell moves outside of a contained filed can reduce the potential for horizontal gene transfer even further, although EU Respondent 2 (Lab Researcher) argued that "it's uncertain whether existing scientific capabilities are developed enough to control horizontal gene transfer with efficiency, or whether mutations within engineered cells could become problematic within the pharmaceutical's life cycle." Overall, respondents agreed that the potential for gene transfer is low and could be further mitigated through engineering controls, yet disagreed on the capability of such controls to allow regulators to entirely rule of gene transfer from engineered cells to human hosts and the environment.

Other discussed risk considerations included the potential for unintentional environmental releases of artificial organisms into the natural environment, as well as the potential for synthetic biology research to be used in a manner that could directly or indirectly produce harmful diseases or viruses to humans and animals. For the former, respondents noted the potential for pharmaceutical material with novel genetic information to proliferate within the environment via improper containment and disposal of such materials by medical professionals or consumers. Further discussed in Konig (2016), Redford et al (2013), and Jeschke et al (2013), the concern of such proliferation is that engineered microorganisms could upset local ecosystems and negatively impact biodiversity in a given area by competing for resources with naturally-derived competitors, which could cause permanent changes in ecosystem health. For the latter, respondents discussed the potential for dual-use synthetic biology research to potentially enable nefarious groups or individuals to make use of developing knowledge of synthetic biology processes to manipulate viruses or bacteria to produce harmful mutations in such organisms with the intention of delivering negative health consequences to humans, animals, or the environment (see also Konig et al 2016 and Kelle 2013). Such dual-use concerns are discussed further below as a 'biosecurity' risk concern.

5.4.2 Discussion of Biosafety and Biosecurity Risk

With these general perceptions of synthetic biology pharmaceutical novel health risk, respondents were next asked to offer their opinions on two important considerations within European and international regulation of synthetic biology, including (i) biosafety and (ii) biosecurity (Schmidt 2008; Serrano 2007; Kelle 2009 Starkbaum et al 2015). Below, Figure 11 includes responses from the nine experts interviewed solely for this dissertation research.

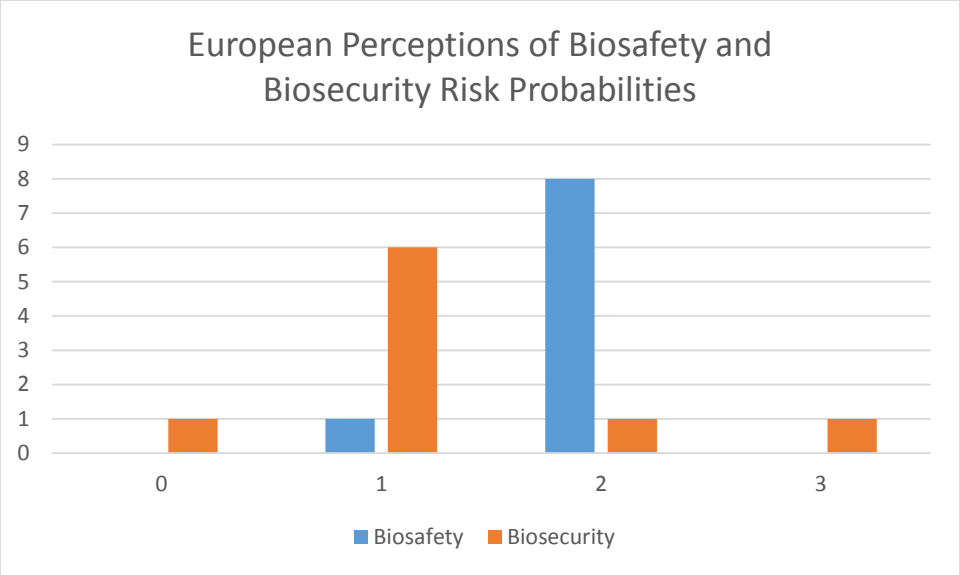

Figure 11 European Perceptions of Synthetic Biology Pharmaceutical Risks Associated with Biosafety and Biosecurity. Responses are coded on a scale from 0-3, where increasing values indicate greater likelihood of novel health risk. 0 = no novel health risk; 1 = possible but proportionally limited novel health risk; 2 = likely health risk; 3 = guaranteed novel health risk (n=9)

Looking first at biosafety, 8 of 9 respondents viewed the potential for accidental release and exposure scenarios to be the primary umbrella of risk events that could generate novel health hazards to human and natural environmental organisms. In this way, eight of nine surveyed respondents articulated a belief that somewhere along the life cycle of a synthetic biology pharmaceutical, there exists a somewhat likely potential for a novel risk event to occur, with such scenarios including failures in lab safety and exposure to scientists and staff within early stage research, a potential for novel genetic material to accidentally be released from the lab to proliferate in the environment, and improper storage and disposal of relevant pharmaceutical materials, among others.

Within this topic, respondents noted that while laboratory safety standards are generally robust in their ability to prevent the release of novel genetic material, although they did note that accidental release events are still plausible – particularly as the technology becomes more commercially available for pharmaceutical companies and for other uses as well (Schmidt and de Lorenzo 2012). EU Respondent 5 (Social Scientist) stated that "a lot of this risk potential is going to stem from the restrictions placed upon syn bio research […] like with how it must be stored, who has access, and whether materials will be used outside a secure lab. Right

now, it's probably too soon to tell how this will end up, making biosafety risk tricky to ignore or dismiss outright." In a similar vein, EU Respondent 4 (Social Scientist) argued that "there are lots of limiting factors to prevent biosafety risk […] such as with reporting and oversight by regulatory authorities, […] but the potential for accidents and release scenarios makes synthetic biology a potential driver of novel biosafety risk, particularly to the environment." Overall, EU-based respondents collectively argued that novel synthetic biology pharmaceutical biosafety risks have a significant probability of occurrence due to "the high potential for accidental exposure, lax lab safety, and poor packaging and disposal of synthetic biology drugs and vaccines."

With respect to the target of potential novel health risks, respondents expressed a greater degree of general concern for environmental rather than human biosafety hazards. Such concerns are regulated Union-wide by the European Medicines Agency (EMA), which can provide guidance for the protection of animal and human health from pharmaceutical products while also harmonizing the differing medicinal regulatory authorities in Member States (Gøtzsche and Jørgensen 2011; Trotta et al 2011). However, the EMA lacks centralized authority over the medicinal regulatory process, where such abilities are reserved to Member State regulatory bodies (Trotta et al 2011). As such, the EMA can offer advice and review emerging medicinal products for quality, safety, and efficacy, yet lacks the authority such as with the United States' Food and Drug Administration to establish hard law that is legally binding for Member States to follow (Regnstrom et al 2010; Isaac et al 2011).

Speaking to perceptions of environmental health risk, EU Respondent 3 (Social Scientist) explained this position where "it is likely that these [synthetic biology] drugs will be improperly disposed of, making it possible for artificial genetic material to reach the environment." Agreeing with this position, EU Respondent 7 (Lab Researcher) discussed how "we're already seeing harmful levels of conventional drugs in waterways and in the environment, generating harms to plant and animal life. […] I don't think we can rule out synthetic biology drugs and vaccines from such scenarios yet." When polled about potential human health concerns, respondents were less concerned, with EU Respondent 6 (Lab Researcher) arguing that "clinical trials and testing for premarket approval is pretty robust [across the European Union], and the

only real concern for humans would be off-label and improper use as well as pre-clinical trial testing early on." EU Respondent 8 (Lab Researcher) stated even more plainly that "clinical trials and drug testing is sort of a black box for pharmaceuticals, […] we only have to be particularly concerned with potential health risks before and during the testing." Most respondents (7 of 9) agreed, yet 6 of 9 did note that it is important to review the potential for harmful side effects associated with vaccine or pharmaceutical use (discussed further in the discussion of pharmaceutical life cycle risk below).

In general, however, EU-based respondents argued that opportunities for novel genetic material to enter the environment (where such concerns require oversight by Directorate-General for Health and Food Safety and its Scientific Committees) may pose as a more likely risk in the immediate term, the mechanisms of which include concerns of horizontal gene transfer, biopersistence as an invasive species, and the potential for health consequences of the novel genetic material upon a non-target organism (concerns consistent with those general items raised by the European Commission Scientific Committees in May 2015). Of these, horizontal gene transfer was seen as the least likely, with EU Respondent 5 (Social Scientist) indicating that "we can already program cells to prevent gene transfer, which will become more efficient and sophisticated as the science evolves." Likewise, EU Respondent 9 (Lab Researcher) argued that "the chances of horizontal gene transfer occurring in a manner that generates serious health complications is incredibly minute." However, several respondents did argue that horizontal gene transfer had the potential for particularly harmful risk outcomes, with EU Respondent 2 (Lab Researcher) noting that "while unlikely, horizontal gene transfer could trigger harmful and uncontrollable genetic mutations in a non-target organism that might have the potential to negatively affect animal and plant life by subjecting them to harmful mutation and other side effects."

For biopersistence, respondents noted that the probability of novel genetic material proliferating in the environment is currently unlikely given the current state of the technology, yet is a future concern that is likely to challenge regulators in their attempts to protect the natural environment. EU Respondent 2 (Lab Researcher) argued that "while cells with artificial DNA aren't likely to multiply in the natural environment without a lot of help in their current

state, as these cells become more biologically resilient and are able to survive outside of a contained environment, the issue of persistence is one that we'll have to be worried about." The main concern of biopersistence was noted by EU Respondent 4 (Social Scientist) as "synthetic biology materials becoming an invasive species", where such materials could disrupt the local ecosystem (European Commission Scientific Committees 2015). Such concerns are described by respondents as unlikely to materialize soon due to the inability of synthetic biology cells to survive independent of a controlled environment, yet would become a greater issue as the cells become more capable of surviving outside of a laboratory setting.

Lastly, non-target exposure and the harmful consequences thereof were viewed as the most likely biosafety concern at present, where substances containing novel genetic material have multiple avenues of exposure to the natural environment. EU Respondent 5 (Social Scientist) noted that "we could see cases of unintended exposure before and after clinical trials – but particularly in cases of by-product waste and disposal – making exposure scenarios likely as the technology comes to market." Unintended exposure was argued by EU Respondent 2 (Lab Researcher) as "causing various potential health problems with plant or animal life that could impair quality of life and potentially cause death." When asked to explain this point, EU Respondent 2 (Lab Researcher) further discussed that "exposure of pharmaceuticals with novel genetic material to an unintended plant or animal host could cause acute reactions that could range from relatively unnoticeable and maybe mildly irritating to quite painful in manner […], a similar process as with traditional chemical exposure."

Related to this point, The European Commissions' Scientific Committees used their authority to provide the European Commission with independent scientific advice on emerging scientific concerns to discuss potential biosafety concerns pertaining to synthetic biology. Specifically, the Committees noted in their 2015 report that such risks are of particular concern to European regulators, with a major issue centering on the ability of scientists to contain novel genetic material via a variety of physical barriers (European Commission Scientific Committees 2015). However, EU Respondent 2 (Lab Researcher) argued that "barriers and control mechanisms for lab safety will likely eventually fail to prevent an exposure scenario – the only question is how bad the health consequences will be." For now, the Scientific Committees

argued similarly to these interview respondents that the consequences of such risks are difficult to estimate at present, yet direct field and laboratory trials would be necessary to accurately gauge the risk consequences of such novel genetic material on specific plant and animal species (European Commission Scientific Committees 2015).

Looking next at biosecurity risks, most respondents (7 of 9) argued that the potential for synthetic biology research capabilities to be used for a deliberately harmful product are unlikely, although 8 of 9 did note that the concerns raised via the 'dual-use' dilemma noted in White et al (2015), Edwards (2014), and Marris et al (2014). Of particular concern here includes both the maturation and development of the 'do-it-yourself' synthetic biology movement such as with the International Genetically Engineered Machine (iGEM) competition, as well as the spread of genetic engineering research and technological processes outside of secure laboratories and stringent government oversight that, in some instances, may enable a nefarious actor to deliberately construct and engineer an organism to deliver harms to human, animal, or environmental health (Vogel 2014; Jefferson et al 2015; Perkins and Nordmann 2012). While most respondents (8 of 9) did note that biosecurity risks are probabilistically plausible, 7 of 9 argued that such risks are highly unlikely due to the difficulties and technological limitations such a nefarious actor would face in their attempt to foster harmful material with novel genetic information. EU Respondent 8 (Lab Researcher) in particular argued that such risks were highly unlikely, where they stated that "accidental release is far more likely, because there are too many oversight checks, resource requirements, and scientific capabilities needed to build an organism that could do real damage."

The general sentiment of oversight, resource requirements, and technological limitations serving as a barrier to biosecurity risk arose in 7 of 9 European interviews. For oversight, EU Respondent 3 (Social Scientist) stated that "various governmental and lab-based oversight mechanisms would prevent someone from abusing resources to make a harmful organism. […] This task would take a considerable amount of time, increasing the likelihood for the perpetrator to get caught." Likewise for resource requirements, EU Respondent 1 (Social Scientist) argued that "it'd be difficult for someone to pull this off [a biosecurity threat] without a well-stocked lab and the participation and help of knowledgeable scientists", where the

hypothetical researcher would generally be hard-pressed to engineer a virus or construct a harmful pathogen in a limited amount of time and in a manner that would yield actual health hazards. Lastly, respondents argued that synthetic biology capabilities at current were limited in their ability to allow scientists to engineer and control virus and bacteria information in a manner necessary to generate a biosecurity threat. EU Respondent 9 (Lab Researcher) stated that "This will become more plausible in the future, but for now it's currently difficult to get a cell to behave in a specific manner in a general sense, let alone for a virus or engineered disease." Overall, while biosafety risks were viewed as plausible yet generally unlikely, biosecurity was generally viewed with skepticism in the field's existing state given the various limitations an actor would have to overcome to make such a threat possible. However, 8 of 9 respondents did note that such risks will be more concerning in the future, and require the consideration of regulators in order to ensure that existing regulation is capable of reviewing research material for comparison with known pathogens as well as monitor various 'do-it-yourself' activities as with iGEM and Kickstarter for unlikely yet plausible biosecurity threats (Bar-Yam et al 2012).

5.4.3 Pharmaceutical Product Risk Across Life Cycle

After general discussion of biosafety and biosecurity risks for synthetic biology pharmaceutical products, respondents were next asked to describe the probabilities of novel biosafety risks to occur at various stages of the pharmaceutical's life cycle. Figure 12 (below) indicates the different viewpoints of such risks from the nine experts targeted for interview. Overall, respondents tended to argue a greater concern for the probability of novel risk in the 'End-of-Life' and 'Research' life cycle stages, respectively. Likewise, respondents offered a mixed opinion on the perception of health risk for the 'Manufacturing' and 'Commercialization' life cycle stages, with some respondents (n=5 and n=4, respectively) describing the plausibility of novel risk events happening at these stages while others noted that such events are rare or are preventable with existing technological and oversight mechanisms. Discussion for each of these life cycle stages are covered further below.

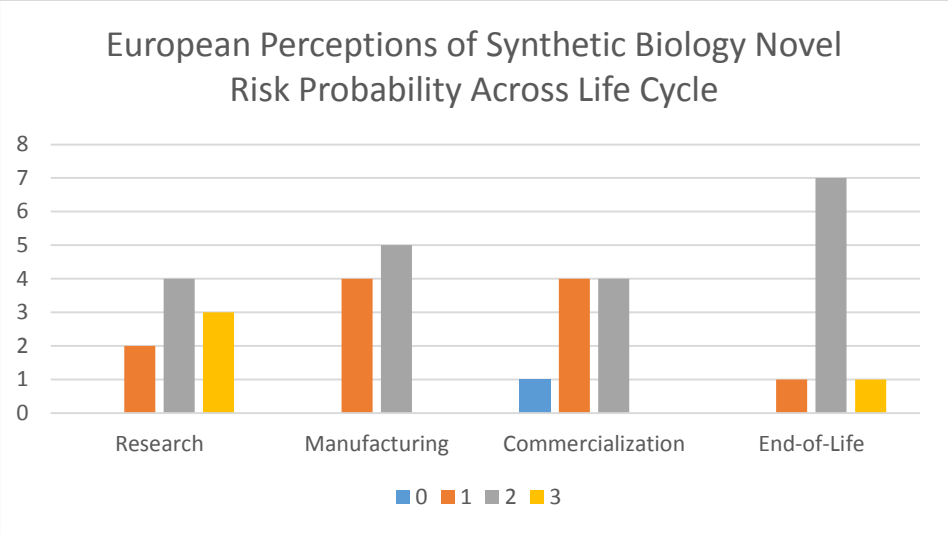

Figure 12. European Perceptions of Synthetic Biology Pharmaceutical Biosafety Risks Across Product Life Cycle. Blue = No Risk; Orange = Unlikely yet Possible Risk; Gray = Moderately Possible Risk; Yellow = Likely Risk (n=9)

For the End-of-Life life cycle stage, all respondents noted the potential for novel risk events to occur upon the disposal and containment of synthetic biology pharmaceuticals. A significant point raised at the onset of most conversations included the differentiation between those products that contain novel genetic material as opposed to those without novel genetic material in the end product, where respondents argued that only those products containing novel genetic material within their end-product can produce novel health risks at the End-of-Life life cycle stage to humans and the environment. However, for those pharmaceutical products which do contain novel genetic material in their end-product, most respondents (8 of 9) noted the potential for improperly disposed or contained to reach natural environmental sources, with particular emphasis on such novel biological material entering into the water table. Where conventional pharmaceuticals such as with ibuprofen, ciproflaxin, or warfarin have already been noted as contaminating rivers, lakes, and other drinking water sources (see Mompelat et al 2009), a concern amongst several respondents is that novel genetic material may also persist within public water sources and be carried into the natural environment and gain exposure to various plant and animal life – and potentially yield harmful health consequences as a result. EU Respondent 7 (Lab Researcher) argued that "particularly for areas with unreliable or outdated treatment plants […] it's likely that synthetic DNA and similar

genetic material will enter into the natural environment as such pharmaceuticals become more widely available." EU Respondent 6 (Lab Researcher) credited this relatively high likelihood due to "improper use and disposal of pharmaceuticals and pharma-byproducts", where consumers are likely to misuse or dispose of various pharmaceuticals for a variety of applications (Mompelat et al 2009). Overall, EU Respondent 4 (Social Scientist) summed up this discussion where they argued that such a risk scenario is "an inevitability", where "novel DNA is going to gain exposure to the environment and outside of the oversight of regulatory authorities and clean-up crews."

While these respondents argued that risks at the End-of-Life life cycle stage are fairly likely to occur, they disagreed on the health endpoints that could arise from such exposure events. As noted in the discussion of general biosafety risk above, respondents argued that biosafety concerns such as with horizontal gene transfer or biopersistence were unlikely given the limited probability of these events occurring, yet also argued the health risks of such events were potentially significant and could yield acute health concerns to humans, animals, and plant life (European Commission Scientific Committees 2015). On the other hand, EU Respondent 8 (Lab Researcher) contended that "even if such events do occur, there's no guarantee that a novel hazard would arise, or that the novel genetic information would have anything to do with the incurred health hazard." EU Respondent 4 (Social Scientist) addressed this point by noting that "the consequences of end-of-life health hazards are case dependent, where some products would have a significantly greater chance of yielding harms than others."

Similar to the End-of-Life life cycle stage, 7 of 9 European Union-based respondents viewed the 'Research' stage as being an area of particular concern relative to the probability of occurrence for synthetic biology novel health risks. EU Respondent 9 (Lab Researcher) argued that "At the research stage, we have to be concerned with opportunities of exposure of novel genetic material with laboratory researchers and their assistants, particularly when oversight is limited and high risk material is involved." Asked to explain their meaning behind 'high risk material', EU Respondent 9 (Lab Researcher) further stated that "experiments involving viral components or other microorganisms with a known potential to harm human or environmental health will likely pose significant concerns to synthetic biology regulators [in the respective

Member States]." EU Respondent 2 (Lab Researcher) further stated that "there's greater uncertainty at the research stage, because a lot of this experimental material is untested, and a more synthetic organism would have little to draw comparisons with from a biosafety perspective."

This is consistent with claims levied by Konig et al (2016), Tucker (2011), and Carter et al (2014), which indicate that particularly for instances where researchers seek to manipulate increasingly artificial genetic material, researchers have the potential to exposure themselves to novel genetic material that could cause acute health hazards as well as the potential for horizontal gene transfer. EU Respondent 9 (Lab Researcher) further argued that "the consequences of such events are serious enough that we'll need to monitor whether existing regulation covers synthetic biology, but I doubt the probabilities of novel risk events are high given existing biosafety protocols for GMOs and the physical barriers required to contain such material." For human health risk, respondents generally agreed with the points raised here that the potential consequences of novel health risks at the Research stage are quite high, they also generally argued that the probability for such events to occur are quite low due to existing oversight and conventional containment procedures that have already been used for GMO research in Europe. EU Respondent 5 (Social Scientist) summed up this argument by noting that "Novel risk here [in the Research stage] is possible, but generally unlikely with proper biosafety protocol. However, as the technology becomes more widely available and these protections are less available, these risks may become more likely and problematic."

A further point of discussion raised for the Research life cycle phase includes concerns related to environmental health risks, with particular emphasis on the potential for genetically engineered microorganisms escaping containment in a research lab and proliferating in the environment. The focus here was particularly on laboratory accidents with increasingly synthetic bacteria cells, described by Moe-Behrens et al (2014) and Pei et al (2012) as biosafety risk situations with potentially challenging outcomes for ecosystem health and biodiversity. EU Respondent 1 (Social Scientist) articulated that "Europe has been concerned with environmental effects of accidental releases of GMOs, and synthetic biology could be the latest, albeit potentially more dangerous, manifestation of this." When asked to explain this point, EU

Respondent 1 (Social Scientist) replied "Engineered microorganisms would enter the environment and potentially impact the ecosystem by competing with natural organisms for sustenance and the ability to procreate […], which could have harmful effects for an area's biodiversity."

Other respondents noted the potential risks associated with horizontal gene transfer during breaches in containment by early-stage research material as having potentially harmful consequences, but also argued that "the chances of gene transfer are pretty slim to occur with existing technology." For now, the greater concern raised by these respondents centered on whether or not a microorganism with a significant degree of artificial DNA could proliferate in the environment and upset the local ecosystem via acute health risk and chronic effects for biodiversity (see also Marliere 2009). EU Respondent 5 (Social Scientist) noted that "as these cells become more robust and capable of surviving outside of a contained environment, these scenarios become more plausible, and make proper containment even more important."

While not viewed collectively as problematic as the End-of-Life and Research life cycle stages, European Union-based respondents did note the potential for novel health risk at the 'Manufacturing' stage. Konig et al (2016), Giese and von Gleich (2015), and de Lorenzo (2010) all indicate that the novel health risk scenarios at the mass production stage of synthetic biology development are generally limited and currently conventional in scope due to the limited degree of 'synthetic-ness' associated with engineered cells – a sentiment held by most respondents (5 of 9) here. In general, interview discussion indicated that while there exists some potential for manufacturers (those working in biological production plants) to be exposed to novel genetic material and/or such genetic material is able to escape containment and gain exposure to the environment, respondents generally argued that the potential for *novel* health risk was limited. EU Respondent 8 (Lab Researcher) noted that "the risk here is more of a conventional nature in terms of proper production and containment of biological material, and where the novel risk scenario would be something like gene transfer from a breach in containment, which is generally unlikely given the state of the science." EU Respondent 8 (Lab Researcher) further stated that "oversight and containment regulation for manufacturers in Europe are pretty robust when it comes to GMOs, and I don't see synthetic biology being much

different or challenging biosafety regulations [2009/41/EC] in a manner that makes new risk likely […] particularly when the pharma products under production have been engineered to limit their potential for gene transfer and exposure effects."

Of greater concern to respondents included the potential for environmental health risk in a manner similar to that described in the Research life cycle stage, EU Respondent 4 (Social Scientist) argued that "the proper handling of biomaterial with novel DNA and containment of by-product waste during manufacturing could contribute to an environmental release scenario with potentially damaging effects to biodiversity." While respondents further argued that such risks scenarios are currently unlikely, they are likely to increase in probability as the technology spreads beyond sophisticated laboratories and well-resourced corporate research facilities in favor of those organizations with less history and familiarity with GMO biosafety protocol. In a statement consistent with Marliere (2009), EU Respondent 3 (Social Scientist) noted that "the potential for accidents or improper storage and disposal of manufacturing waste and novel genetic material increases as new players for genetic engineering emerge, with my concern leaning towards those organizations with limited premarket oversight in their product development." However, EU Respondent 3 (Social Scientist) concluded their statement on manufacturing risk by indicating that "current governance gives the European Union enough premarket approval over drug development that these risks should be mitigated, although this may change as synthetic biology research allows researchers to make cells with increasingly artificial DNA."

Lastly, respondents argued that the 'Commercial' life cycle stage was the area with the least probability of novel health risk to arise to human and environmental health. As EU Respondent 8 (Lab Researcher) argues, this is due to the fact that "there isn't any novel genetic material that goes into the consumed drug, where synthetic biology is primarily the production process to make conventional parts to pharmaceuticals like with artemisinic acid for malaria treatments." EU Respondent 6 (Lab Researcher) argued that "as new syn bio pharmaceuticals enter the market, they'll have been engineered in a manner that controls for novel health risks, and tested within clinical trials to view the odds that these events arise – so it's unlikely to see such events occur very often."

When asked to think of more futuristic products such as with an engineered probiotic with fully synthetic DNA intended for use in the human gut, respondents became a bit more concerned at the risk potential, where "novel DNA would then have a route of exposure to humans *in vivo.*" For such cases, respondents argued that novel health risk would be more uncertain, where high risk, low probability events such as horizontal gene transfer may arise at the commercial stage that had not previously been viewed in clinical trials (see also Heinemann and Traavik 2004). On this subject, EU Respondent 6 (Lab Researcher) noted that "for drugs that actually contain synthetic DNA like with viral material in vaccines, the potential for side effects is likely greater, although whether this contributes to novel health risk in the manner of horizontal gene transfer is less certain. Possible, but hard to tell currently."

5.5 Regulatory Mechanisms within the European Union

After discussing perceptions of synthetic biology pharmaceutical risks and benefits, respondents were next asked to offer their views and expertise regarding (i) the hard and soft law regulatory authorities applicable to synthetic biology research, and (ii) discussion of weakness and limitations of such regulation as they apply to pharmaceutical research. This exercise is important in order to determine existing capabilities to cover synthetic biology research and development while also indicating potential loopholes or areas of concern where regulatory guidance and best practices are unable to appropriately govern synthetic biology research.

5.5.1 Respondent Discussion of European Regulation of Synthetic Biology Products

After reviewing the regulatory authorities pertinent to European regulation of synthetic biology products (see Section 5.2.2 for more information), respondents were asked to identify the laws and regulatory bodies in a manner similar to Kelle (2009). As noted in Chapter 4.2, each of the 9 interviewed respondents were able to identify, without prompting, either a regulation or regulatory body involved within synthetic biology regulation, with three respondents noting able to identify and both. Figure 13 below indicates that such identification was greatest with the ability of respondents to identify a regulatory body within their given

state or within the European Union proper, with 7 of 9 being able to do so. These respondents were able to provide specific descriptions regarding the responsibilities and powers held by such authorities relative to the process of synthetic biology development. Likewise, 5 of 9 were able to identify and describe the major statutes, regulations, and guidance noted in Bar-Yam et al (2012) as issued by the European Commission.

A significant point raised within the course of European interviews included the notion that "it is important to account for regulation in the European Union, and within the individual Member States." In this way, Directives are discussed and voted on by the European Commission proper, which are then often implemented by individual Member States (Buhk 2014; Bar-Yam et al 2012). Pan-European Bodies such as the European Medicines Agency can review concerns and call for shifts in regulatory policy, yet the responsibility of carrying out such regulation generally remains with relevant domestic authorities for each Member State (European Commission Scientific Committees 2014). As such, respondents often identified their own domestic regulatory authorities yet also discussed awareness of pan-European synthetic biology regulation (where possible).

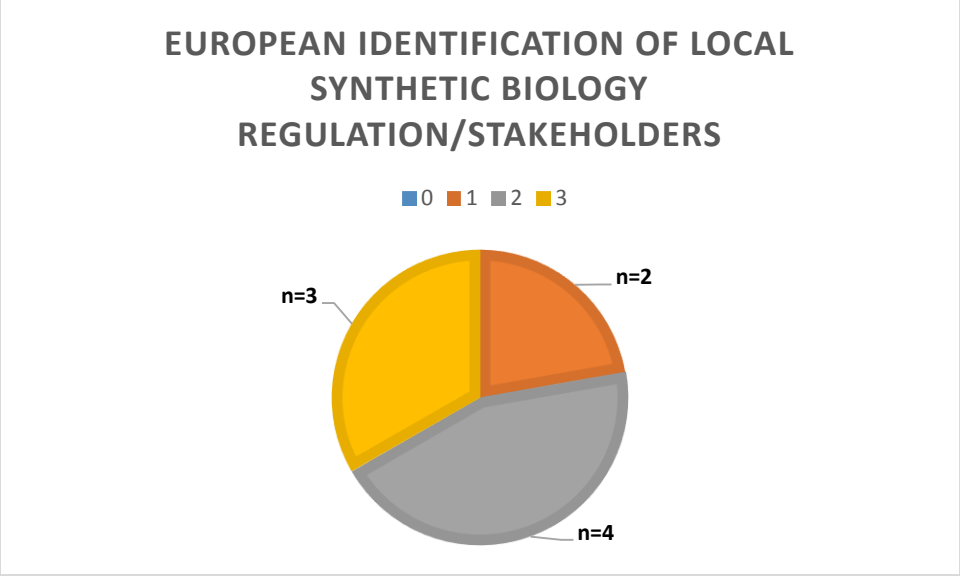

Figure 13. Familiarity and Recognition of Synthetic Biology Regulation by European Respondents. 0 = no recognition, 1 = recognition of a piece of hard/soft law regulation but not an agency, 2 = vice versa, 3 = recognition of both hard/soft law regulation and relevant agencies (n=9_

A tangential yet important inquiry asked of each interview respondent included respondent perceptions of when synthetic biology pharmaceutical products would reach

commercialization. As noted in Chapter 4.2, such responses serve only as 'best guesses' by respondents, and should not be taken for more than an academic exercise to gain a general idea of what we may expect relative to the development of synthetic biology products in the European Union in the future. As such, the responses provided below should not be taken as an assessment of a concrete timeline for commercialization.

Figure 14 below includes a summary of such responses, with European Union-based respondents being divided with respect to when products containing novel genetic material as with engineered vaccines or advanced therapeutics would enter the market, with equal proportions arguing for greater than ten years and between five and ten years, respectively. For the former, EU Respondent 7 (Lab Researcher) noted that "we're making strides towards early syn-bio drugs, but more advanced pharmaceuticals or even vaccines using genetically altered DNA are currently beyond the scope of most research trials that I know of." Similarly, EU Respondent 1 (Social Scientist) argued that "no heavily engineered syn-bio drugs are currently undergoing clinical trials […] so you have to account for the time delay for regulatory approval prior to commercialization."

For the latter, four respondents argued that emerging pharmaceutical applications of synthetic biology research will push companies and universities to derive increasingly synthetic genetic information for use in drugs and vaccines for various purposes, but particularly for those diseases with limited options for treatment or vaccination. EU Respondent 4 (Social Scientist) noted that "there are a variety of medical challenges to public health that synthetic biology may be uniquely able to address […] like Ebola, malaria, or dengue fever." Synthetic biology has also been described in literature as a tool to address neglected diseases with no known cure, treatment, or vaccine, and are scientifically difficult to resolve (Van Den Belt 2013; Tucker and Zilinskas 2006). In this vein, EU Respondent 4 (Social Scientist) further argued that "the breakthroughs that synthetic biology could offer will cause research to accelerate within the next few years […] making commercialization a lot sooner than you'd think."

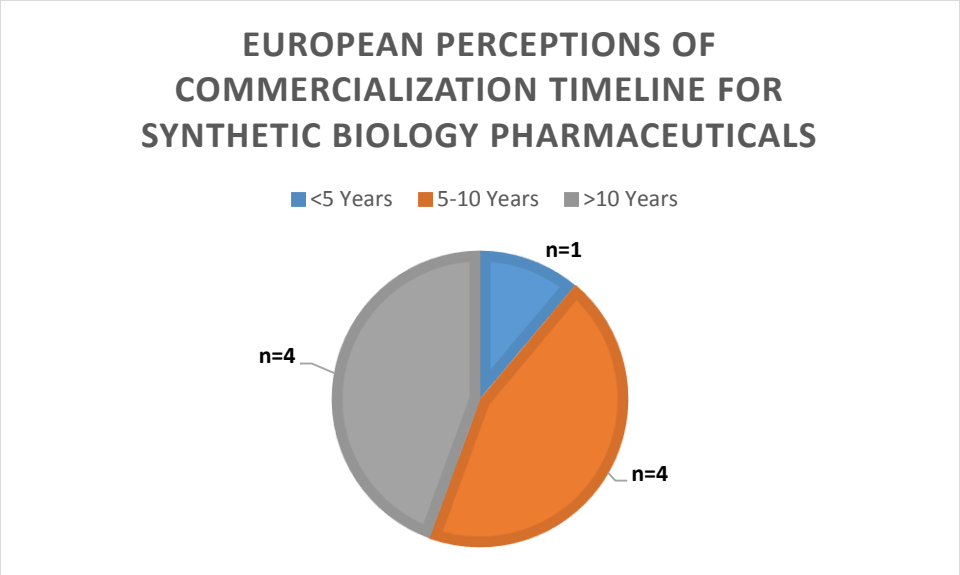

Figure 14. European Perceptions of Distance in Time for Synthetic Biology Products to Enter Marketplace (from December 2014; n = 9)

5.5.3 Evaluating Existing Regulatory Capabilities within the European Union

After gaining an understanding of both the regulations and regulatory bodies responsible for synthetic biology regulation in Europe, this section includes those comments made by European interview respondents on the subject of whether or not such regulation is capable of covering synthetic biology research and development, and if not, where further improvements or extensions of regulation are needed in order to mitigate novel health risk while also allowing the technology to develop in an efficient and helpful manner (Mandel et al 2014). Discussion was framed around concerns for biosafety and biosecurity concerns stemming from research around synthetic biology pharmaceuticals.

The concern over the future direction of synthetic biology research and the capability to foster fully synthetic organisms served as the greatest concern raised by interviewees relative to the ability of existing regulatory instruments to capture the technology's potential novel risks. EU Respondent 3 (Social Scientist) argued that "[European] governance of immediate future technologies is robust, but future developments may challenge regulation. […] This is because of the current dependencies of comparative risk analysis with similar non-GMO alternatives to the proposed product." This sentiment is further established in Pauwels et al

(2013), which indicated that existing biosafety regulation geared towards synthetic biology product testing and preapproval is centered on a comparative risk analysis with a known history of safe use with proper production, management, and disposal protocols.

Given this general requirement as within Directive 90/220/EEC, EU Respondent 3 (Social Scientist) further argued that "we will need a risk assessment protocol to review synthetic organisms with few parallels to conventional organisms […], something that we currently lack and may find difficult to accomplish." Likewise, EU Respondent 8 (Lab Researcher) stated that "existing technological capabilities generally use well-known cellular inputs and components similar to natural cells, which would not be the case for a more fully synthetic cell." EU Respondent 8 (Lab Researcher) continued by concluding that "biosafety governance will run into trouble here [for cases of increasingly synthetic cells], as it will be difficult to conduct a risk analysis for a product that we have little information about or by which to compare it to."

While most respondents (8 of 9) and noted literature generally concurred that the production of fully synthetic cells as being several years off (Blain and Szostak 2014; Stano and Luisi 2013), European regulation will eventually have to grapple with the question of how to govern fully synthetic cells which lack clear comparisons with products derived from naturally-occurring components – including offering a definition of what is and is not an organism and thereby classified as a regulated product under specific EU Directives (Konig et al 2016). Without such an alternative to quantitative and comparative risk analysis between such products on a case by case basis (Pauwels et al 2013), European regulatory protocols and requirements may hinder the further development and commercialization of potentially beneficial products as with new pharmaceuticals and vaccine components (Konig et al 2016).

An additional tangential concern raised by European interview respondents relative to biosafety includes concerns relative to controlling unintended releases of artificial genetic material, with particular emphasis on tracking the spread and effects of such materials. EU Respondent 5 (Social Scientist) noted the need for genetic 'watermarks', where they stated that "placing some identifying barcode or watermark inside the genetic code of an engineered cell may help us track the movement and consequences of biosafety events […] as well as potential cases of theft or negligent containment."

Such statements are consistent with Gibson et al (2010) and Liss et al (2012), who argued that such watermarks may collectively (i) allow investigators to quickly identify where a novel genetic organism was produced and stored, (ii) better track the spread and potential proliferation of such organisms, and (iii) provide evidence of theft of proprietary information via the watermark's identifying information. EU Respondent 4 (Social Scientist) also described the benefits of such watermarks as "reducing the potential burden of risks that we aren't as focused on currently, like with economic losses from the theft of company property and ensuring biosafety violators are accountable for their actions." While a small addition to synthetic biology regulation, Liss et al (2012) and Konig et al (2016) argue that such watermarks would be particularly helpful for high risk organisms, and would serve as another layer of containing such material and tracking its environmental proliferation in the case of containment breaches.

While European Union-based respondents only expressed particular biosafety concern over long-term technological development issues, they did note more short-term concern over biosecurity concerns related to dual-use synthetic biology innovation that could be used for deliberate harm. This is in contrast to statements by respondents that biosecurity events are unlikely, where most agreed that despite the unlikely chance of such a hazardous event, its plausibility and potentially widespread harmful consequences is enough to warrant a strengthening of regulation to protect against both 'lone-wolf' and 'group-supported' efforts at constructing harmful engineered microorganisms (Konig et al 2016; Konig et al 2014; Jefferson et al 2014; Tucker 2011). Explaining this position, EU Respondent 9 (Lab Researcher) noted that "the potential for such events are quite small, and the resource requirements for an event quite high, yet we still need to adequately protect against biosecurity events."

To address these concerns, several interview respondents noted that little compliance or control mechanisms exist to prevent the production of biological weapons using synthetic biology innovation. EU Respondent 1 (Social Scientist) stated that "International agreements like the Biological and Toxin Weapons Convention don't really have stiff control over the production and sale of bioweapons, so a separate body geared to the control of such biomaterial may be necessary in Europe." EU Respondent 5 (Social Scientist) noted that

"biosecurity is a particularly complex issue for medical applications like with pharma, and its governance needs to be relatively tight to ensure that the wrong people don't get access to synthetic biology technologies and information." EU Respondent 5 (Social Scientist) further continued agreeing with the above statement that "a separate body related to reviewing biosecurity issues is needed for certain categories of synthetic biology research, including with pharmaceuticals and drug development."

The issues raised here are consistent with discussion noted by Garfinkel et al (2007) and Tucker (2010), among others. The explicit concern for such cases was described by EU Respondent 2 (Lab Researcher) as "the possibility of a terrorist or a group to direct evolution of viruses in bacteria to harm humans or the environment in a particularly harmful and unnatural manner", where synthetic biology's 'dual-use' capabilities of advancing helpful properties of science while also allowing for the potential for weaponization or malicious use of genetically engineered material remains possible (Konig et al 2016). Specific dual-use examples include the potential modification of viruses for predetermined purposes such as with promoting the airborne transmission of bird-flu viruses in ferrets to study similar influenza transmission in human populations (Imai et al 2012; Herfst et al 2012). To combat the potential misuse of dual-use synthetic biology techniques and research, the respondents above noted the need for a pan-European regulatory body to review biosecurity concerns, including duties such as with classifying various research topics into various bins, where certain bins will encounter a more thorough review prior to receiving funding from the European Commission while also having greater controls over information that may and may not be published or publically disseminated. Malakoff (2013) and Konig et al (2016) contend that such an approval process would identify those projects with dual-use applications and require data control and publication limitations in order to prevent the public dissemination of such material.

While several respondents (5 of 9) noted the need to consider improvements to European regulation related to long-term biosafety concerns and dual-use biosecurity risks noted above, there were disagreements related to how that should be accomplished (detailed in Figure 15 below). Specific disagreement centered on whether changes to national regulatory capabilities are currently necessary to govern such risks, with 2 of 9 respondents stating that

the European Union should move towards EU-wide regulatory changes to address synthetic biology regulation directly. Likewise, 3 of 9 argued that it would be premature to make such changes, where regulators instead should rely on existing Directives (such as Directive 2001/18/EC and Directive 2009/41/EC) to cover synthetic biology risks while also allowing for the research community to establish its own standards and risk management protocols for general synthetic biology research.

Within such self-governance, Douglas and Stemerding (2014) and Hilgartner et al (2015) note that public-private partnerships as well as multi-stakeholder guidance committees serve as more common sources of soft law development for the European Union. Wendler (2005) describes one such option as the European Food Safety Authority (EFSA) as a public-private soft law approach. Specifically, Wendler (2005) notes that the EFSA's industry partnerships allow it to (i) acquire information about emerging risks to food within the European Union from industry stakeholders, (ii) communicate priorities and best practices to such industry stakeholders, and (iii) communicate to the European Commission findings and opinions regarding such food-based risks and threats – genetically modified organisms included. Further, Van Broekhuizen and Schwarz (2010) note the rise of multi-stakeholder committees for emerging technology soft law development, where they explicitly reference the 'Nanocap' consortium. In further detail, Nanocap serves as a multi-stakeholder meeting of industry professionals, NGOs, and academic researchers to discuss and debate risks posed by nanotechnology (Van Broekhuizen and Schwarz (2010). The consortium reinforced the 'no data, no market' rule, which sought to reinforce best practices where developers demonstrated safe use and best practices of nano-based products.

While not legally binding, Van Broekhuizen and Schwarz (2010) and Wendler (2005) note that such codes of conduct can have a strong effect to influence industry behavior and inform government stakeholders of potential risks posed my emerging technologies. This drive for self-governance and soft law (such as with the W3C approach noted by Maurer 2012 as deriving consumer driven-standards and consensus-driven best practices by a collection of subject experts) operates under the notion that existing governmental controls are sufficient to control for potential biosafety and biosecurity risks, where one EU Respondent 6 (Lab

Researcher) noted that "the research community may help indicate to government stakeholders where novel risk is realistic, and where it's improbable." Lastly, 4 of 9 respondents argued that no new regulation of any form was appropriate at this time, with EU Respondent 8 (Lab Researcher) contending that "Europe has already addressed synthetic biology directly via the precautionary principle and clear directives, and more law now will probably be unnecessary and might hinder research." The sentiment held by these four respondents was not that hard or soft law changes to synthetic biology regulation would never be needed, but that no new regulation should be established until warranted by new research conducted under existing law.

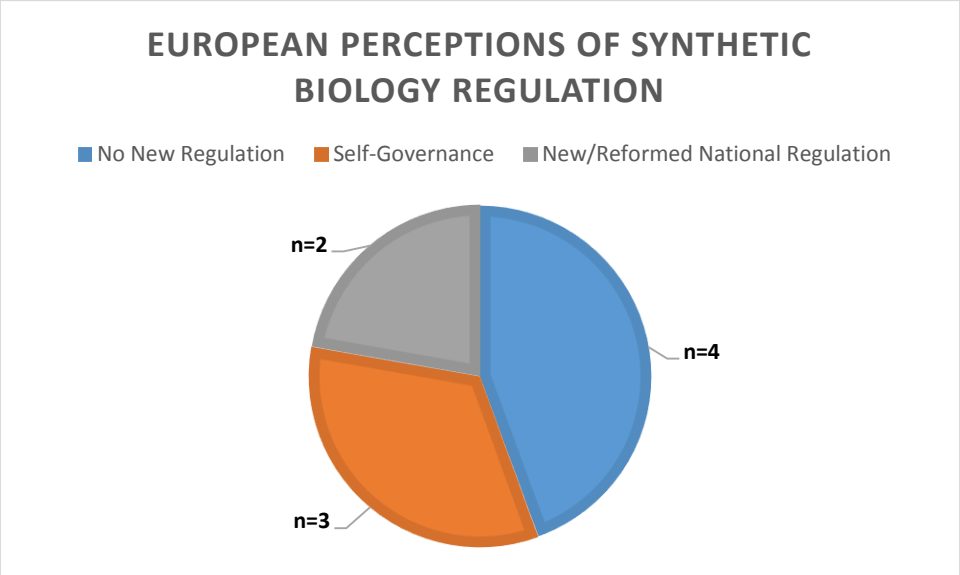

Figure 15. Perceptions Amongst European Experts Regarding the Regulatory Needs for Synthetic Biology Research and Development

5.6 Discussion

Overall, European respondents raised several points related to where they perceived novel health risk as being possible as well as whether existing hard and soft law within Europe were capable of covering such risks in the immediate and long-term future. For the former, this included considerations of general perceptions of risk as well as where along a pharmaceutical product's life cycle such novel risk was likely to arise. Generally speaking, respondents indicated

that both biosafety and biosecurity risk scenarios are plausible to occur, with biosafety events related to laboratory accidents, accidental exposure, and environmental release scenarios being some of the common avenues when harmful events may arise. Risks here include the potential for horizontal gene transfer (viewed as plausible but unlikely), environmental proliferation (plausible but unlikely given the current state of the science), and exposure effects where the engineered microorganism could negatively impact local ecosystems and biodiversity (highest probability of the three).

For the latter, respondents viewed European regulation as generally being capable of covering synthetic biology product development in the near future, where they argued that these Regulations, Directives, and Recommendations with historical applications to genetically modified microorganisms capture the process of synthetic biology development. Such statements are consistent with Konig et al (2016) and de Lorenzo (2010), which noted that early iterations of synthetic biology research are likely to be covered within European hard law directives and soft law synthetic biology-specific guidance to university, government, and industry researchers alike.

Overall, the respondents did note some potential challenges to the effectiveness of such Directives and Regulations, including (i) the ability of these regulatory structures to prevent an unlikely biosecurity threat via the promotion of dual-use synthetic biology products as with viral material for vaccines, and (ii) the ability of regulators to conduct quantitative risk assessments on microorganisms with increasingly artificial DNA. For biosecurity, respondents noted that despite the unlikely probability that such risks would materialize into a tangible threat via bioterrorism or weaponized products, further pan-European regulation was needed in order to screen research proposals for those that may produce dual-use material that, if disseminated and published widely, could empower a nefarious actor to pursue harmful research.

For biosafety, respondents argued that risk assessment protocols using the comparative method to review the potential for novel risk between a synthetic biology product and a naturally-derived, safe product (see Pauwels et al 2013) will become difficult to reliably conduct as synthetic biology microorganisms become increasingly synthetic. In this way, European regulators will need to adopt new measures of reviewing the potential for harmful health risks

associated with these products, including considerations of human and environmental health (Konig et al 2016). Overall, however, European respondents articulated that the precautionary principle that has encompassed discussion around genetically engineered microorganisms and synthetic biology alike will continue to play a significant role in the hard and soft law regulation of such research (see also Carter et al 2014; Vogel and Lynch 2001; Buhk 2014; Kelle 2013).

Chapter 6:

Synthetic Biology and Risk Regulation – The Case of Singapore

6.1 Introduction

Singapore's health sciences research identity has centered on the need to advance treatments and therapeutics for conditions and diseases that are endemic and problematic for Southeast Asia such as malaria, dengue fever, and several others. Since its de jure independence in 1965, the Lion City's leadership has actively advocated for an aggressive research agenda in virtually all scientific fields, leading to collaborative relationships with most developed nations such as the United States and European Union alongside the development of a number of industrial, governmental, and academic research ventures over the past several decades (Phan et al 2005; Lee and Win 2004). Over the past 50 years, Singapore has grown from one of the poorest nations in the world in the 1960s to become a fully developed and scientifically advanced country (Davis and Gonzalez 2003; Wee 2007; Olds 2007). Due largely to its business-friendly stances and substantial funding for research and development, this progress has given the city-state a reputation as a technological innovator, contributing to substantial funding for emerging technologies research in nanotechnology, biotechnology, information systems technology, and many other developing fields (NUS 2015; Olds 2007; Wee 2007; Altbach and Salmi 2011).

Among these areas of interest includes synthetic biology, where two major universities (the National University of Singapore and Nanyang Technological University), research groups, a biologics plant (Novartis), and a growing cohort of private companies and for-profit research ventures individually investigate various elements of synthetic biology research. Discussed more explicitly below in Section 5.2, synthetic biology has emerged as a research venture in Singapore due to the potential for its scientists to engage with topical research questions and

policy problems related to Southeast Asia such as with biofuels and combating tropical diseases such as dengue fever and malaria (Liang et al 2011).

This chapter adopts a similar structure as the US and European chapters by reviewing (i) the recent history and practice of synthetic biology within Singapore, (ii) perceptions of health risk produced by synthetic biology pharmaceuticals amongst interviewed subject experts, and (iii) perceptions and opinions of existing and future regulation of synthetic biology products within Singapore. As with Chapters 4 and 5, expert discussion and findings from discourse analysis within this chapter will be discussed and compared in Chapter 7.

As the last case chapter, Sections 6.2 and 6.3 seek to indicate how elements of risk culture can influence synthetic biology regulation in Singapore. Specifically, this includes discussion of how the country's soft-authoritarianism yet cooperational and informal nature to facilitate regulatory reform applies to synthetic biology regulation and governance. Later sections build off of this discussion by reviewing expert perceptions of synthetic biology risk and regulation within Singapore.

6.2 Regulatory Culture and Regulatory Decision Making in Singapore

6.2.1 History and Background of the Political and Institutional Structure of Synthetic Biology Regulation in Singapore

Singapore's political and institutional identity centers on its status as a 'soft-authoritarian state', which Turner (2015), Reilly (2016), Ortmann (2012), and Olds (2007) describes as where opposition parties are legally allowed to operate without significant fear of reprisal, but are generally too weak or ineffective to seriously challenge power. For Singapore, the People's Action Party has served as the primary soft-authoritarian power, with effective control of the national government since 1959 (Hill and Lian 2013; Turnbull 1989). A Center-Right Party by nature, the People's Action Party has operated on the principles of pragmatism, meritocracy, multiracialism, and communitarianism, with the general motivation of the Party to improve Singapore's economic position and the purchasing power of its citizenry through continual technological and economic investment within a racially and ethnically diverse

population while also leveraging Singapore's historical advantages as a center for shipping and trade (Tremewan 1996).

The People's Action Party retains control over the three branches of government, including the Executive, Legislative, and Judicial branches. Governmental structure is defined by the Westminster constitutional model (driven by Singapore's history prior to independence as a British colony), with a Prime Minister heading the national government and chosen amongst the body of Parliamentary members (Sheehy 2004) and a President exercising largely ceremonial power as Head of State (Sheehy 2004; Hill and Lian 2013). Lastly, an independent judiciary checks executive and legislative actions that may be interpreted as violating the Singaporean Constitution, although judicial authority is limited and defers by law to the executive for instances where court authority it limited or uncertain (Hill and Lian 2013; Turnbull 1989).

Lawmaking in Singapore is held by Parliament, where ministers may propose bills (yet most legislative proposals are initiated by a member of the Prime Minister's Cabinet) (Vasil 2004; Tan 2013). However, Parliamentary lawmaking is limited in cases of (i) those bills that seek to impose, increase, or abolish a tax, (ii) those bills that seek to borrow money on behalf of the government, and (iii) deposits or changes to the Singaporean Consolidated Fund (Constitution of Singapore; Tan 2013). Further, bills are screened for potential harms to minority rights, where those deemed to be explicitly harmful to a particular subsection of Singaporean society are removed from further consideration in Parliament (Constitution of Singapore) (Tan 2013; Vasil 2004). Bills allowed to circumvent screening for minority rights considerations include both those bills that the Prime Minister certifies as affecting the defense or security of Singapore, or that relate to public safety, peace or good order in Singapore, and bills the Prime Minister certifies are so urgent that it is not in the public interest to delay enactment (Turnbull 1989; Sheehy 2004; Hill and Lian 2013). In this way, both the President and Prime Minister exert control over the lawmaking process and retain the ability to (i) guide the legislative process by instructing a Cabinet member to propose and defend a bill, or (ii) use their power to circumvent certain requirements of the deliberation of a bill in order to meet emerging public health and security concerns (Olds 2007; Tan 2013).

Specific to synthetic biology regulation and governance, Singapore captures the process of the technology's development using existing hard and soft law previously crafted to govern genetically-modified organisms. Two such instruments include The Biological Agents and Toxins Act as well as The Singapore Biosafety Guidelines for Research on Genetically Modified Organisms. This is in lieu of using existing chemical regulation to capture elements of synthetic biology development such as within the United States, where such regulation has been used instead to cover biosecurity (The Strategic Goods (Control) Act) as well as product-driven regulation (The Medicines Act and The Health Products Act). Each of these will be discussed in turn below.

The Biological Agents and Toxins Act (2005) represents Singapore's key legislative instrument that shall most likely capture the process of synthetic biology development. Those with more knowledge of the law particularly referenced Chapter 24A, which was added as a revision to the original act in 2006. Chapter 24A is specifically geared to address regulatory policy to:

"prohibit or otherwise regulate the possession, use, import, transhipment, transfer and transportation of biological agents, inactivated biological agents and toxins, to provide for safe practices in the handling of such biological agents and toxins" (Biological Agents and Toxins Act 2006).

Administered by the Singaporean Ministry of Health, the Act states that those facilities which handle biological agents and toxins deemed "high risk" are required by law to acquire certification as "containment facilities", with inspection and recertification to occur on an annual basis.

This particular statue was directed at monitoring, reviewing, and assessing risk related to various elements of life sciences research, with several respondents in government and academia noting its coverage of synthetic biology research based upon the abilities of the Director of Medical Services and his or her appointed officers to monitor and review the possession, use, transportation, and production of biological agents. Biological agents are divided into a series of classes called 'Schedules', with Eight schedules referenced in Chapter 24A of the Biological Agents and Toxins Act (Biological Agents and Toxins Act 2006). Synthetic biology is not explicitly referenced within any of these schedules, although government and

academic interviewees noted that such products would most likely fall in the First, Second, or Third Schedule based upon the type of product that synthetic biology research would be conducted on. These schedules include some of the more tightly controlled and vigorously monitored biological agents by Singaporean officials, with explicit requirements of permitting and certification for most activities related to large scale production, transport, possession, and use of such agents. Within the statute, these laws explicitly reference the Ministry of Health's ability to protect and preserve Singapore's biosafety with respect to biological agents and life sciences research (Biological Agents and Toxins Act 2006).

A further legislative instrument includes the Strategic Goods (Control) Act (Chapter 300) of 2002, which lists biological agents and toxins that are administered and reviewed by the Singaporean Customs Authority. This particular law addresses preserving both the nation's security relative to monitoring the brokering and exchange of goods "*capable of causing mass destruction*", along with the review of technologies moving in and out of the country that would otherwise be of interest to national security (Salerno & Gaudioso 2015). Geared more towards the biosecurity debates discussed since synthetic biology's modern inception in the early 2000s, these statutes seek to control the import and export of various materials that are potential threats to national security.

Specific to the Strategic Goods (Control) Act, it is not explicitly clear how the Singaporean Customs Authority communicates with other bodies such as the Ministry of Health to identify and label certain technologies and products as being of concern for Customs agents at the nation's borders (Strategic Goods (Control) Act 2003). However, the statute does offer the Director-General of Singapore's Customs Authority the ability to, at their discretion:

> *"prescribe any military or dual-use technology as strategic goods technology for the purposes of [the] ACT."*

This allows the Customs Authority to update their schedules and guidance regarding those technologies deemed strategic and of interest to the Singaporean government (Strategic Goods (Control) Act, Section 4a, 2003). Where all Singaporean government interviewees noted that greater flexibility was needed with respect to applying regulatory oversight to synthetic biology products, this Act offers a relatively adaptive and flexible approach to identifying biosecurity threats now and in the future, and empowering Customs to regularly update their

schedule of strategic goods and technologies based upon notable threats and developments in areas ranging from energetics to life sciences. For purposes of synthetic biology and pharmaceuticals research, such flexibility would allow the Customs Authority's leadership to apply principles of soft law to include specific synthetic biology products on their list of materials requiring permits and certification for travel and exchange.

Another important regulatory instrument related to synthetic biology development includes workplace safety considerations. Specifically, this includes The Ministry of Manpower (MOM) and The Workplace Safety and Health (WSH) Council. For the former, MOM includes 14 divisions (with 1 centered on Occupational Health and Safety), and is empowered by The Workplace Safety and Health Act to ensure workplace safety. Specifically, Part 4 of the Act asserts that:

> *"It shall be the duty of every occupier of any workplace to take, so far as is reasonably practicable, such measures to ensure that —*
>
> *(a) the workplace;*
>
> *(b) all means of access to or egress from the workplace; and*
>
> *(c) any machinery, equipment, plant, article or substance kept on the workplace,*
>
> *are safe and without risks to health to every person within those premises, whether or not the person is at work or is an employee of the occupier."*

Further, the WSH works in tandem with The Ministry of Manpower to review workplace safety concerns as laid out in the Workplace Safety and Health Act. This relationship is codified in Part 8 of the Act, where the WSH Part 8 Section 40a notes:

> 40A. The functions of the Council shall be —
>
> *"(a) to develop or facilitate the development of acceptable practices relating to safety, health and welfare at work;*
>
> *(b) to promote the adoption of acceptable practices relating to safety, health and welfare at work;*
>
> *(c) to devise, organise and implement programmes and other activities for or related to providing support, assistance or advice to any person or organisation in preserving, improving and promoting safety, health and welfare at work;*

(d) to facilitate and promote the development and upgrading of competencies, skills and expertise of the workforce relating to safety, health and welfare at work;

(e) to research into any matter relating to safety, health and welfare at work;

(f) to grant prizes and scholarships, and to establish and subsidise lectureships in universities and other educational institutions in subjects relating to safety, health and welfare at work;

(g) to provide practical guidance with respect to the requirements of this Act relating to safety, health and welfare at work; and

(h) to do all the things that it is authorised or required to do under this Act."

Such legal jurisdictions apply to genetically modified substances via the Fifth Schedule of the Act (Machinery, Equipment or Hazardous Substances). Discussed further below, The Singapore Biosafety Guidelines for Research on Genetically Modified Organism also indicates how MOM and WSH interact with the Genetic Modification Advisory Council and other agencies to explicitly cover workplace safety for genetically modified substances, where the legal authority of the two agencies derives from The Workplace Safety and Health Act.

With respect to soft law, various members of the academic, industry, and governmental axis referenced The Singapore Biosafety Guidelines for Research on Genetically Modified Organisms (GMOS) (2013), which serves as a more explicit connection to synthetic biology regulation than the hard law case of the Strategic Goods (Control) Act or the Biological Agents Control Act of 2005. While the term 'synthetic biology' does not appear in the 2013 iteration of the Guidelines, the focus on genetically modified organisms and the various products which make use of such organisms drove most stakeholders knowledgeable of the document to argue for synthetic biology being thoroughly covered under the Guidelines. Within its contents, the Guidelines offer instruction on (i) the types of products and activities to be governed, (ii) the various governmental institutions and agencies with authority to review practices, adaptively improve regulatory mechanisms over time, and mete out consequences associated with those who defy best practices, and (iii) clear structure regarding governmental authority and work flows related to protecting Singaporean biosafety and biosecurity within the context of genetically modified organisms and their related research. Overall, the Guidelines do not carry

the force of law as with The Biological Agents and Toxins Act, yet have been adopted by Singapore's research universities and are required for research organizations that receive funding from the Singaporean government (Tun et al 2009; Asadulghani and Johnson 2015).

Looking first at the types of activities and products explicitly covered by The Singapore Biosafety Guidelines for Research on Genetically Modified Organisms, Section 2.1 (Extent of Guidelines) references the Guidelines' ability to offer guidance to:

> *"experiments that involve the construction and/or propagation of all biological entities (cells, prions, viroids, viruses or organisms) which have been made by genetic manipulation and are of a novel genotype and which are unlikely to occur naturally, or which could cause public health or environmental hazards."*

While it is important to note that the Guidelines *"do not cover work involving human subjects",* the risk and hazard discussion centered on governing genetically modified organisms does consider both public health and environmental health outcomes as they arise from the research, manufacturing, use, and disposal of such materials (for regulation explicitly related to these materials and human subject testing, interview respondents noted that the Biological Agents Control Act was better equipped to address such issues). Further, the Guidelines note that they consider both the intentional and unintentional release of biological material deriving from genetically modified organisms, yet also state that certain work or research may be subject to additional hard or soft law regulation depending on whether such work was able to get an exemption from external oversight, or that such work falls under a specific class of genetic modification research that the Singaporean government has denoted as not possessing significant biosafety risks to humans or the environment (Section 2.3).

Next, the Guidelines address at length the governmental institutions empowered to govern and regulate activities outlined in Section 2. Specifically, the Guidelines name 8 agencies with some degree authority to regulate research related to the genetic modification of biological material for pre-defined purposes, including:

- the Genetic Modification Advisory Committee of Singapore.
- the Agri-Food and Veterinary Authority of Singapore
- the Ministry of Health, Singapore

- the National Environment Agency, Singapore
- the Ministry of Manpower, Singapore
- the Institutional Biosafety Committee
- the National Advisory Committee for Laboratory Animal Research
- the Bioethics Advisory Committee

Using this guidance, the Guidelines divide the regulation of genetically modified products or technologies into four general categories, including (i) the regulation of laboratories dealing with GMO research, involving animal pathogens and plant pests, (ii) the importation of organisms including GMOs, (iii) the certification or Inspection of Laboratories handling biological agents or toxins regulated under the Biological Agents and Toxins Act, and (iv) the regulation of workplace safety and health. Government interviewees noted that synthetic biology biosafety guidance is likely to currently fall under parts (i) and (iii), where soft law best practices guidance alongside notions of hard law certification and monitoring requirements of laboratories conducting genetic modification research. For these biosafety provisions (parts i and iii), the Guidelines states that both the Agri-Food and Veterinary Authority of Singapore alongside the Ministry of Health respectively serve as the two regulatory organizations empowered to govern such activities. With respect to part ii, the Guidelines notes a collection of the Agri-Food and Veterinary Authority of Singapore, the MOH, and the National Environment Agency charged with the regulatory authority to oversee the importation of genetically modified organisms and products into Singapore, and includes a Risk Classification report regarding the proper shipping and assessment of such materials both as an import and with respect to internal transport within the country. Lastly, part iv is noted as being governed by the MOM, where occupational safety was discussed by interviewees as an element of regulation that was on the horizon of synthetic biology and pharmaceuticals research, yet greater consideration of imminent regulatory concerns remained both within the research and disposal stages of a generic pharmaceutical's life cycle.

Under this four-tiered framework of regulation and activity, Genetic Modification Advisory Committee of Singapore is empowered to expand or add to such guidance where technologies emerge or research involving the genetic modification of biological material is

uncertain or emerging (Section 5). As noted above, the nature of this guidance is nonbinding in a manner similar to The Biological Agents and Toxins Act, yet are adopted within research universities and organizations receiving government funding in Singapore (Tun et al 2009). After describing the types of experiments covered by The Guidelines as well as characteristics which make certain experiments exempt, Section 4 indicates that the Genetic Modification Advisory Committee is empowered with the ability to include further developments with research and experimentation to effectively expand the ability of The Guidelines to cover such projects as with synthetic biology – an important element in fostering an adaptive regulatory framework via iterative improvements to soft law regulation for the technology moving forward. Further, the Genetic Advisory Committee is empowered by The Biological Agents and Toxins Act to oversee, regulate, and approve of research related to genetic engineering.

To accomplish this goal, The Guidelines note that that novel experimentation and genetic manipulation techniques may be reviewed by an Institutional Biosafety Council (IBC) relevant to the organization conducting synthetic biology research – the recommendations and observations of which may be submitted to the Genetic Modification Advisory Committee prior to the Committee's determination of how that particular product or experimental technique may be regulated. Singapore Respondent 6 (Social Scientist) noted that "if [The Guidelines] can be clearly connected to synthetic biology, which they basically are, then this is going to be an important argument in favor of in-house governance of synthetic biology research."

Third, the Guidelines offers transparent work flows regarding which agency is responsible for monitoring a given activity alongside guidance for researchers and developers regarding how to identify the agency and regulations relevant to their vein of work. This is described in detail in Sections 3 and 5, respectively, where prospective researchers would be able to determine the degree of oversight their research requires as well as the various agencies involved in such oversight throughout research and development.

First, Section 3 indicates the 'Summary of Procedures', which is a decision chart describing the assessment protocol and notification timelines for researchers engaging with work related to genetically modifying biological organisms. This includes considerations of self (IBCs) and external regulation (the Genetic Modification Advisory Committee and private

government investigators). Next, Section 5 includes explicit notation of the roles and responsibilities held by the various government agencies throughout the regulatory process of genetic research. An important inclusion here is a notion from Singapore Respondent 6 (Social Scientist) that "IBCs are vital for executing these guidelines", an indication that Singapore Respondent 1 (Lab Researcher) described as "evidence of a respect for the ability of institutions to conduct their own risk assessment activities, and report potential biosafety hazards to external government authorities." Collectively, the information found in Sections 3 and 5 serves as a measure of reducing uncertainty regarding the structure and actions taken by government for cases of research as with synthetic biology, further described by Singapore Respondent 3 (Lab Researcher) as "the rules that will probably be most important for synthetic biology research in the near future, […] particularly as it outlines how the Singaporean government will oversee research activities."

Generally speaking, Singapore's Constitutional structure is an emulation of its colonial past under the British Empire, with modifications driven by paternalism and pragmatism that drives Singaporean regulation since the 1950s (Li-Ann 1993). The soft-authoritarian nature of regulation via the People's Action Party is enhanced by a centralization of power under the Prime Minister, who together with the President retains significant control over the legislative process (Tan 2013; Li-Ann 1993).

6.2.2 Risk Culture in Singapore

With this general background on the functions of Singaporean government and the influence of the People's Action Party on the country's lawmaking process, it is important to next unpack considerations of Singapore's risk culture, or the institutional and political factors that influence their approach to regulation more generally, and with a specific focus on of emerging science and technology. To cover this topic, this section begins by first discussing the historical path of synthetic biology regulation, or noting how the regulation of genetically modified organisms in Singapore developed over time as well as the legal and regulatory mechanisms to cover related research, production, commercialization, and disposal of such material. The section then builds upon this by reviewing how elements of risk culture may

influence Singaporean regulation of emerging technologies. In Section 6.2.3, this information will then be reviewed for its applications within interview data acquired by Singaporean subject experts.

6.2.2.1 Historical path of synthetic biology regulation

In a manner similar to the European Union, Singapore's synthetic biology regulation is generally perceived to derive from the regulation of genetically-modified organisms, and includes a mixture of adherence to international regulation as well as domestic hard and soft law such as with the Biological Agents and Toxins Act (Chapter 24) as well as the Biosafety Guidelines for GMOs (Genetic Modification Advisory Committee, n.d.). Early regulation of such materials is driven by the need to govern food importation into Singapore, where genetically modified foods are viewed by the Government as one avenue to improve food security and local nutrition for a nation with 90% of its food supply being imported from neighboring countries (Genetic Modification Advisory Committee, n.d.; Tey et al 2009). However, such regulation also grew to cover other activities ranging from laboratory experimentation of genetically-modified organisms to pharmaceuticals and other research ventures (Oriola 2002a; Oriola 2002b).

Prior to 2005, Singaporean regulatory authority over genetic modification was covered by formal legislation in specific research areas as with pharmaceutical development, agriculture, or food labelling) (Ho 2011). Regulation specifically directed at genetic modification and emerging biotechnology research remained limited and informal until 2005, when Singapore's Parliament passed the Biological Agents and Toxins Act (Singapore Ministry of Health 2007: Ho 2011). This Act will be discussed in detail in Section 6.6 below, yet it is important to note here that Chapter 24A of the Act was designed to govern the research, production, sale, distribution, transport, and disposal of genetically modified material (Singapore Ministry of Health 2007). The Act also included a system of approvals for those laboratories that sought to conduct such research – the process of which included biosafety risk considerations that researchers were required to discuss with regulators prior to receiving a permit for research (Singapore Ministry of Health 2007).

Later, Singapore's Genetic Modification Advisory Committee released the Singapore Biosafety Guidelines for Research on Genetically Modified Organisms in 2006, which served as a legally non-binding approach to the regulation of research involving genetic modification that offered recommendations to counter biosafety and biosecurity risks for research involving genetic modification (Ho 2011; GMAC 2016). The Guidelines were further modified in 2008 and 2013, and included guidance on the biosafety and biosecurity concerns that researchers should work with their respective Internal Review Boards to address (GMAC 2016).

Singapore's regulatory history for genetically modified organisms that currently cover synthetic biology research is a relatively limited one, with most guidance coming from soft law recommendations and applications from specific product development prior to 2005 (Ho 2011). From 2008 to 2013, this was bolstered via hard law (Biological Agents and Toxins Act) and soft law (the Guidelines) geared explicitly to governing research related to genetic modification. Such guidance will likely continue to incorporate developments in domestic and international research pertaining to such modification, and the potential biosafety and biosecurity concerns therein (Ho 2011).

6.2.2.2 Assessment of the Risk Culture influencing regulation of novel compounds and scientific processes like synthetic biology

After reviewing the historical path of regulation for genetically-modified organisms and synthetic biology products in Singapore, the next review element to consider includes the institutional, social, and political values and behaviors that fashion Singaporean risk culture within the context of technology regulation. Specifically, risk culture considerations here include (i) the soft-authoritarianism and centralization of decision making authority practiced by government leaders, and how this relates to technology regulation, (ii) the cooperational yet informal approach to overcoming regulatory disputes and driving technology regulation, and (iii) the more 'proactionary' nature of Singaporean government leaders relative to innovation in order to strengthen the country's economic prospects (Olds 2007; Tan 2013; Li et al 2009; Ho 2011). These three characteristics will explain the factors that local regulators must consider when reviewing options to govern specific emerging technologies as with synthetic biology

pharmaceuticals, and will offer context regarding the viewpoints and perspectives of those Singaporean subject experts contacted for interview for the case of synthetic biology pharmaceutical regulation.

For the first item, the soft-authoritarian nature of the Singaporean government's behavior serves as a pervasive characteristic that drives Singaporean lawmaking, regulatory behavior, and coordination of governmental and industry representatives (Olds 2007; Nasir and Turner 2013). Building off of the introductory discussion of soft-authoritarianism within Singapore in Section 6.2.1, further characteristics that arise from this political and institutional arrangement include a centralization of decision-making authority within government alongside a lesser degree of transparency in the regulatory reform process as would be expected in a liberal democracy (Nasir and Turner 2013). More specifically, soft-authoritarian governments act in a manner where decision making power is centralized amongst a powerful elite with limited checks on authority and little real competition in terms of election (Nasir and Turner 2013; Turner 2015). Such centralization includes the ability for government subject experts to introduce and implement regulatory reform in an efficient manner in comparison to a state where power is shared amongst more players (as is the case within the United States and the European Union) (Nasir and Turner 2013; Neo and Chen 2007). An additional factor behind this includes Singapore's relatively small size in comparison to the United States and European Union, which limits democratizing factors and preserve the country's soft-authoritarian regime (Huat 2015; Lim and Lim 2016; Ufen 2015). Further, a limited tolerance alongside the ability for the Prime Minister as elected by the majority party in Parliament to also serve as the chief executive in a Westminster-style government further limits opportunities for regulatory reform to be hindered in passage (Tan 2013; Haque 2004).

However, even within an 'imperfect democracy' and limited transparency in government, another characteristic of Singapore's soft-authoritarianism includes a general need to identify regulation that mitigates risk to the local population and the environment (Ortmann 2012; Turner 2015). Such behavior can differ from a 'full authoritarian' state that seeks to enrich elites and cadres often at the expense of the general public, where Roy (1994) and Olds (2007) argue instead that soft-authoritarian states like Singapore generally seek to

represent the best interests of the general citizenry by promoting public safety, public health, and improved economic status. This is accomplished by the controlling political party's maneuvering within the Singaporean government and abiding by the Singaporean Constitution, although no serious challenge is raised by opposing political parties for those regulatory issues deemed higher priorities by elites in the People's Action Party (Roy 1994; Nasir and Turner 2013; Mauzy and Milne 2002). Within such a soft-authoritarian government, it is important to note that the Singaporean government is unlikely to use their controlling power to 'force' hard or soft law through a resistant public, but instead wait until international research developments or domestic necessity offers political and scientific reason to improve technological regulation in a specific manner (Mauzy and Milne 2002; Nasir and Turner 2013; Roy 1994).

For the second item, Singapore generally adopts a cooperational approach to resolve regulatory disputes and build regulation for emerging technologies like synthetic biology (Beng-Huat 1985; Srivastava and Teo 2009; Lim 2005). Such behavior is similar to that of within the European Union, where government stakeholders collaborate with stakeholders in industry, academia, and non-governmental institutions to construct regulation in a manner that is responsive to industry needs of promoting responsible innovation while balancing government requirements of upholding public health and safety (Kelemen 2011). However, the motivations for such behavior strongly differ in Singapore, where soft-authoritarianism limits the potential for significant resistance, dissent, or adversarial legalism in the process of technology regulation (with similar operational and political structures existing in examples as Malaysia and Russia – Shevtsova 2014; Ufen 2015). Instead, the 'socially-minded' approach to furthering the welfare of Singaporean citizens as described in Roy (1994), Nasir and Turner (2013), and Olds (2007) drives governmental elites to procure information about regulatory needs and innovation potential from members of industry and other stakeholders and use such information to make decisions about furthering the public good. With no real challenges to their political authority or significant threats of having their regulatory agendas seriously challenged in court, the People's Action Party can engage within informal regulation-building exercises with concerned stakeholders in a manner that (i) allows them to acquire information on emerging technologies

that allows them to balance risk and benefit in the regulatory process, and (ii) identify concerns and needs of industry researchers that would allow for a continued economic and technological pattern of growth within Singapore – a value central to the nation's identity (Beng-Huat 1985; Lim 2005; Mauzy and Milne 2002).

Thirdly, Singapore's drive to innovate and grow economically allows it to take on a more proactionary nature (Li and Fang 2004). Specifically, Singaporean government agencies seek to empower universities and companies to conduct research related to emerging technologies in a less restrictive regulatory environment, with oversight driven both by internal mechanisms such as with internal review boards as well as informal contact with regulatory agencies such as with the Economic Development Board or the Genetic Modification Advisory Committee (Hobday 1995; Edquist and Hommen 2009; Peebles and Wilson 2002; Chieh 1999; Olds 2007). Such research is geared to commercialize as soon as safely possible and benefit the Singaporean economy and/or public health, with little government investment allocated without such intentions in mind (Williams and Narendran 1999). Overall, Singapore's adherence to technological proaction is driven by the wishes of the government to further boost its economic and technological capabilities in order to achieve greater development and promote the welfare of its citizens (Williams and Narendran 1999; Olds 2007; Li et al 2009).

6.2.3 Applications to Interview Data

Given the discussion of Singaporean risk culture above, implied discussion by Singapore-based respondents was consistent with the themes of cooperational decision making, an appetite for proaction in the technology innovation process, and accounting for a soft-authoritarian governmental structure for regulatory reform. Discourse here indicated the unique regulatory reform process that Singapore maintains, where such reform seeks to balance the government's desire to improve the nation's economic status and quality of life in an environment of centralized authority and limited transparency in the reform process. Applications of these three general themes of Singaporean risk culture to interview data are discussed individually below.

Looking first at the cooperational approach to regulatory decision making, several (8 of 23) Singapore-based respondents noted how government agencies frequently reach out informally to innovators and other technology stakeholders when reviewing options for technology regulation reform. Singapore Respondent 1 (Lab Researcher) noted that "Lots of [Singaporean] agencies interface with companies engaging with technology research. For synthetic biology, this includes some like the GMAC [the Genetic Modification Advisory Committee] or the Economic Development Board, which tries to get developers to come to Singapore […] and meet to identify what regulation can balance innovation against risk." Singapore Respondent 2 (Social Scientist) argued that "there's very frequent discussion between developers and government officials on technology development and possible risks, and the two work together to identify needs for reform." Such sentiments are consistent with Roy (1994), Nasir and Turner (2013), and Phillips and Yeung (2003) which discuss how actors within government and innovators interact collaboratively to resolve potential concerns or uncertainties regarding technological best practices, project funding, and the ability of innovations to enter the market.

Next, many respondents inferred the importance of accounting for a soft-authoritarian governmental structure in the regulatory reform process for new technologies like synthetic biology. Specifically, discussion was noted about the ability of government officials to generate speedy regulatory reform to keep up with emerging technology development or developments within other countries relative to best practices or regulatory guidance for such technologies. Singapore Respondent 3 (Lab Researcher) argued that "there isn't really a need to push regulation for synthetic biology just yet, because regulators can institute reform pretty quickly once we have better information about hazards." Further, Singapore Respondent 4 (Social Scientist) stated that "when reform is needed for The Guidelines [The Singapore Biosafety Guidelines for Research on Genetically Modified Organisms] or The Biological Agents and Toxins Act, government ministers can initiate reform quickly with Parliament to protect public health, so pre-emptive reform isn't always necessary." The inferred discussion amongst these and other interviews was that there were few serious limitations on the ability of government officials to institute regulatory reform for synthetic biology in an expedient manner and without

political contestation that would be found in a more democratic and multipolar government like the United States or European Union – consistent with arguments presented in Olds (2007), Means (1996), and Sim (2007), among others.

Lastly, many respondents noted the capability for Singaporean researchers and government officials to have a slightly higher appetite for risk in pursuit of scientific innovation than Western governments like the European Union or the United States. Similar to Li et al (2009) and Li and Fang (2004), Singapore Respondent 5 (Lab Researcher) argued that "we [Singaporeans] aren't as precautionary as the West, and promote technology research like SynBio in ways that might not be possible in a more strict set of regulations." Further, Singapore Respondent 1 (Lab Researcher) indicated "there's a general feeling that we don't want to prohibit research because it's risky, at least until we understand these risks to be serious threats." Li et al (2009) and Li and Fang (2004) identify a slightly higher mentality for risk acceptance for research in many Asian nations such as with Singapore, often where such actors believe that a technology's risks may be overstated or otherwise controlled with proper regulation. Such sentiments were discussed or inferred within this body of interview subjects, and should be accounted for when reviewing feedback from such interviews.

6.3 Synthetic Biology in Singapore

Synthetic biology research has been directly explored and discussed in Singaporean Universities since at least 2011 (Dhar Lab 2011). However, Singaporean researchers and laboratories had connections with Western partners pertaining to synthetic biology research such as with the Massachusetts Institute of Technology since 2001. Singaporean students had begun to participate in the international iGEM competition by 2008, with specific participation centered on the health track of the competition (NTU 2015).

By the end of 2011, Singaporean researchers at A*Star had begun to conduct research on DNA sequencing and metabolic engineering (Mitchell 2011), while by 2012 the National University of Singapore and Nanyang Technological University began to receive government grants to pursue metabolic and circuit engineering research (Oldham et al 2012). Between 2012 and 2015, the Singaporean government funded various projects at the two universities, with

the latest development on September 2015 including approximately $18 million in funding for the National University of Singapore's Synthetic Biology for Clinical and Technological Innovation, with funding specifically originating from the Singaporean National Research Foundation as well as the Singaporean Economic Development Board (NUS 2015). Comparatively, governmental synthetic biology funding in Europe total just over $100 million and in the United States to over $200 million in 2014. Related to recent funding and regulatory support for research ventures setting up within Singapore's borders, Singapore Respondent 6 (Social Scientist) stated that "the Singaporean government has been interested in developing this technology that may yield health benefits to its citizens and residents […] with the Economic Development Board serving as a guide for foreign organizations seeking to break into the Singaporean market."

As of this writing, synthetic biology research is conducted within two universities (Nanyang Technological University and the National University of Singapore) and a large government-funded research institution at Biopolis (A*STAR). One of the primary pursuits of such research is geared towards clinical and medical innovation, with pharmaceutical development serving as one strain of inquiry within that regard. This trend is likely to continue (NUS 2015), where Singapore Respondent 6 (Social Scientist) noted that "the Government is well aware of the potential to generate health benefits through synthetic biology, and we believe that funding and a supportive environment are necessary to develop such benefits within Singapore."

6.4 Synthetic Biology: Perceptions of Health Risk and Benefit amongst Singaporean Stakeholders

This chapter centers on a specific country's synthetic biology stakeholders and experts, with specific emphasis on their opinions and beliefs regarding synthetic biology pharmaceutical risks and regulatory options. This section includes discussion of the former, where Singaporean subject experts were asked to give their views on synthetic biology pharmaceutical risks to human and environmental health. These risks were reviewed based upon whether such novel health risks may arise as well as where experts perceived novel risk could arise at different

stages of a pharmaceutical product's life cycle. A breakdown of the type of interview respondents included is noted in Table 8 below.

As noted in Chapters 4 and 5, interview respondents in this chapter have a PhD-level education in biology, chemistry, or similar field in science, or have a PhD in a social science background pertinent to the risk analysis and regulation of emerging technologies. Such interviewees also had a formal position of employment at a Singaporean institution at the time of interview, such as with a post doctorate or research professorship at a Singaporean university or a position at a Singaporean company based within Singaporean borders. As noted in Chapter 2, these respondents were selected based upon their history of publications or conference presentations on relevant to synthetic biology experimental research or risk regulation.

Table 8. Breakdown of Research Backgrounds of Singapore Respondents			
	Lab Research	Social Science/Implications	Total
Academia	11	5	16
Government	1	1	2
Industry	3	1	4
NGO	0	1	1
Total	15	8	23

Table 8. Breakdown of Research Backgrounds of Singapore-based Respondents. 'Lab Research' includes those respondents who work primarily in an experimental, laboratory-driven setting. 'Social Science/Implications' includes those respondents who work outside the lab and comment upon risk and regulatory needs for synthetic biology.

6.4.1 Conventional and Novel Risks from Synthetic Biology Pharmaceuticals

Consistent with interview protocols outlined for all interviews for this research project, Singaporean subject experts within academia, industry, government, and non-governmental organizations were asked about their perceptions of whether synthetic biology could yield novel health risk that, if exposed to humans and/or the environment, could generate health concerns that are not currently fully governed under existing measures and methods of chemical risk assessment.

Specific to discussion of novel risks associated with synthetic biology pharmaceuticals, Singapore-based respondents were less inclined to state that novel health risks associated with such products were likely to arise at any stage of their life cycle. In comparison to United States (1.59) and Europe (1.78), Singapore-based respondents collectively indicated a novel risk likelihood score of 1.13, indicating a belief in possible yet highly unlikely novel health risk occurring throughout a synthetic biology pharmaceutical product's life cycle. Figure 16 below indicates a breakdown in proportional responses regarding general perceptions of such novel risk likelihood, with 9% arguing for no novel risk, 69% stating that minimal yet unlikely novel health risk, and 22% indicating likely novel health risk with moderate health consequences. Within this dissertation's interview responses, no Singapore-based respondent (out of 23) stated that novel health risk from synthetic biology pharmaceuticals was essentially guaranteed to materialize (indicated by a score of '3').

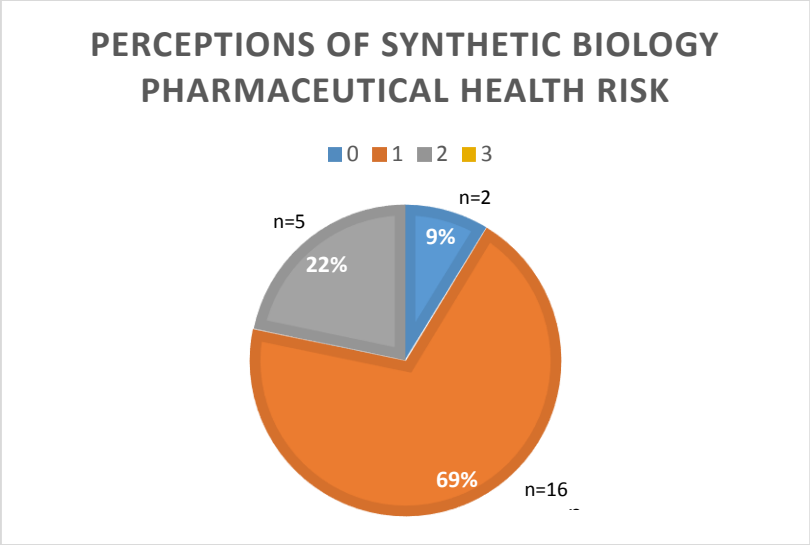

Figure 16. Singaporean Perceptions of Synthetic Biology Pharmaceutical Health Risks (n=23). Responses are coded on a scale from 0-3, where increasing values indicate greater likelihood of novel health risk. 0 = no novel health risk; 1 = possible but proportionally limited novel health risk; 2 = moderate chance of novel health risk across large populations; 3 = guaranteed novel health risk

Turning to interview discourse, the explanations offered by experts regarding their belief in the limited potential for novel health risk are varied. Three Singaporean academics noted in separate interviews that the ability to engineer a kill switch within engineered cells allows for greater control to prevent such cells from breaking containment or growing beyond certain population limits. Singapore Respondent 7 (Lab Researcher) explicitly noted that

"…novel risk might occur, but the exposure potential would be limited by cellular controls that scientists could use to keep synthetic cells from engaging in unintended behavior or reaching unintended exposure points." In other words, these respondents noted that biosafety risks in particular were unlikely as the probability of unintended exposure is limited and such cells would be controlled using built-in genetic manipulations to prevent the uninhibited growth of synthetic cell populations while also keeping them from proliferating outside of a controlled environment.

Specific to pharmaceutical products, respondents noted that the 'kill switch' mechanism to terminate cell growth and proliferation *in vivo* would prevent active biological as therapeutic agents from proliferating and engaging with harmful activity within the human body, and would be quickly and efficiently removed from the bloodstream via preprogrammed cellular controls after delivering medicine or performing its intended function.

Similar responses were derived when respondents were asked about their perceptions of biosafety and biosecurity risks from pharmaceutical products, respectively. Using the same scale noted in Figure 16, Figure 17 indicates that 74% of respondents believed that there exists little to no novel biosecurity risk associated with synthetic biology research, with 83% of such respondents indicating that there exists little to no realistic biosafety threat from synthetic biology research. Likewise, only 6 respondents (26%) articulated a belief of a moderate concern of synthetic biology biosafety risks, with 4 respondents stating a moderate concern of biosecurity risks (17%). Singapore Respondent 8 (Lab Researcher) noted that "dual-use concerns are possible, but not easily to accomplish at present because of the difficulties that a researcher would face in using their research for deliberate harm."

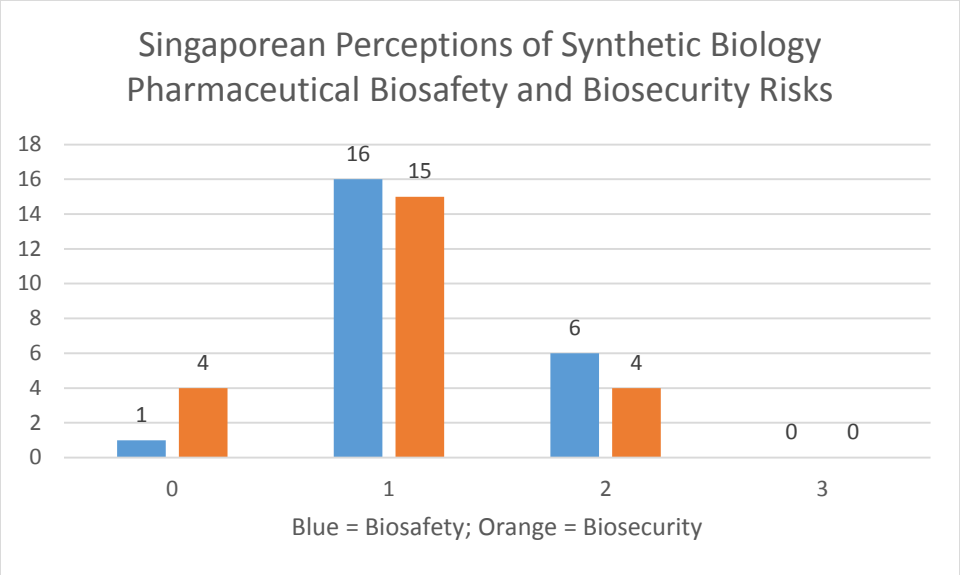

Figure 17. Singaporean Perceptions of Synthetic Biology Pharmaceutical Risks Associated with Biosafety and Biosecurity. Responses are coded on a scale from 0-3, where increasing values indicate greater likelihood of novel health risk. 0 = no novel health risk; 1 = possible but proportionally limited novel health risk; 2 = likely health risk; 3 = guaranteed novel health risk

Contextually, Singapore-based respondents generally stated (with strong exceptions) a belief that biosecurity and biosafety risks were generally not a significant concern and are unlikely to accrue for a variety of reasons. Specific to biosecurity, 83% of respondents noted that the potential for a nefarious agent to produce a virulent virus or pathogen and successfully release such materials into the environment is a highly unlikely scenario, where Singapore Respondent 4 (Social Scientist) noted that "even within internal governance, there exists enough oversight mechanisms to prevent someone from stealing or misusing biological material and engaging with involved research to produce harmful agents." Likewise, the four respondents (17% of the total Singaporean response pool) who stated that there was essentially no biosecurity threat pertaining to synthetic biology research all stated that both the scientific knowledge and capabilities alongside the resource requirements to synthesize and engineer harmful agents would make deliberative work towards producing harmful and infectious agents almost prohibitively difficult.

Of the 23 completed interviews within Singapore, four (17%) did note that biosecurity threats were possible due to the relative open source nature of much academic synthetic biology research, although each respondent here did note the technical and scientific

difficulties that nefarious agents would face to achieve such ends. Responses here were varied, but included opinions such as “synthetic biology as bioterror would be difficult for the terrorist to control and deliver to a specific target”, “resource limitations would restrict such research to well-resourced labs”, and “one would need to possess a scientifically adept and resource rich scientific network in order to pull off such a scheme.” Overall, respondents were skeptical of a deliberate biosecurity threat posed by synthetic biology pharmaceutical research, with only a small number (4) noting potential concerns where a “lone wolf attacker” may be able to deliberately engineer a virus or pathogen to harm society. Within this context, it is important to understand that biosecurity was understood as a ‘deliberate attempt to use synthetic biology research methods to derive harmful infectious substances and materials’, where virtually all respondents (22 of 23) noting that an accidental release of such a substance would be a much more likely risk scenario.

Looking at such an accidental release scenario, biosafety risks were assessed as those that potentially harm workers, non-laboratory organisms, and/or the environment in the process of conducting biological research. Singaporean interviewees noted a similar level of doubt as with biosecurity risks related to the potential for novel biosafety risks to arise via synthetic biology pharmaceutical production, yet responses were more varied in contextual response. Overall, while 17 of 23 respondents noted that novel biosafety risks are unlikely within synthetic biology research and development, 16 of those 17 did admit that some potential for unintentional exposure of novel genetic material to human and environmental health. The mechanism that was described as the vehicle for such risk to arise included both horizontal gene transfer and efficacy concerns.

For the former, respondents noted that, while highly unlikely, the transfer of novel genetic material from an engineered pharmaceutical to natural human or environmental cells had the potential to cause synthetic genetic information to transfer to the natural cells in question, which could contribute to substantial negative health harms (further discussed in Wright et al 2013; Endy 2005). For the latter, efficacy was determined to be an issue where the synthetic biology pharmaceutical product fails or does not perform in its intended manner, contributing to a loss of resources and potential negative health consequences for patients.

Overall, 22 of 23 respondents noted the potential for biosafety risk resultant from synthetic biology pharmaceutical development, where such risk could occur at various stages of the given product's life cycle. Further discussion of these risks are described in the section below.

6.4.2 Pharmaceutical Product Risk Across Life Cycle

Given that 22 of 23 Singapore-based respondents noted the potential for biosafety risks associated with synthetic biology pharmaceutical development, a natural extension of such narrative analysis included discussion of where along a pharmaceutical product's life cycle such risks may materialize. Figure 18 below serves as a visualization of interviewee responses of where health risks are perceived to occur across a generic pharmaceutical product's life cycle, while Table 9 indicates aggregated responses relative to pharmaceutical biosecurity risk along each life cycle stage, with further discussion regarding risk perception within each life cycle stage noted further below.

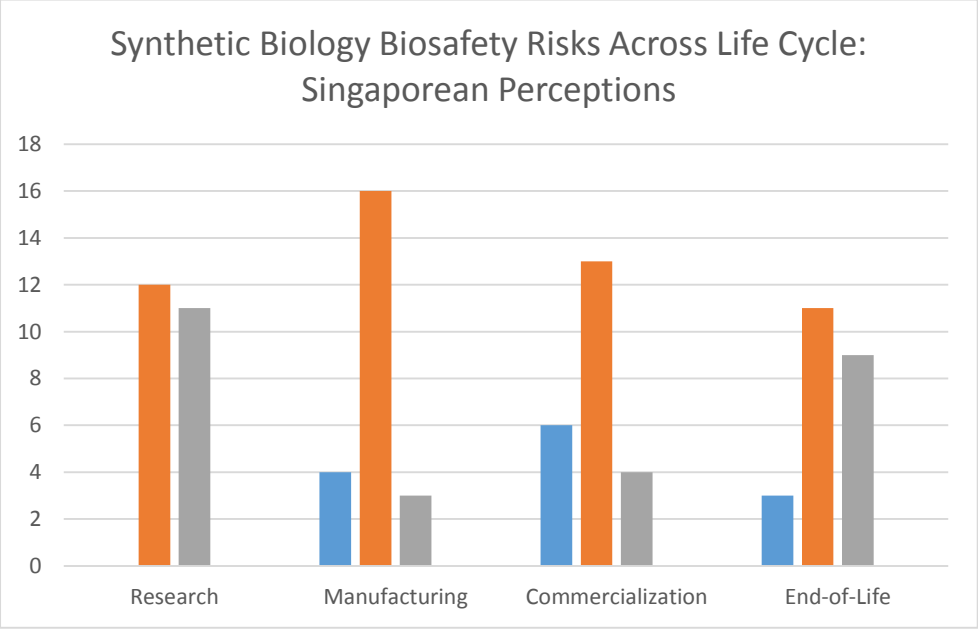

Figure 18. Singaporean Perceptions of Synthetic Biology Pharmaceutical Biosafety Risks Across Product Life Cycle. Blue = No Risk; Orange = Unlikely yet Possible Risk; Gray = Moderately Possible Risk; Yellow = Likely Risk (n=23)

Research	Manufacturing	Commercialization	End-of-Life
1.5	0.9	0.9	1.3

Table 9. Aggregate Pharmaceutical Biosecurity Risk Responses (n=23).

From a life cycle perspective, respondents collectively noted greater probabilities of novel biosafety risks at the 'Research' and 'End-of-Life' stages within pharmaceutical development and use. The six respondents who stated a moderate fear of novel biosafety risk from synthetic biology pharmaceuticals were particularly concerned with the 'Research' life cycle stage, where researchers and scientists could be accidentally or inadvertently exposed to novel genetic material and risk the potential for horizontal gene transfer or negative interaction effects with such novel biologic materials *in vivo*. Singapore Respondent 9 (Lab Researcher) noted that "where in early research synthetic biology cells lack the engineered controls to prevent proliferation or spread outside of containment […], if scientists get exposed to this material, it could have really harmful effects." Singapore Respondent 10 (Social Scientist) went a bit further by arguing that "we have to assume, despite all of our planning, that there will be a breach in containment […] it's happened before with terrible viruses, and it may likely happen for synthetic biology."

These sentiments focused upon the potential for the improper containment and/or unintentional exposure of genetically modified material that results in their exposure to lab scientists, where built-in genetic controls such as with a 'kill switch' are not yet fully developed and utilized to prevent the proliferation of such novel genetic material outside of an area of intended use. All responses (n=23) noted that while the probability of containment and exposure issues is moderately worrisome, the probability that such exposure results in significant novel health risks and harms for researchers is very unlikely. Singapore Respondent 6 (Social Scientist) described this notion by saying "we have to worry about research exposure scenarios because there is a small chance […] like one lab experiment in a year […] where exposure could produce health hazards, but by and large most exposure scenarios would result in the novel genetic material harmlessly dying off without producing gene transfer or harming the health of the scientist."

This sentiment was echoed by virtually all respondents who noted some biosafety concern at the 'Research' life cycle phase (n=22), where even though risk is possible, they argue that synthetic biology-derived pharmaceuticals either would not possess harmful characteristics that would yield acute novel biosafety hazards (such as with artemisinic acid produced via

Keasling's anti-malarial drug) or would be unlikely to survive and reproduce outside of a contained and controlled environment (such as with a potential synthetic biology-derived probiotic). Such discussion did not dismiss the potential for 'conventional' biosafety health risks, although Singapore Respondent 3 (Lab Researcher) noted that "the risk and exposure profiles for such scenarios are more well-known […] and probably don't require new regulation to control."

Ultimately, a point raised within all interviews included the notion that "some synthetic biology processes do not generate synthetic genetic material, but instead serve as a vehicle to more easily produce conventional therapeutics and vaccines." In other words, ongoing research activities such as with Keasling's method of producing artificial artemisinic acid do not yield novel biological compounds in their own right, but instead use yeast to grow biological compounds that can be used in lieu of naturally produced alternatives. In such scenarios, multiple respondents noted that if no novel biological material exists within the eventual pharmaceutical, then it is unlikely for novel risk to arise from such novel genetic material. One respondent noted that scientists may be at risk of exposure to novel compounds within the 'Research' life cycle phase, yet the route of such exposure is conventional in nature and is combatted using traditional measures of lab safety.

Another life cycle stage with higher levels of biosafety concern by interviewed experts includes the End-of-Life disposal of synthetic biology pharmaceuticals and therapeutics. Where discussion of biosafety risks within the 'Research' life cycle stage focused upon laboratory accidents and containment errors, this life cycle stage instead was discussed from the perspective of improper disposal and release of novel biological materials in a manner that allows for the exposure of such material to the natural environment. On one hand, three respondents noted that the risks within the End-of-Life stage were essentially nil, where Singapore Respondent 11 (Lab Researcher) argued that "such materials will not be able to survive and proliferate in nature for more than a few hours at most, […] and the risk of truly harmful gene transfer is so remote that it will eventually be dismissed outright."

On the other hand, nine respondents (39%) noted that where conventional pharmaceuticals are already disposed of in a manner that allows certain pharmaceutical

compounds to enter into the water table (Westerhoff et al 2005), there exists the potential for synthetic biology-derived pharmaceuticals to be improperly disposed of and eventually proliferate in the environment. Singapore Respondent 12 (Lab Researcher) noted that "while the case-by-case chances are slim of [contamination and exposure] happening after drug disposal, our current experience with other pharmaceutical drugs and their improper disposal forces us to consider the likely possibility that these novel drugs may reach the environment unintentionally."

Each of the nine respondents that noted the End-of-Life phase as containing likely novel health risk noted that both the risk of potential horizontal gene transfer as described by Heinemann and Traavik (2004) as well as the potential for engineered bacteria cells to compete with natural cells for resources and survival in a post-release scenario is a problematic scenario that scientists and regulators must consider when engaging with the production and distribution of synthetic biology pharmaceutical products. In a group interview, Singapore Respondent 10 (Social Scientist) and Singapore Respondent 13 (Lab Researcher) discussed that "while the controlled use of synthetic biology drugs within secure labs heavily reduces the risk of environmental exposure concerns at the disposal stage of a pharmaceutical's lifespan, we have to consider whether issues such as gene transfer and environmental competition may be issues that arise from improper disposal if we agree to distribute these drugs to the lay public."

An important vein of discussion included those pharmaceutical products created via synthetic biology processes yet do not inherently contain novel or artificial genetic information in the end product. As noted above, two discussed cases that fell into this category include Keasling's antimalarial precursors as well as Novartis' described method to more rapidly produce vaccine components for various strains of influenza. Rather than yield novel health risks, 21 of 23 Singapore-based respondents stated that these innovations would not yield novel health risk such as with horizontal gene transfer or threats to biodiversity at the End-of-Life phase, with two respondents stating that it was too soon to tell. Instead, respondents noted that novel health risk would likely arise from only those products which contain novel genetic material within the pharmaceutical proper, which would then serve as a potential

vehicle of exposure for such novel biological material to gain exposure to humans and the natural environment.

Aside from the 'Research' and 'End-of-Life' life cycle stages, Singapore-based respondents were skeptical of novel risk occurring within the 'Manufacturing' and 'Commercialization' stages due to rigorous testing of pharmaceutical safety and efficacy prior to mass pharmaceutical production and commercial release. Respondents were slightly more concerned with risks at the 'Manufacturing' life cycle stage, with 19 respondents (83%) noting the potential for improper containment of engineered biological material breaking containment and gaining exposure to workers. Singapore Respondent 1 (Lab Researcher) described this as "an inherently conventional risk profile", where "the novel risk is not the vector of exposure, but instead that the material workers could be exposed to is novel and unpredictable in nature."

While 19 of 23 respondents did note some concern over the potential of workers being exposed to such biological material and experiencing either gene transfer or acute and harmful health consequences, 20 of 23 stated that these risks "may be easily mitigated through existing governance and safety practices", where "safety protocols and clothing will make exposure scenarios probabilistically highly unlikely." Likewise, general perceptions of novel health risk at the 'Commercial' stage generally included beliefs that such risks were highly unlikely, and would only arise for cases where the pharmaceutical in question contains novel genetic material and is not simply the result of a synthetic biology production process. Singapore Respondent 6 (Social Scientist) noted that "the likely risk profile here would be for vaccine synthesis and engineering, where interaction effects *in vivo* could result in unintended health consequences to the patient." All 23 respondents noted that such cases were highly unlikely and may never occur, Singapore Respondent 13 (Lab Researcher) did state that "we have to be wary of side-effects […], there could be something new here that produces harms to humans in a manner that is very debilitating or even fatal in very small numbers of cases."

From a life cycle perspective, 18 of 23 Singapore-based respondents regardless of vocation expressed skepticism that synthetic biology pharmaceuticals may generate novel health concerns, although most did note that further research was needed to clarify this point

and that the potential for harmful risk scenarios were scientifically plausible, if probabilistically unlikely. Most argued that the same conventional exposure scenarios and health risks as with traditional pharmaceuticals, therapeutics, and vaccines would apply to synthetic biology-derived alternatives, yet "the risk and exposure profiles for such scenarios are more well-known […] and probably don't require new regulation to control." Given the general belief within 18 of 23 interviewed participants regarding the unlikely yet plausible potential for novel health risk to arise, the section below discusses perceptions of how these various experts understood existing regulation to cover synthetic biology research and development alongside discussion of how, if at all, such regulation must shift in order to provide optimal guidance and best practice for synthetic biology researchers moving forward.

6.5 Synthetic Biology: Hard and Soft Law Regulation Within Singapore

6.5.1 Existing Regulations and Law to Govern Synthetic Biology

Singapore's status as a growing economic power via capitalism and its subsequent ability to drive forward technological research in various areas as synthetic biology is often viewed as a paradox based on the common scholarly discussion described by Rodan (2004) and Bhasin (2007), which note that such regulatory regimes rarely succeed in advancing successful capitalistic markets or a robust research base to drive innovation. Instead, the 'soft-authoritarianism' in Singapore described by Olds (2007) has driven it to be a state that pursues global research and education opportunities in the spirit of forging new scientific opportunities beneficial to the Singaporean people and state. Synthetic biology includes one of these opportunities, with particular academic attention and governmental resources paid to pharmaceutical and therapeutic product development.

Of the three cases discussed within this dissertation, Singapore differs in political structure and smaller economic size from the European Union and United States. This is driven by Singapore's status as a soft-authoritarian state yet continued economic success and capitalistic tendencies with respect to advancing technological innovation and development, making it difficult to ascertain the regulatory mechanisms in place to guide synthetic biology regulation or whether such mechanisms are *de facto* effective and valid (Ortmann 2011; Lingle

1996; Rodan 2004). With respect to synthetic biology, Singapore Respondent 14 (Social Scientist) described regulation of the technology's products as "generally emerging, but the attitude we take away is that our research is important and risk is handled internally though internal review boards and other university governance regimes." Singapore Respondent 5 (Lab Researcher) stated that "No one is 100% sure what laws and regulations apply to synthetic biology, but government involvement with issuing our grants and advocating for synthetic biology research signals their general approval of our work." Such sentiments were widespread, where all respondents (n=23) noted some uncertainty regarding where governmental oversight and regulation factored in to synthetic biology research, both from a hard and soft law perspective.

Such uncertainty was particularly high with respect to identifying a specific regulatory statue or authority that governs risk related to synthetic biology research and development. From the perspective of external regulation, no respondent stated a particular law or regulation explicitly dedicated to external synthetic biology regulation. Instead, most respondents (14 of 23) pointed to existing laws and regulations related to biological agent development and biosafety as sufficient cover for synthetic biology products. Specifically, these included The Biological Agents and Toxins Act (2005) and The Singapore Biosafety Guidelines for Research on Genetically Modified Organisms (2013).

As with respondents from the United States (Chapter 4) and the European Union (Chapter 5), this dissertation sought to acquire information relative to such familiarity amongst Singaporean stakeholders. A further extension of this included discussion of whether such regulatory authorities were actually utilized and were functionally valid from a regulatory practice perspective, where early Phase 1 interviews indicated that such regulation may not actually be useful in its current state and may be less structurally derived in favor of general administrative authority by governmental regulators within agencies such as the Singaporean Economic Development Board along with the Customs Authority (information here is included in the 'Limitations of Existing Regulation' section below).

Looking first at general awareness of reach respondent regarding the hard and soft law pertinent to synthetic biology research, Singapore-based respondents were generally able to

identify and describe those regulatory authorities that had oversight to their work. Figure 19 below indicates the ability of Singaporean respondents to name and describe the regulation applicable to synthetic biology research as well as the government agencies charged with executing such regulation. Every respondent was able to name either an agency or regulation previously discussed above, with six respondents expressing intimate familiarity with all of the discussed regulatory items above along with the various government agencies empowered by such regulation to govern synthetic biology research and development. This level of response is generally consistent with findings from Chapters 4 and 5.

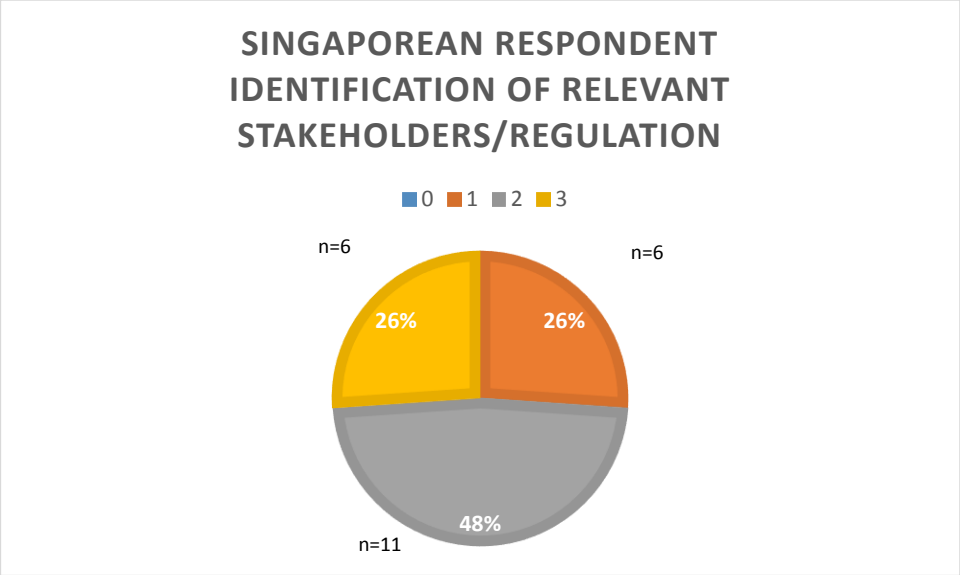

Figure 19. Identification of Synthetic Biology Regulation by Singapore-based Respondents. 0 = no recognition, 1 = recognition of a piece of hard/soft law regulation but not an agency, 2 = vice versa, 3 = recognition of both hard/soft law regulation and relevant agencies

An additional line of questioning conducted alongside perceptions of local hard and soft law regulation included discussion around collective opinion of roughly when synthetic biology pharmaceuticals would commercialize and enter the marketplace. As noted in Chapter 4.2, such responses serve only as 'best guesses' by respondents, and should not be taken for more than an academic exercise to gain a general idea of what we may expect relative to the development of synthetic biology products in the European Union in the future. As such, the responses provided below should not be taken as an assessment of a concrete timeline for commercialization.

For Singaporean respondents (Figure 20 below), general discussion here elicited a common belief that such products, both for vaccine and therapeutic development, have a strong likelihood to commercialize in the near future, with 10 respondents indicating a belief in early commercialization within 5 years, and 11 arguing for commercialization within 5-10 years. Only two respondents noted that such commercialization was unlikely to occur within a 10-year timeframe from 2014. The reasons noted for this general level of optimism are varied, but include responses from Singapore Respondent 15 (Social Scientist) such as "the ability of synthetic biology to produce drugs and vaccines for neglected tropical diseases will pressure innovators to move quickly" by Singapore Respondent 15 (Social Scientist). However, as will be discussed in this section below, such perceptions that synthetic biology pharmaceuticals will develop relatively soon did not translate into a strong belief in the need for novel hard or soft law regulation, where many respondents noted that existing regulation such as with The Guidelines was sufficient, or extensions of self-regulation within existing soft law regulation were all that was necessary to review uncertain or currently unregulated risk factors for the immediate future.

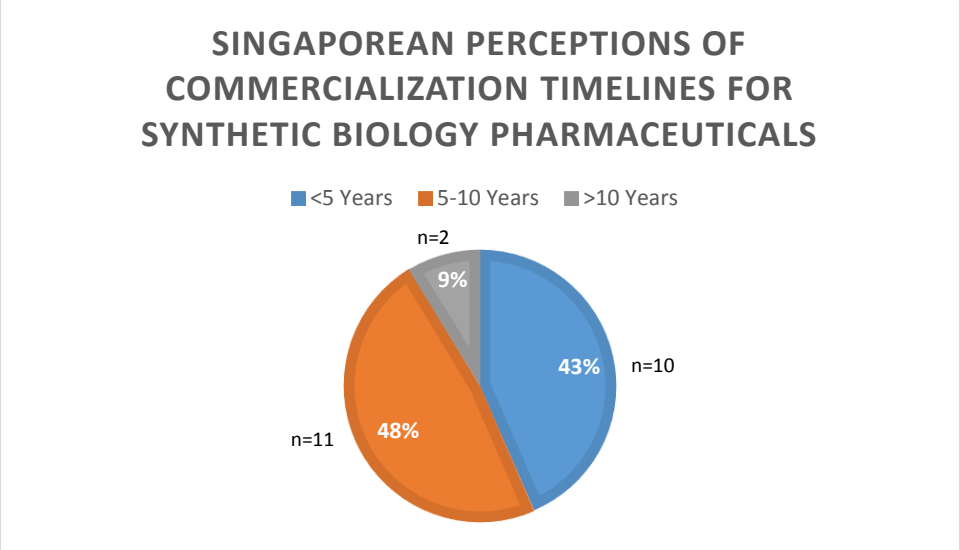

Figure 20. Singaporean Perceptions of Distance in Time for Synthetic Biology Products to Enter Marketplace (from December 2014)

6.5.2 Discussion of How Existing Regulation Captures Synthetic Biology Research in Singapore

Overall, Singapore-based respondents argued that extensions or improvements of national hard and soft law were largely unnecessary in the technology's current state of development. Figure 21 below indicates that of the 23 interviewed experts, 9 argued that no new regulation of synthetic biology research was needed or helpful. Likewise, 7 argued that extensions and improvement to national regulation were unnecessary and all concerns that the novelties posed by synthetic biology from a risk perspective could be resolved via internal self-regulation, where internal oversight in the form of review boards and other research groups would be adequate to review the risks and hazards of the technology's development (where existing national hard and soft law would supplement such review boards as with The Biosafety Guidelines and the Biological Agents and Toxins Act). Finally, 7 respondents argued that explicit improvements and additions to existing national hard and soft law were required to adequately cover synthetic biology risks throughout product development, where existing hard and soft law were not directly tied to synthetic biology and new regulation would clearly outline government responsibilities and capabilities for synthetic biology product research.

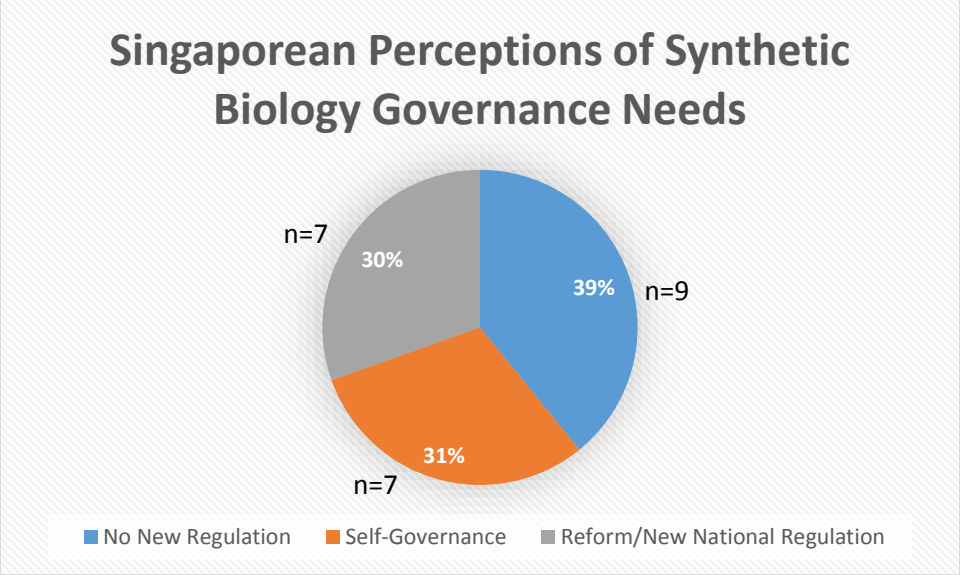

Figure 21. Perceptions Amongst Singaporean Experts Regarding the Regulatory Needs for Synthetic Biology Research and Development

Those against any new regulation focused on the idea that the technology was simply not mature enough to pass regulation without either (i) leaving open the potential for unanticipated health risk, or (ii) unnecessarily and prohibitively preventing research that may

not be risky or hazardous at all. This is consistent with discussion presented by Mandel and Marchant (2014), who described this tradeoff as one that regulators within a given country must grapple with when deciding how to govern the technology in its various iterations now and in the future. Relevant statements here include notions that "synthetic biology may not need new regulation aside from existing law related to genetically modified organisms", where "these regulations as with The Biosafety Guidelines are *de facto* used to govern the technology already." Similarly, Singapore Respondent 3 (Lab Researcher) and Singapore Respondent 4 (Social Scientist) described how "it would be better to wait for the technology to mature and demonstrate true scientific capabilities rather than regulate based upon what we think *may* happen", with many describing a fear that preemptive regulation would only stymie research.

These beliefs were generally shared by those who argued for self-regulation to cover any novel risks associated with synthetic biology research, with Singapore Respondent 16 (Social Scientist) stating that "these review boards are scientifically competent and can more directly review health risk of this developing technology." Similarly, Singapore Respondent 15 (Social Scientist) stated that "such review boards and self-governance would help us air on the side of caution by looking for potential concerns, while avoiding burdensome and potentially unnecessary regulation." Throughout both groups, the shared belief centered on the ideal that science should continue to refine and improve synthetic biology capabilities, where further national regulation would only be needed in the future when synthetic biology research is close to producing commercial goods.

Out of 23 respondents, 7 contended that new regulation would be necessary and helpful to demonstrate best practices and safety guidelines with producing, consuming, and disposing of genetically modified material resultant from synthetic biology research. Singapore Respondent 6 (Social Scientist) stated that "commercialization of early stage Synthetic Biology products is not far away, and it is important to head off health risk before such commercialization becomes widespread." Even amongst these respondents, however, it is important to note that none argued for creation of a sui generis legislative instrument that would pertain explicitly to synthetic biology, but instead argued that regulation and guidance as attachments to soft law like The Biosafety Guidelines would better demonstrate best practices

and safety measures that companies and researchers could emulate during their research. Singapore Respondent 9 (Lab Researcher) stated that "having best practices like The Biosafety Guidelines, but more specific to synthetic biology, can both make the public feel safer about purchasing such products, and offer companies certain benchmarks to meet in order to demonstrate safe research and production practices." In this way, these 7 respondents sought to add extensions of synthetic biology to relevant soft law and regulatory guidance as with The Biosafety Guidelines – something that "can easily be revised and changed as new information on risk and exposure becomes available." Given the soft-authoritarian nature of the country and the involvement of government within many stages of the funding and oversight of academic research, Tan (2009) denotes that such soft law would be derived via public-private partnerships. In such an arrangement, government agencies such as with the Economic Development Board or GMAC would work with developers in industry to engage with information-sharing and guidance exercises designed to improve the governance of synthetic biology in an iterative an adaptive manner.

6.5.3 The Role of the International Community in Informing Future Regulation

Across the vocational respondents from Singapore, a recurring theme brought up on the subject of synthetic biology regulation includes the need for Singapore to continue to monitor legislative responses to synthetic biology within governments as with the European Union or the United States. Academic respondents particularly focused on the need to remain active within scholarly discussions, peer-reviewed journal submissions, and international conferences specific to synthetic biology research and development. Singapore Respondent 14 (Social Scientist) noted that "there is a belief here that we can learn much from the West's experience in regulating synthetic biology", a sentiment that was stated in at least six other Singaporean interviews. Further from Singapore Respondent 14 (Social Scientist), paying attention to scientific developments in the field can allow Singaporean universities and research agencies to "understand the possibilities that the technology may yield, and recruit talent to pursue such goals."

Likewise, government respondents spoke more on the need to follow emerging debates and developments taken by the United States and the European Union, respectively, to govern and regulate synthetic biology products such as with pharmaceuticals. Such attention to external regulatory mechanisms included a review by Singaporean government stakeholders of the guidelines, regulations, and publications related to the regulation of genetically modified organisms by Australia, the United States of America, the European Union, the World Health Organization, and the United Nations Environment Programme. The subsequent results and collective opinion of this review was utilized to form The Singapore Biosafety Guidelines for Research on Genetically Modified Organisms (the soft law guidelines discussed above), and empowered the Genetic Modification Advisory Committee of Singapore to adaptively and flexibly modify such Guidance as new technologies related to genetic modification arise (driving all government interviewees to state the relevance of such soft law as a governing authority of synthetic biology).

Overall, many respondents noted that while national hard or soft law shifts in regulation may currently be inappropriate, indications of weakness or concerns within existing regulatory paradigms within Western hard and soft law may incent regulators and stakeholders within Singapore to shift their regulatory capabilities and follow suit. Such discussions of regulatory limitations offer evidence of where such legal bodies or regulatory best practices may not apply to synthetic biology research, and would indicate where Singaporean regulatory authority does not sufficiently cover related research on pharmaceuticals as well as other products. For now, the current belief held by many respondents is to "wait and see […] and find out if change to national regulation is really needed."

6.6 Discussion

Within this case, 23 respondents engaged within one or more interviews to discuss the novel risks associated with synthetic biology pharmaceutical products alongside existing regulatory capabilities and limitations (where perceived) to properly govern this emerging technology. As with Chapters 5 and 6, interview responses were coded based upon general perceptions of biosecurity risks as well as biosafety risks across a generic pharmaceutical

product's life cycle, offering a notion of where novel health risk may occur, the probability of such risks occurring, and the mechanisms that may cause such risks to arise. Likewise, contextual discourse facilitated feedback regarding the regulation of such risks under existing hard and soft law paradigms, where each respondent was asked to offer feedback regarding whether such hard and soft law was robust in terms of governing synthetic biology research and development, or whether novel soft law regulation was needed in the short term to protect against potential novel health risks.

Unique from results found within Chapters 5 and 6, Singaporean interview respondents were less concerned with the potential for novel health risk associated with synthetic biology pharmaceutical products. The reasons for this are varied and are discussed in the sections above, but are generally centered on (i) the various resource requirements and scientific education needed to synthesize and engineer a harmful virus or pathogen, (ii) the highly unlikely possibility of horizontal gene transfer resulting in harmful health consequences, and (iii) the general inability of novel biological material resultant from synthetic biology product research to proliferate outside of containment and above certain population thresholds due to various controls engineered into the cell's DNA. This contributed to a belief by 70% of all respondents that either no new regulation or self-regulation alone was needed to properly guard against potential risks associated with synthetic biology pharmaceuticals across a product's life cycle, leaving most to argue that existing hard and soft law was sufficient to govern this research activity. However, respondents equally indicated that future efforts of reform would be facilitated by a centralized governmental structure and an adaptive history of regulatory reform related to genetically modified organisms.

Chapter 7:

Synthesis

7.1 Introduction

The overall focus of this dissertation was to review whether variations in synthetic biology regulation existed across the United States, the European Union, and Singapore. Further, elements of risk culture were used as hypotheses to test why such variations may occur, if they do at all. Where Chapters 5-7 reviewed such information for each of the three case governments, this chapter seeks to comparatively address the effect of risk culture on synthetic biology regulation across the collective cases.

This dissertation reviewed three separate cases to review such variations in synthetic biology regulation due to components of risk culture. The United States, European Union, and Singapore all individually contain their own unique political, technological, and institutional characteristics which drive their regulation and subsequent perception of risk – a phenomenon described by Jasanoff (1986), Parthasarathy (2012), Kelemen (2011), and many others. However, certain elements of risk culture may have had a greater influence upon regulatory decision making within specific governments (Kagan 2009; Kelemen 2011; MacKenzie 2000; Vogel and Lynch 2001). To recall such elements from Chapter 3, these include:

i) The degree of centralization in government power

ii) The degree of formality in regulatory dispute resolution

iii) The general appetite by local stakeholders for risk acceptance

iv) The historical path of regulatory reform within a given government

v) The perceived domestic benefit of a particular innovation

Below, information from the three cases are discussed to review whether or not how each of these items have come to influence regulatory decision making within each case.

7.2 Comparative Assessment: Three Cases

7.2.1 Common Themes Presented Across Cases

Within each case, respondents were asked to discuss their opinions and beliefs related to novel synthetic biology health risks that could arise throughout the life cycle of a synthetic biology product, with particular focus levied to pharmaceuticals. Below, Table 10 includes the number of respondents that discussed each theme without prompting, where the respondent discussed the given item as a measure of potential novel risk that a synthetic biology pharmaceutical would provide (later in the interview, specific questions were asked about biosafety and biosecurity risks – the responses of which are detailed in Chapters 5-7). It is important to note that the sample size for each case is small and must be viewed based upon the fact that such data should be expanded upon as more synthetic biologists arise in the field over the next few years.

Risk	**USA** (n=17)	**Europe** (n=9)	**Singapore** (n=23)
Horizontal Gene Transfer	13	7	12
Biodiversity	15	8	15
Exposure (Human or Environmental)	14	8	17
Dual-Use/Biosafety	13	6	11
Accidental Release	16	8	19
Long-term Effects	5	4	7
Proper Disposal	15	8	19

Table 10. Common themes raised by interview respondents across all cases

Of the general risk themes raised by interview respondents, the issues most commonly raised as potential issues of concern included *Accidental Release* and *Proper Disposal.* For the former, respondents noted to varying degrees that the potential for an event such as a breach in laboratory containment or manufacturing center could generate potential risks to humans and the environment. Most respondents went on to state more specifically that such risks contribute to a *Biodiversity* (n=38) or *Exposure* (n=39) threat, making *Accidental Release* an

umbrella theme of concern related to an unintentional release of novel genetic material outside of a controlled environment. *Proper Disposal* was treated as an independent theme where concerns raised about the potential for novel genetic material within synthetic biology pharmaceuticals were noted explicitly here and not double counted as *Accidental Release.* In this manner, both *Biodiversity* and *Exposure* received similar levels of attention by interview respondents when asked to raise their perceptions of potential issues that synthetic biology pharmaceuticals could generate.

A notable point of discussion includes the relatively lower levels of attention paid to *Horizontal Gene Transfer* or *Long-term Effects*, with no case breaking an 80% discussion rate for either theme prior to specific questions pertaining to such risks later on in the interviews. Such results are in contrast with the degree of attention that these issues receive within published literature such as within Endy (2005), Wright et al (2013), Cardinale and Arkin (2012), and several others for horizontal gene transfer or Andrianantoandro et al (2006), Elowitz and Lim (2010) and Tucker and Zilinskas (2006). However, *Horizontal Gene Transfer* still was raised as a potential risk consideration at the onset of such interviews by a majority of respondents in all three cases, and was further unpacked by all respondents as a potential measure of health risk for synthetic biology pharmaceuticals when such gene transfer was explicitly discussed later in the interview.

The same could not be said for *Long-term Effects,* where no majority was reached across any of the three country cases. When asked explicitly about considerations for long-term and/or chronic risks that such products may yield (such as with extended harm to human or environmental health over time), a Singaporean academic social scientist 3 noted that "these [long-term risks] should be considered, but most concern is for acute issues that can be clearly linked as being caused by the drug with engineered genetic material." Likewise, US Respondent 12 (Lab Researcher) argued that "acute health risks are more troublesome for a product to get past regulation, particularly pharmaceuticals […] so this is likely the first thing that comes to mind." Some respondents (n=32) who noted *Biodiversity* concerns also discussed the potential for permanent or otherwise long-lasting harms to animals or the natural environment, although

such responses were not double counted as *Long-term Effects* unless a time horizon was explicitly stated in such comments.

7.2.2 Discussion of Probability of Novel Risk and Mechanism of Such Risk Across Cases

Within the sample size covered by Interview Phases I-III (n=49), several trends emerged when reviewing aggregate responses comparatively across each of the three country cases. These may be divided into two general veins of discussion, including (i) discussion of where on a pharmaceutical product's life cycle risk may arise, and (ii) the probability of individual types of risk that may arise to human or environmental health. This information is comparatively discussed across each of the three cases below.

For the first item (Table 11 below), respondents typically viewed the Research and End-of-Life life cycle stages as having the greatest potential for novel health risk from a synthetic biology pharmaceutical product. Such responses are consistent with concerns raised by Carter et al (2014), Bates et al (2015), and Dana et al (2012), where preclinical and disposal scenarios for pharmaceuticals containing engineered biological material could generate hazards to humans, animals, and/or the environment. As noted in Chapters 5-7, common explanations here include the potential for laboratory accidents and exposure scenarios to humans in a laboratory environment (see also Schmidt 2008; Moe-Behrens et al 2014), the unlikely yet possible threat of horizontal gene transfer, and threats to biodiversity and risk of exposure of novel genetic material to the environment via improper containment and storage upon material disposal (Schmidt and de Lorenzo 2012; Oldham et al 2012). Respondents argued that such risks were elevated for a variety of reasons, including the propensity for breaches in biosafety protocol to occur once synthetic biology pharmaceutical research becomes more commercialized, the uncertainty surrounding horizontal gene transfer and threats to biodiversity, limitations in the ability to control novel genetic material in accidental release scenarios, and limited existing oversight to mitigate or effectively control such risks in preclinical research or end-of-life disposal.

While Research and End-of-Life were viewed by respondents as being areas with enhanced potential for novel risk events, the Manufacturing and Commercialization life cycle

stages were generally viewed as areas with less likelihood for such events. Among other points of discussion, general reasons for this were expressed as less uncertainty and improved oversight within these life cycle stages, such as the need for pharmaceutical products to pass preclinical trials prior to Commercialization as well as the engineering of cellular controls within engineered cells to prevent cell populations from growing beyond certain cell counts and/or reducing the probability that such cells would engage in gene transfer or survive outside of a contained field (Moe-Behrens et al 2014; Oye et al 2014; Schmidt and de Lorenzo 2016).

Not all respondents agreed with this point of view, yet generally these stages were viewed as areas with somewhat less uncertainty relative to health risk along with oversight controls within each of the three cases that reduce the potential for widespread hazard. Such comments were not designed to indicate that regulators should not be concerned at all with risk in these life cycle stages, but instead to indicate general feelings that *novel* risk is probabilistically less likely than in preclinical research or product disposal where oversight is limited and uncertainty is greater (Carter et al 2014).

From a comparative perspective, Table 11 further indicates that European and American respondents generally voiced greater levels of concern for the potential of health risks to arise at various life cycle stages as opposed to their Singaporean counterparts. Where Table 11 is addressed on a scale from 0-3 (0 indicating a perception of no risk, and 3 indicating substantial risk), Singaporean respondents generally viewed risks across the life cycle of a synthetic biology pharmaceutical as being relatively limited in nature, while US and Europe-based respondents expressed more heightened levels of concern. As noted above, this is particularly true for the *Research* and *End-of-Life* stages, where all three cases expressed more heightened levels of concern as opposed to the *Manufacturing* and *Commercialization* life cycle stages.

Life Cycle Stage	USA	Europe	Singapore
Research	1.8	2.1	1.5
Manufacturing	1.3	1.6	0.9
Commercialization	1.4	1.3	0.9
End-of-Life	2.1	2.0	1.3

Table 11. Life Cycle Perceptions of Novel Risk Probability Across Cases

For the second item, general discussion of biosafety and biosecurity risks revealed a general trend across all three cases to view novel Biosafety risks as probabilistically more likely to occur (see Table 12 below, with the same scale as Table 11). Such discussion was relatively mild amongst Singaporean respondents, where experts across academia, government, and industry noted that while biosafety risks are plausible, they are generally unlikely for pharmaceutical products. Such sentiment was due to a belief that harmful horizontal gene transfer is extremely unlikely to occur, while threats to biodiversity or exposure-driven risks to humans, animals, or the environment are minimal and mitigated by various engineering controls such as with killswitches that limit engineered cell population count or the movement of such cells outside of a predesigned area. Respondents from the United States and Europe were more concerned with biosafety risks, where they viewed pharmaceuticals which contain novel genetic material in the commercialized product (i.e. live-attenuated viral material for vaccines or engineered bacteria for probiotics) as having a plausible chance of producing biosafety events via laboratory accidents, improper containment and disposal of pharmaceutical materials, and unintentional exposure of such materials by laboratory researchers or workers.

Risk Category	USA	Europe	Singapore
Biosafety	1.8	1.9	1.2
Biosecurity	1.3	1.2	1.0

Table 12. Expert Views on the Probability of Novel Health Risk by General Category

Unlike biosafety risks, respondents across the three cases generally viewed biosecurity risks as generally improbable (though not entirely impossible) due to constraints pertaining to existing oversight preventing such behavior, extensive resource requirements to produce reliable and effective agents that produce deliberate harms to humans or the environment, and the current limitations in the field to successfully engage in such work even if resource barriers were overcome. A frequent point of discussion here included the promotion of dual use technologies, where synthetic biology pharmaceutical research for helpful purposes could also be repurposed for nefarious means by certain individuals or groups (see also Kelle 2009;

Mukunda et al 2009). To varying degrees, respondents from each of the three cases described such scenarios as unlikely, although they did articulate a need to continue to bolster international oversight for such cases and potentially limit the dissemination of small amounts of material that could directly facilitate the production of a harmful virus or infectious agent outside of laboratories with clear oversight and regulation (see Kelle 2009; Mukunda et al 2009). Despite such precaution, however, most respondents throughout each of the cases expressed doubt that synthetic biology pharmaceutical innovation could be successfully utilized to produce a virulent and efficient method of health hazard for biological organisms.

Where each individual case had responses that addressed particular concern of novel health risk from synthetic biology pharmaceutical research and development, the general trends noted above may triangulate discussion of the technology's novel health risks while also providing further insight into the regulatory concerns that various countries may have related to synthetic biology regulation. In Section 7.2.3 below, such feedback is further reviewed against the various elements of risk culture that may have a hand in influencing individual government regulation of synthetic biology, where such political and institutional factors may drive government regulators and policymakers to act in unique ways to regulate the technology and its subsequent products.

7.2.3 The Effect of Risk Culture Upon Variations in Synthetic Biology Regulation

Given the assessment and discussion within literature and interviewed experts within Chapters 4-6, this section comparatively reviews the three cases to determine to what extent and why local variations of synthetic biology regulation have arisen. Specifically, feedback from each of the three cases are reviewed to determine whether and to what extent the elements of risk culture listed in Section 7.1 have influenced such synthetic biology regulation.

Table 13 below comparatively reviews key components of regulatory risk culture within the three cases discussed within this dissertation. Comparisons between the risk cultures and institutional frameworks of the United States and European Union have been well documented in works such as Kelemen (2011), Kagan (2009), Parthasarathy (2012), Jasanoff (2002), and Jasanoff (1986). Such authors generally note the divide between the environment in which

regulatory proposals are discussed and disputed as well as the options for dispute resolution taken by each government as being among the primary differences in regulation of new technologies between the United States and the European Union (Kelemen 2011; Kagan 2009).

As described within Chapter 4, the United States generally expresses an adversarial form of regulatory discussion as well as a reliance upon formal institutions to resolve disputes around differences of opinion related to technology regulation (Kelemen 2011; Kagan 2009).The United States' risk culture and values pertaining to government regulation cause it to differ from its European and Singaporean counterparts by relying on formal mechanisms of regulatory dispute resolution, allowing for several actors and potential veto-points within the policymaking process, and generally containing an adversarial nature where disputes frequently require legal adjudication and require substantial financial and political resources in order to overcome (Kelemen 2011; Volcansek 2014). Within this framework of institutional rigidity and adversarial legalism amidst an environment of high transparency, American regulators and policymakers must be mindful of the limitations and problems they may experience in the effort to initiative and implement regulatory reform for new technologies. While such concerns are shared by other democratic governments, a risk culture grounded in adversarial legalism and frequent gridlock is noted by Fisher (2007) and Coleman (1999) as making it difficult to enact hard law legislation and reform. A notable concern here described by Epstein and O'Halloran (1999) and North (1992) includes the high transaction costs associated with triggering such reform, where Coleman (1999) asserts that such transaction costs are generally prohibitively difficult to overcome for regulatory reform.

Given such considerations, the aggregate response by American respondents indicates that the historical path of regulatory reform plays a role in influencing local synthetic biology regulation. US Respondent 15 (Social Scientist) noted that "even if regulatory reform were necessary, policymakers have to deal with entrenched laws and old political fights that can't be ignored". Further, US Respondent 11 (Lab Researcher) argued that "it'd be difficult to reform SynBio regulation [in the United States] unless there was some damning study or significant accident [..] because otherwise policymakers will just fall back on existing policies even if they're outdated." Overall 13 of 17 respondents argued similar points of view, and generally

indicated that the historical path of regulatory development in the United States has limited the potential for and shape of regulatory reform for synthetic biology.

A further consideration includes the formal style of adversarial legalism within the United States government, where regulatory reform is often hindered by a confrontational and politically-costly court-driven process of regulatory dispute resolution. US Respondent 2 (Social Scientist) argued this point directly by stating "[American] regulatory reform moves slowly and can easily be held up in court. […] Governance for synthetic biology should navigate these issues by making use of existing regulations than fashioning brand new ones." Such sentiments were expressed by 9 of 17 respondents regardless of whether they perceived regulatory reform as necessary, where such individuals argued that reform can take years to even decades to achieve.

A factor that was not determined as having a significant effect in American variations of synthetic biology regulation included an acceptance of risk or perception of benefit. US Respondent 1 (Social Scientist) indicated that "commercial benefit from SynBio drugs won't ease the passage of regulatory reform or break policy logjams". Likewise, US Respondent 2 (Social Scientist) noted that "Even though [the United States] might be more open to exploring SynBio and dealing with its risks, reform is complicated more so by the courts and reliance upon the status quo."

The European Union, however, generally experiences a more cooperative risk culture that often turns to more informal means of dispute resolution – a process that often involves the collective input of government regulators, industry professionals, academics, and non-governmental researchers to discuss technology risk as well as the regulatory options required to resolve or mitigate such risks (Kagan 2009; Kelemen 2011). Such cooperation is not universally true, however, where Kelemen (2011) notes in his concept of 'Eurolegalism' that the European Union may be trending slowly towards a more adversarial nature that utilizes legal rulings and court decisions to resolve regulatory disputes – although Kelemen (2011) and Kagan (2009) do generally argue that this has not yet advanced to a degree similar to the experience of within the United States.

Similar to their American counterparts, most European Respondents (8 of 9) articulated points that the historical path of biotechnology regulation has played an important role for local synthetic biology governance. EU Respondent 1 (Social Scientist) argued that "past efforts at biotechnology regulation have made the Commission and Member States more reactive to GMO risks like with synthetic biology." Generally speaking, 8 of 9 respondents indicated similar points of view, where European regulatory authorities have adopted a more adaptive and anticipatory view to synthetic biology hazards (see Bar-Yam et al 2012).

However, other elements of risk culture were not viewed as substantial drivers on European Union variations of synthetic biology regulation. Specifically, respondents generally rejected the notion that risk appetite or perception of benefits influenced such regulation, with EU Respondent 8 (Lab Researcher) going so far to say as that these were "non-factors in shaping local regulatory policy." Most (6 of 9) indicated that government centralization was an important consideration, but such insight was grounded in the belief that historical path dependency was by far a more important variable to account for. EU Respondent 9 (Lab Researcher) reflected upon this point where they stated that "the most important factor to deal with for future SynBio reform is past regulation of local biotechnology" and that "Union-wide and Member State regulators will abide by such past efforts."

Case	**Adversarial/ Cooperative**	**Degree of Transparency in Regulatory Process**	**Formal/Informal Reliance on Dispute Resolution**	**Multiple Veto Points in Regulation Development**	**Concentration of Regulation**
USA	Adversarial	High	Formal	Yes	Centralized
European Union	Cooperative	High	Informal	Yes	Decentralized
Singapore	Cooperative	Low	Informal	No	Centralized

Table 13. Cross-comparison of Regulatory Risk Culture of Three Cases

Lastly for Singapore, unique considerations to keep in mind include the island nation's 'soft-authoritarianism' and ability to utilize input from international players like the United States or the European Union to guide elements of its regulatory best practices (Roy 1994; Haque 2004; Tan 2000; Sheehy 2004). For the former, Singapore's status as a soft-authoritarian (Roy 1994) or non-liberal democratic regime (Thio 2010) serves multiple functions with respect

to technology regulation, including (i) facilitating a cooperational atmosphere where a generally benevolent regime interacts with private and academic stakeholders to develop technological guidance and best practices via soft law (Thio 2010), (ii) promoting the relatively rapid imposition of regulatory change (often via soft law reform, see Thio 2010) via a less transparent approach to regulatory reform, and (iii) the reduction of potential veto points in the regulatory approval process through a concentration of legislative and executive authority in the ruling government (Tan 2000; Roy 1994). For the latter, Singapore observes the regulatory development process of Western partners such as the European Union and United States, where they emulate technological guidance and soft law in many cases where such technological risk is uncertain or limited in development (Rajah 2012; Sheehy 2004; Haque 2004). In this way, Singapore's risk culture is one that must account for both a regulatory system with limited transparency yet also contains a historical tendency towards promoting effective technological regulation where such hard and/or soft law becomes more well-known (Roy 1994; Rajah 2012; Sheehy 2004). As such, while Singapore is not likely to export its regulatory guidance or values to their Western partners, they will review developments in the Western world for such guidance that they will be able to adopt and implement on a relatively rapid timeline – particularly via soft law (Thio 2010; Sheehy 2004; Haque 2004).

Singaporean respondents generally (16 of 23) indicated that regulatory path dependency was an important factor to consider relative to local synthetic biology regulation, where Singapore Respondent 3 (Lab Researcher) indicated that "a major consideration for future reform will center on The [Biological Agents and Toxins] Act]." However, unlike the United States and the European Union, many respondents (19 of 23) argued that the high centralization of government power was an important driver in the Singaporean regulatory process for synthetic biology. Singapore Respondent 2 (Social Scientist) stated that "Specific [Singaporean] agencies wield a lot of power in the policy process, and can make or break efforts at regulatory reform." Specifically, such respondents indicated that the ability of a small number of government regulators to exhibit substantial power in the reform process was a key consideration to explain Singaporean regulation of synthetic biology pharmaceuticals, although

Singapore Respondent 2 added a caveat that "such agents are unlikely to abuse their power and only act when there is enough information to justify reform."

A smaller number of respondents indicated that a greater appetite for risk (13 of 23) and perceived local benefits (14 of 23) served as influencing factors for Singaporean synthetic biology regulation. However, many argued that the effects of such factors were explained by government attitudes and centralization of power, where Singapore Respondent 8 (Lab Scientist) indicated that "Government elites set research priorities based upon the benefits that the technology might bring, and regulate accordingly." Similarly, only 9 of 23 respondents indicated that the local style of legalism served as an important measure of influencing local synthetic biology regulation, where several respondents indicated that public regulatory disputes were generally uncommon in Singapore due to a centralized governmental authority.

The differences in these risk cultures and the political and institutional values that guide regulatory decision making within a given governmental unit can explain both the discussion noted by respondents relative to improvements for synthetic biology regulation. Specifically, respondents in each of the three cases indicated that the historical path of local regulatory reform as being a strong influence in synthetic biology risk perception and regulation – something that is further validated in literature as with Jasanoff (1986), Parthasarathy (2012), Douglas and Wildavsky (1983), and Lash (2000). Respondents in the United States and European Union both also indicated that the local style of legalism and reliance upon formal or informal institutions to resolve regulatory disputes as playing an important role in influencing regulatory reform, although this notion was generally rejected by Singaporean respondents. Third, centralization of government authority was found to be a strong influence upon variations in synthetic biology in Singapore, but less so in the United States and the European Union where the historical path of regulatory reform had more bounded and shaped available options of regulatory discussion and movement. Lastly, respondents within each of the three cases generally dismissed the importance of local risk appetites and perceived benefits as influencing synthetic biology regulation, where such factors were viewed as secondary to historical path dependency and (in the case of Singapore) government centralization of authority.

7.3 Towards Anticipatory and Adaptive Regulation

Both within literature as well as within interview discussion, a recurring theme emerged related to the need for an adaptive regulatory paradigm for synthetic biology research, where scholars indicated that a central goal within all countries should be to adopt adaptive governing strategies that would allow regulators and policymakers to shift guidelines and policies pertaining to synthetic biology governance as the technology continues to mature and develop (Mandel et al 2014). This sentiment is driven by the evolutionary nature of the technology's development that may continue to stretch the capabilities of existing regulatory paradigms and expose regulatory gaps related to a nation's ability to govern the latest iteration of synthetic biology research. Such sentiments are stated by Kuzma and Tanji (2010), Tait (2012), Garfinkel et al (2007), and Wiek et al (2012), among others, which collectively argue that a more anticipatory and adaptive approach to synthetic biology regulation is required to eliminate any gaps in coverage that governmental regulation and oversight have within various iterations of synthetic biology research and commercial development.

Likewise, Mandel et al (2014) take this belief a step further where they argue that a focus on soft law regulation is necessary to further anticipatory regulation for synthetic biology, where the ultimate goal of synthetic biology regulation is to balance the potential benefits that may accrue as synthetic biology research matures against the potential for novel health risk that could damage human and environmental health. Specifically, Mandel et al's (2014) argument indicates that where soft law regulation is politically and bureaucratically easier to fashion, implement, and revise at regular intervals, the formation and regular revision of soft regulation as with regulatory best practices and guidelines is likely the optimal path forward to establish regulatory traditions of anticipatory and adaptive regulation.

While these and other authors have begun to address the concern of 'what style of regulation should we adopt with synthetic biology', the question that this dissertation seeks to contribute to centers on 'are there variations in the manner of how governments regulate synthetic biology, and why'? In this spirit of this dialogue, political and institutional factors may

influence the ability of individual governments to achieve an adaptive form of synthetic biology governance.

Specifically, the historical pathway of synthetic biology regulation within a given government is shown in this dissertation as having an effect upon such regulatory variation, where such regulatory history instills a path dependency that limits how and to what extent regulation is updated or replaced (see also Parthasarathy 2012). Further factors such as the style of local legalism (specifically the degree of formality in the regulatory dispute resolution process) may also have such an effect, where a more formal and judicially-driven approach to dispute resolution may disincentivize regulatory revisions and updating by making the political transaction costs for doing so excessively high (see also Kelemen 2011 and Volcansek 2014). Given such assessments, adaptive regulation is easier for certain governments to achieve than others, where Kelemen (2011) and Mandel et al (2014) indicate that a less formal dispute resolution framework alongside a history of collaborative regulatory decision making may ease the process of regulatory reform.

7.4 Study Limitations and Opportunities for Future Research

Over the course of research, several limitations became apparent that, with enough resources and time, would be addressed via methodological adjustment. Given the importance of noting a study's limitations in any style of research, such issues across each of the three cases are noted below.

One of the first limitations of note includes the use of a more rigid interview structure as outlined in Chapter 3. Specifically, interview discussion centered on considerations of biosafety and biosecurity risk as defined in papers such as Carter et al (2014), Kelle (2013), and Schmidt et al (2011), where other considerations of novel health risk and challenges to existing regulatory structures may have arisen in interview discussion if each interview's format was more open-ended in structure and questioning (Wengraf 2001; Low 2012). This option was not selected at the onset of formal interview acquisition in 2014 in order to structure responses around significant topics introduced in published literature, yet would be useful for future synthetic biology research to gain considerations outside of high visibility publications on the subject for

areas such as with implications research and the public perception of synthetic biology (Kuiken 2015; Pauwels 2009). In order to generate such feedback via subject expert interviews, a less rigid interview structure would be needed in order to allow respondents to discuss various subjects, including those that may not be discussed in published literature very often.

Where a rigid interview structure may have limited the richness and diversity of responses on synthetic biology novel health risk, the lack of inclusion of a more postpositivist survey design may have offered more comparable responses across all interviewees in the study. A similar approach within synthetic biology research includes Bates et al (2015), who used quantitative surveys to indicate, based upon the perceptions of identified subject experts, how each respondent viewed risk associated with synthetic biology's potential as an agent of bioremediation in comparison with a conventionally-derived bioremediation process. While Bates et al (2015) note that limitations regarding the robustness of such a rank-ordered survey's results may have their own limitations due to the relative uncertainty in the field and the ability of such experts to offer confident estimations of risk probability and consequence without tangible products to review, yet the upside of such research is to derive quantitative and directly comparable feedback across respondents without the need for qualitative interpretation. Such an approach may also lack the ability of more interpretive methods of narrative analysis to acquire greater context into a given risk evaluation, yet such an interpretative approach may be used in tandem with surveys to generate both textual and numerical assessments from each subject expert regarding the risks and benefits of synthetic biology products (see Creswell 2012 for discussion on a mixed survey-interview approach using qualitative methods).

Another limitation centers on the sample size for each case included for discussion. For narrative research, larger sample sizes often contribute both additional context and feedback by which to understand a given research problem while also serving as additional points of triangulation to verify claims and better indicate robustness in any research findings from such interviews or surveys. At the onset of this research project (early 2014), few subject experts were available to discuss synthetic biology risks and benefits in general and for pharmaceutical research in particular, an issue also discussed by Bates et al (2015) and Roberts et al (2015) in

their own respective searches for relevant interview contacts. However, this is likely to change in the coming years as more companies and academic researchers become involved with synthetic biology research (Kuiken 2015; Carter et al 2014). With additional time and funding, further contacts would be derived using purposeful sampling across academia, industry, government, and non-governmental organizations in order to strengthen findings and discussion of regulation for synthetic biology pharmaceuticals.

A further topic-based limitation of this study includes the need to consider the potential efficacy of soft law approaches to synthetic biology regulation. Kelemen (2011) and Idema and Kelemen (2006) note that such soft law may be a 'red herring' in the search to resolve regulatory challenges for systems of high transparency, high rigidity, and contain elements of adversarial legalism, where soft law reforms would still be delayed and mitigated via legal disputes and political and institutional roadblocks in a manner similar as the passage of hard law within a given government. However, others such as Mandel et al (2014), Marchant et al (2013), and Douglas and Stemerding (2014) have noted that such soft law approaches may be beneficial specifically for synthetic biology regulation, where such approaches can enable a more anticipatory approach to shift regulation and guidance of synthetic biology products as new information about risk emerges and the field becomes less uncertain. While this dissertation cannot and does not seek to dismiss those arguments raised by Kelemen (2011) and Idema and Kelemen (2006), it does acknowledge amongst other published literature that soft law approaches to synthetic biology regulation may be beneficial to many countries dealing with the concern of how best to regulate synthetic biology in an efficient and robust manner.

Lastly, a significant limitation inherent within this research topic includes the high uncertainty surrounding synthetic biology, and the fact that few synthetic biology products have materialized in at least early prototypes of proofs of design. The complication here is that while subject experts may offer beliefs, opinions, and projections of where they think novel health risk may occur, its consequences, and general likelihood of occurrence, there remains an undertone of uncertainty in their responses that is very difficult to remove within the context of regulation (also discussed in Bates et al 2015). Such uncertainty ultimately makes it difficult for interview respondents to give definitive answers to questions related to the probabilities and

consequences of novel health risks, leaving them to offer 'best guesses' and 'general beliefs' of what they believe on these matters (see Roberts et al 2015). This situation will likely change as the technology matures and becomes more widely used, yet for now researchers within the subject of synthetic biology regulation must contend with the field's uncertainty in an effort to better understand the technology's risks alongside the political and cultural factors that influence the perception and regulation of such risks.

7.5 Risk Culture and Comparative Variations in Synthetic Biology Regulation

As noted within several Chapters, the purpose of this dissertation was to review to what extent and why variations in synthetic biology have arisen in the United States, European Union, and Singapore. Policymakers and regulators within these governments are already facing the task of producing robust regulatory guidance in the form of hard and/or soft law to govern the creation of synthetic biology products such as with pharmaceuticals (Marchant et al 2014; Kelle 2009; Kelle 2013; Oldham et al 2012). The pressure to produce such guidance and best practices in the face of uncertainty and novel risk to human and environmental health will only grow as such research expands both in terms of financial investment into synthetic biology innovation as well as the number of projects worldwide seeking to use synthetic biology as an approach to foster technological development in fields ranging from pharmaceuticals to biofuels to environmental remediation (Kuiken 2010; Kuiken 2015).

Coupled with this uncertainty includes the unique political and institutional factors that influence the regulatory decision making process, and can cause governments to vary in their regulation of emerging technologies like synthetic biology (Carter et al 2014; Bar-Yam et al 2012). This dissertation sought to review how elements of such risk culture generated variations of synthetic biology regulation in the United States, European Union, and Singapore. Ultimately, this dissertation's three-system comparative approach found some evidence to indicate that the historical path of regulatory reform within a given government fosters regulatory path dependency and limits the feasible options open to synthetic biology regulation within a given government – consistent with discussion in Parthasarathy (2012), and Jasanoff (1986). To a lesser extent, this dissertation found that the degree of formality in regulatory

decision making also influenced local risk culture and generated variations for synthetic biology regulation – also consistent with findings by Kelemen (2011), Volcansek (2014), and Kagan (1991).

The approach utilized within this dissertation included a two-stage narrative analysis via (i) a literature review on the subject of synthetic biology development, risk, and regulation, and (ii) a multi-stage effort to acquire subject expert interviews on the same subjects This two-stage process is effective due to its ability to build understanding regarding the existing consensus on the novel risks imposed by synthetic biology products, the existing regulatory structures that may cover such risks, and potential weaknesses and limitations within such structures. Such insight allows for a firsthand account of both the perception of risk as well as the perception of regulatory needs by local experts, and facilitates an assessment of how elements of local risk culture influence variations in emerging technology regulation like with the case of synthetic biology pharmaceuticals.

Appendix 1

Coding Information and Quotations Used for Subject Experts

Respondents – United States

US Respondent 1 – Government Social Scientist 1

- "a big concern that we have to keep in mind includes how easy new regulations would be adopted, and sweeping reform is unlikely without a lot of evidence to back it up."
- "history isn't on our side here […] we need to be very cautious about advancing [syn bio] research moving forward, because the potential for biosafety risks and the unique health consequences coming from such risks may negatively harm the lives of many."
- "We can impose rigorous biosafety protocols"
- "yet there's always going to be a chance for mistakes or downright failures in safety to prevent some of these synthetic organisms from breaking containment."
- "this [synthetic biology] research is going to go global, and won't be conducted only at BSL-4 (Biosafety Level 4) facilities. Carelessness, ineffective containment measures, simple accidents that occur one out of a thousand times a veteran bench scientist conducts research […], these biosafety risk incidents are bound to occur."
- "when these engineered products become available, we'll have to consider whether our governance capabilities are adequate to cover the potential for gene transfer or harmful side effects in vivo."
- "While EPA under TSCA and APHIS under the PPA [Plant Pest Act] have post-market review capabilities for some synthetic biology products […], their ability to conduct post-market assessment and approval of pharmaceuticals over environmental risk concerns remains uncertain and potentially nonexistent with current governance."
- "without a regulation or law clearly referencing 'synthetic biology', there exists potential loopholes or gaps in coverage where best practices aren't enforced and these novel risks could arise."

US Respondent 2 – Academia Social Scientist 1

- "[American] regulatory reform moves slowly and can easily be held up in court. […] Governance for synthetic biology should navigate these issues by making use of existing regulations than fashioning brand new ones."
- "particularly in less secure or modern labs, it is almost guaranteed that novel genetic material will unintentionally reach the environment as more and more countries conduct such research for drugs and other applications."
- "post-market assessments for environmental health are absolutely necessary for syn-bio pharmaceuticals, but aren't rigorously defined."

- "we [government regulators] need to be able to monitor for potential environmental risks such as environmental gene transfer, however unlikely these risks are, […] because we just don't know enough about how these risks could impact environmental health."

US Respondent 3 – Academia Social Scientist 2

- "it's probably not a good time to advocate for significant regulatory change for synthetic biology, because it'll be difficult to prove to lawmakers that it's worth it to change existing laws like TSCA until there's a clear reason to make such changes happen."
- "The FDA is going to be the organization in power to regulate syn-bio pharmaceuticals […] and they'll need the capability to adapt to technological capabilities as we're better able to engineer cells and viruses for medical purposes."

US Respondent 4 – Non-Governmental Organizational Social Scientist 1

- "synthetic biology governance reforms will have to account for what is required by law for technological risk management […] and anything outside of these requirements would be difficult to implement ."
- "The FDA is currently the major pre-market approval authority for synthetic biology-derived drugs, and regulatory guidance is needed to close loopholes about what types of trials they can and cannot review […] because they should be involved in all early stage medical trials."

US Respondent 5 – Academia Social Scientist 3

- "improvements to synthetic biology governance will probably be stepwise and incremental, because it'll probably be unrealistic to replace established regulation quickly."
- "existing oversight capabilities are fairly thorough to prevent something like bioterrorism in the United States […] where all biological material acquired by a lab is screened to make sure you aren't weaponing smallpox, or something like that."
- "The President's Commission of the Study of Bioethics in 2010 (PCSB 2010) was quite clear that preemptive regulation may be unnecessary and unhelpful, and I personally believe that working with scientists in the field to establish best practices may be a better path forward than new regulation or law."

US Respondent 6 – Academia Lab Researcher 1

- "we're already starting to see early commercialization, and I think this will only speed up the process for more synthetically-derived drugs."
- "the horizontal exchange of genetic information is a known concept that, however unlikely, we should be concerned with."
- "the minute probability for artificial genetic material to interact with human or animal DNA is troubling, because the consequences of this could be troublesome […] because we would in effect be manipulating the natural environment and natural cellular interactions without an idea of what the harms could be."
- "the big issue here is that engineered cells may not be as reliable as conventional pharmaceuticals, and would contribute to economic losses and maybe even health concerns."
- "There are a few avenues for these products to generate risk upon disposal"

- "with the two most likely including aqueous disposal […] or the typical disposal of these products into a landfill."

US Respondent 7 – Academia Lab Researcher 2

- "despite recent progress, we're still technologically very far away from building a fully synthetic cell that can perform reliably and efficiently, and it'll take many millions of dollars and years of research across the globe to develop technology to a point where these issues evaporate."
- "once we are able to develop a more robust and reliable library of cellular inputs […] and gain greater control over cellular activity and behavior, we'll make engineered cells more robust and reliable for purposes like with pharmaceuticals."
- "risks occurring post-disposal are those we'll have the greatest difficult monitoring, and while it is unclear the consequences these risks may have, we have to bank on harmful scenarios happening fairly soon after some of these drugs reach the market."
- "in the United States and Europe, facilities are generally well equipped to protect workers during the pharmaceutical production process, and I don't think that synthetic biology products will be much different."

US Respondent 8 – Government Social Scientist 2

- "while commercialization may be years off, regulatory reviews may occur sooner than we think […] maybe in two or three years, and we'll need to have proper guidance to regulate these products before then."
- "the inclusion of novel genetic material within end-product pharmaceuticals is what would trigger the need for stronger governance – otherwise it probably isn't necessary."
- "the precautionary principle likely applies to synthetic biology […], particularly given all of the unknowns surrounding how it may affect humans, animals, and nature."

US Respondent 9 – Industry Lab Researcher 1

- "I guess you can't totally rule such a scenario out because it's possible, but I can't imagine such a situation being likely to occur across globe's biological research capabilities, let alone within the United States."

US Respondent 10 – Government Lab Researcher 1

- "we can't ignore these threats on a policy level, but at the same time, truly malicious biosecurity threats via synthetic biology are a bit unlikely."
- "do-it-yourself synthetic biology has opened up the potential for anyone to get involved with biological experimentation, but the synthesis and programming of biological material into a harmful and virulent pathogen is more complex than simple experimentation."
- "as cells become increasingly synthetic, they'll likely be less able to proliferate outside of ideal circumstances and without supervision […], meaning the consequences of biosafety incidents may be minimal in the rare event that they occur."
- "without novel genetic material, novel health risk is essentially impossible"
- "at that point, we're only concerned with conventional risks that are well covered by the FDA."

- "the exposure scenarios are possible, but biosafety protocols are fairly robust here and various pieces of automation and redundancy limit the potential for human error in the manufacturing process for drugs."

US Respondent 11 – Academia Lab Researcher 3

- "you'd need extensive resources to accomplish something like that […] like an extensive lab, biological samples, and lots of human assistance that just would not be easy to come by for a deliberately harmful exercise."
- "right now, synthetic biology is more of a production process, meaning that it allows us to better produce drugs, rather than make entirely synthetic ones. This will come later, but with no novel gene sequences in a drug candidate, it's hard to argue that something like horizontal gene transfer or novel health risks could occur."

US Respondent 12 – Government Lab Researcher 2

- "even with secure labs, you can't rule out the human element […] and the potential for human error"
- "as pharmaceuticals become more 'synthetic' in nature, there may be a greater risk for novel health consequences in terms of exposure to genetic material like with horizontal gene transfer […] but not likely with existing pharmaceutical candidates."
- "you'd be exposing living organisms (human, plant, and animal) to novel genetic material that, through horizontal gene transfer, has a tiny probability of allowing synthetic DNA to spread into their natural host."
- "while the risk to any one person, plant, or animal is fairly unlikely, when you commercialize these drugs and make them available in millions of doses, side effects and exposure hazards are going to arise."
- "generally speaking, biosafety is taken very seriously, but I think there might be more potential for human error at the Research phase than in Manufacturing, because there's less direct human interaction with novel and potentially unstable and harmful biological material"
- "by the Manufacturing stage, a lot of uncertainty related to novel risk of these products will be reduced by testing and trials […], which would allow for more redundancy and safety precautions to be taken prior to production."

US Respondent 13 – Academia Lab Researcher 4

- "all it takes is one lapse of caution […] to generate a biosafety hazard event"

US Respondent 14 – Academia Lab Researcher 5

- "aside from early stage research, it's unlikely that there are any serious novel biosafety threats from these products, […] conventional risk sure, like with adverse effects and side effects that you'd already see on labels of commercials, but probably no novel risks from exposure to genetically engineered cells."

US Respondent 15 – Non-Governmental Organizational Social Scientist 2

- "we already have concerns of certain drugs proliferating within the water table by being flushed down the toilet or excreted […], and I think it's premature to rule out the possibility that there isn't a risk of this happening for synthetic biology drugs."
- "conventional authorities seem to be working thus far, and self-governance activities like IRBs [internal review boards] and other non-governmental groups would be able to adequately review technological risk and understand the actual implications of such risk."

US Respondent 16 – Industry Lab Researcher 2

- "honestly, while I think biosafety risks may arise within the Research phase of product development, it's far more likely that the synthetic organism would die off fairly quickly."

Europe

EU Respondent 1 – Industry Social Scientist 1

- "New governance for synthetic biology should include inputs from industry and academics, who have also been active in discussion for GMOs for decades."
- "the appetite for uncertainty and risk for synthetic biology is likely lower than the US or other areas of the world"
- "it'd be difficult for someone to pull this off [a biosecurity threat] without a well-stocked lab and the participation and help of knowledgeable scientists"
- "Europe has been concerned with environmental effects of accidental releases of GMOs, and synthetic biology could be the latest, albeit potentially more dangerous, manifestation of this."
- "Engineered microorganisms would enter the environment and potentially impact the ecosystem by competing with natural organisms for sustenance and the ability to procreate […], which could have harmful effects for an area's biodiversity."
- "no heavily engineered syn-bio drugs are currently undergoing clinical trials […] so you have to account for the time delay for regulatory approval prior to commercialization."
- "International agreements like the Biological and Toxin Weapons Convention don't really have stiff control over the production and sale of bioweapons, so a separate body geared to the control of such biomaterial may be necessary in Europe."

EU Respondent 2 – Academia Lab Researcher 1

- "gaining input from stakeholders outside of government in a top-down manner would be important for future synthetic biology regulation […] and will help balance the technology's risks and benefits."
- "it's uncertain whether existing scientific capabilities are developed enough to control horizontal gene transfer with efficiency, or whether mutations within engineered cells could become problematic within the pharmaceutical's life cycle."
- "while unlikely, horizontal gene transfer could trigger harmful and uncontrollable genetic mutations in a non-target organism that might have the potential to negatively affect animal and plant life by subjecting them to harmful mutation and other side effects."
- "while cells with artificial DNA aren't likely to multiply in the natural environment without a lot of help in their current state, as these cells become more biologically resilient and are able to

survive outside of a contained environment, the issue of persistence is one that we'll have to be worried about."

- "causing various potential health problems with plant or animal life that could impair quality of life and potentially cause death."
- "exposure of pharmaceuticals with novel genetic material to an unintended plant or animal host could cause acute reactions that could range from relatively unnoticeable and maybe mildly irritating to quite painful in manner […], a similar process as with traditional chemical exposure."
- "barriers and control mechanisms for lab safety will likely eventually fail to prevent an exposure scenario – the only question is how bad the health consequences will be."
- "there's greater uncertainty at the research stage, because a lot of this experimental material is untested, and a more synthetic organism would have little to draw comparisons with from a biosafety perspective."
- "the possibility of a terrorist or a group to direct evolution of viruses in bacteria to harm humans or the environment in a particularly harmful and unnatural manner"

EU Respondent 3 – Academia Social Scientist 1

- "[the technology's] uncertainty complicates the regulatory environment, and will likely hinder the government's ability to allow products to enter the market without judicial support."
- "a recent history of GMO regulation will keep Europe on a path to entrench the precautionary principle for synthetic biology research."
- "it is likely that these [synthetic biology] drugs will be improperly disposed of, making it possible for artificial genetic material to reach the environment."
- "various governmental and lab-based oversight mechanisms would prevent someone from abusing resources to make a harmful organism. […] This task would take a considerable amount of time, increasing the likelihood for the perpetrator to get caught."
- "the potential for accidents or improper storage and disposal of manufacturing waste and novel genetic material increases as new players for genetic engineering emerge, with my concern leaning towards those organizations with limited premarket oversight in their product development."
- "current governance gives the European Union enough premarket approval over drug development that these risks should be mitigated, although this may change as synthetic biology research allows researchers to make cells with increasingly artificial DNA."
- "[European] governance of immediate future technologies is robust, but future developments may challenge regulation. […] This is because of the current dependencies of comparative risk analysis with similar non-GMO alternatives to the proposed product."
- "we will need a risk assessment protocol to review synthetic organisms with few parallels to conventional organisms […], something that we currently lack and may find difficult to accomplish."

EU Respondent 4 – Government Social Scientist 1

- "academics and industry professionals will play a significant role with synthetic biology governance"

- “there are lots of limiting factors to prevent biosafety risk […] such as with reporting and oversight by regulatory authorities, […] but the potential for accidents and release scenarios makes synthetic biology a potential driver of novel biosafety risk, particularly to the environment.”
- “synthetic biology materials becoming an invasive species”
- “an inevitability”
- “novel DNA is going to gain exposure to the environment and outside of the oversight of regulatory authorities and clean-up crews.”
- “the consequences of end-of-life health hazards are case dependent, where some products would have a significantly greater chance of yielding harms than others.”
- “the proper handling of biomaterial with novel DNA and containment of by-product waste during manufacturing could contribute to an environmental release scenario with potentially damaging effects to biodiversity.”
- “there are a variety of medical challenges to public health that synthetic biology may be uniquely able to address […] like Ebola, malaria, or dengue fever.”
- “the breakthroughs that synthetic biology could offer will cause research to accelerate within the next few years […] making commercialization a lot sooner than you’d think.”
- “reducing the potential burden of risks that we aren’t as focused on currently, like with economic losses from the theft of company property and ensuring biosafety violators are accountable for their actions.”

EU Respondent 5 – Non-Governmental Organizational Social Scientist 1

- “while it’s hard to say definitively that there will be novel concerns, it’s pretty plausible that human, animal, and environmental organisms […] could be at risk of acute health harms.”
- “the probabilities may be small, but horizontal gene transfer could produce dramatic effects to humans and the environment, […] and should be considered for mass produced products like pharmaceuticals.”
- “a lot of this risk potential is going to stem from the restrictions placed upon syn bio research […] like with how it must be stored, who has access, and whether materials will be used outside a secure lab. Right now, it’s probably too soon to tell how this will end up, making biosafety risk tricky to ignore or dismiss outright.”
- “we can already program cells to prevent gene transfer, which will become more efficient and sophisticated as the science evolves.”
- “we could see cases of unintended exposure before and after clinical trials – but particularly in cases of by-product waste and disposal – making exposure scenarios likely as the technology comes to market.”
- “Novel risk here [in the Research stage] is possible, but generally unlikely with proper biosafety protocol. However, as the technology becomes more widely available and these protections are less available, these risks may become more likely and problematic.”
- “as these cells become more robust and capable of surviving outside of a contained environment, these scenarios become more plausible, and make proper containment even more important.”

- “placing some identifying barcode or watermark inside the genetic code of an engineered cell may help us track the movement and consequences of biosafety events […] as well as potential cases of theft or negligent containment.”
- “biosecurity is a particularly complex issue for medical applications like with pharma, and its governance needs to be relatively tight to ensure that the wrong people don’t get access to synthetic biology technologies and information.”
- “a separate body related to reviewing biosecurity issues is needed for certain categories of synthetic biology research, including with pharmaceuticals and drug development.”

EU Respondent 6 – Industry Lab Researcher 2

- “There are a variety of scenarios where these genetically engineered compounds could create risky exposure scenarios […] although the consequences of these events may not be as severe as one could imagine at present.”
- “we just can’t rule these risks out yet, either in the form of accidents or deliberate attempts to use the technology in a harmful manner […]. If synthetic biology takes off and becomes widespread in use, so too do the chances that we’ll see reports of risky events with exposure pathways and health consequences that we haven’t really seen before.”
- “clinical trials and testing for premarket approval is pretty robust, and the only real concern for humans would be off-label and improper use as well as pre-clinical trial testing early on.”
- “improper use and disposal of pharmaceuticals and pharma-byproducts”
- “as new syn bio pharmaceuticals enter the market, they’ll have been engineered in a manner that controls for novel health risks, and tested within clinical trials to view the odds that these events arise – so it’s unlikely to see such events occur very often.”
- “the research community may help indicate to government stakeholders where novel risk is realistic, and where it’s improbable.”

EU Respondent 7 – Industry Lab Researcher 1

- “particularly within the environment, there’s a strong chance we’ll see these organisms multiplying in various environments unless oversight is particularly strict with controlling their release and disposing of waste materials.”
- “there are technological improvements that could limit or eliminate the potential for such risks to occur”
- “these control technologies are in their early stages and aren’t too useful yet.”
- “we’re already seeing harmful levels of conventional drugs in waterways and in the environment, generating harms to plant and animal life. […] I don’t think we can rule out synthetic biology drugs and vaccines from such scenarios yet.”
- “particularly for areas with unreliable or outdated treatment plants […] it’s likely that synthetic DNA and similar genetic material will enter into the natural environment as such pharmaceuticals become more widely available.”
- “we’re making strides towards early syn-bio drugs, but more advanced pharmaceuticals or even vaccines using genetically altered DNA are currently beyond the scope of most research trials that I know of.”

EU Respondent 8 – Non-Governmental Organizational Lab Researcher 1

- “a red herring in the midst of valuable research”,
- “the odds are implausibly small that novel risk events should happen.”
- “clinical trials and drug testing is sort of a black box for pharmaceuticals, […] we only have to be particularly concerned with potential health risks before and during the testing.”
- “accidental release is far more likely, because there are too many oversight checks, resource requirements, and scientific capabilities needed to build an organism that could do real damage.”
- “even if such events do occur, there’s no guarantee that a novel hazard would arise, or that the novel genetic information would have anything to do with the incurred health hazard.”
- “the risk here is more of a conventional nature in terms of proper production and containment of biological material, and where the novel risk scenario would be something like gene transfer from a breach in containment, which is generally unlikely given the state of the science.”
- “oversight and containment regulation for manufacturers in Europe are pretty robust when it comes to GMOs, and I don’t see synthetic biology being much different or challenging biosafety regulations [2009/41/EC] in a manner that makes new risk likely […] particularly when the pharma products under production have been engineered to limit their potential for gene transfer and exposure effects.”
- “there isn’t any novel genetic material that goes into the consumed drug, where synthetic biology is primarily the production process to make conventional parts to pharmaceuticals like with artemisinic acid for malaria treatments.”
- “existing technological capabilities generally use well-known cellular inputs and components similar to natural cells, which would not be the case for a more fully synthetic cell.”
- “biosafety governance will run into trouble here [for cases of increasingly synthetic cells], as it will be difficult to conduct a risk analysis for a product that we have little information about or by which to compare it to.”
- “Europe has already addressed synthetic biology directly via the precautionary principle and clear directives, and more law now will probably be unnecessary and might hinder research.”

EU Respondent 9 – Government Lab Researcher 1

- “we have not really experienced any serious and recurring [novel] risk to human health from similar research related to GMO, and it would be unfair to negatively hype up such risks until there’s a proven scientific reason to be worried about them.”
- “is likely to develop, and somewhat already has on elements of the blogosphere.”
- “the risks of a horizontal gene transfer event happening are quite low, and made essentially improbable by certain genetic controls within engineered cells.”
- “the chances of horizontal gene transfer occurring in a manner that generates serious health complications is incredibly minute.”
- “This will become more plausible in the future, but for now it’s currently difficult to get a cell to behave in a specific manner in a general sense, let alone for a virus or engineered disease.”
- “At the research stage, we have to be concerned with opportunities of exposure of novel genetic material with laboratory researchers and their assistants, particularly when oversight is limited and high risk material is involved.”

- "experiments involving viral components or other microorganisms with a known potential to harm human or environmental health will likely pose significant concerns to synthetic biology regulators."
- "the consequences of such events are serious enough that we'll need to monitor whether existing regulation covers synthetic biology, but I doubt the probabilities of novel risk events are high given existing biosafety protocols for GMOs and the physical barriers required to contain such material."
- "the potential for such events are quite small, and the resource requirements for an event quite high, yet we still need to adequately protect against biosecurity events."

Singapore

Singapore Respondent 1 – Government Lab Researcher 1

- "Lots of [Singaporean] agencies interface with companies engaging with technology research. For synthetic biology, this includes some like the GMAC [the Genetic Modification Advisory Committee] or the Economic Development Board, which tries to get developers to come to Singapore […] and meet to identify what regulation can balance innovation against risk."
- "there's a general feeling that we don't want to prohibit research because it's risky, at least until we understand these risks to be serious threats."
- "an inherently conventional risk profile"
- "the novel risk is not the vector of exposure, but instead that the material workers could be exposed to is novel and unpredictable in nature."
- "evidence of a respect for the ability of institutions to conduct their own risk assessment activities, and report potential biosafety hazards to external government authorities."

Singapore Respondent 2 – Academia Social Scientist 1

- "there's very frequent discussion between developers and government officials on technology development and possible risks, and the two work together to identify needs for reform."

Singapore Respondent 3 – Academia Lab Researcher 1

- "there isn't really a need to push regulation for synthetic biology just yet, because regulators can institute reform pretty quickly once we have better information about hazards."
- "the risk and exposure profiles for such scenarios are more well-known […] and probably don't require new regulation to control."
- "the rules that will probably be most important for synthetic biology research in the near future, […] particularly as it outlines how the Singaporean government will oversee research activities."

Singapore Respondents 3 and 4 – Academia Lab Researcher 1 and Academia Social Scientist 2

- "it would be better to wait for the technology to mature and demonstrate true scientific capabilities rather than regulate based upon what we think may happen"

Singapore Respondent 4 – Academia Social Scientist 2

- "when reform is needed for The Guidelines [The Singapore Biosafety Guidelines for Research on Genetically Modified Organisms] or The Biological Agents and Toxins Act, government ministers

can initiate reform quickly with Parliament to protect public health, so pre-emptive reform isn't always necessary."

- "even within internal governance, there exists enough oversight mechanisms to prevent someone from stealing or misusing biological material and engaging with involved research to produce harmful agents."

Singapore Respondent 5 – Academia Lab Researcher 2

- "we [Singaporeans] aren't as precautionary as the West, and promote technology research like SynBio in ways that might not be possible in a more strict set of regulations."
- "No one is 100% sure what laws and regulations apply to synthetic biology, but government involvement with issuing our grants and advocating for synthetic biology research signals their general approval of our work."

Singapore Respondent 6 – Government Social Scientist 1

- "the Singaporean government has been interested in developing this technology that may yield health benefits to its citizens and residents […] with the Economic Development Board serving as a guide for foreign organizations seeking to break into the Singaporean market."
- "the Government is well aware of the potential to generate health benefits through synthetic biology, and we believe that funding and a supportive environment are necessary to develop such benefits within Singapore."
- "we have to worry about research exposure scenarios because there is a small chance […] like 1 lab experiment in a year […] where exposure could produce health hazards, but by and large most exposure scenarios would result in the novel genetic material harmlessly dying off without producing gene transfer or harming the health of the scientist."
- "the likely risk profile here would be for vaccine synthesis and engineering, where interaction effects in vivo could result in unintended health consequences to the patient."
- "if [The Guidelines] can be clearly connected to synthetic biology, which they basically are, then this is going to be an important argument in favor of in-house governance of synthetic biology research."
- "IBCs are vital for executing these guidelines"
- "commercialization of early stage Synthetic Biology products is not far away, and it is important to head off health risk before such commercialization becomes widespread."

Singapore Respondent 7 – Academia Lab Researcher 3

- "…novel risk might occur, but the exposure potential would be limited by cellular controls that scientists could use to keep synthetic cells from engaging in unintended behavior or reaching unintended exposure points."

Singapore Respondent 8 – Academia Lab Researcher 4

- "dual-use concerns are possible, but not easily to accomplish at present because of the difficulties that a researcher would face in using their research for deliberate harm."

Singapore Respondent 9 – Industry Lab Researcher 1

- “where in early research synthetic biology cells lack the engineered controls to prevent proliferation or spread outside of containment […], if scientists get exposed to this material, it could have really harmful effects.”
- “having best practices like The Biosafety Guidelines, but more specific to synthetic biology, can both make the public feel safer about purchasing such products, and offer companies certain benchmarks to meet in order to demonstrate safe research and production practices.”

Singapore Respondent 10 – Academia Social Scientist 3

- “we have to assume, despite all of our planning, that there will be a breach in containment […] it’s happened before with terrible viruses, and it may likely happen for synthetic biology.”

Singapore Respondents 10

- “while the controlled use of synthetic biology drugs within secure labs heavily reduces the risk of environmental exposure concerns at the disposal stage of a pharmaceutical’s lifespan, we have to consider whether issues such as gene transfer and environmental competition may be issues that arise from improper disposal if we agree to distribute these drugs to the lay public.”

Singapore Respondent 11 – Academia Lab Researcher 5

- “such materials will not be able to survive and proliferate in nature for more than a few hours at most, […] and the risk of truly harmful gene transfer is so remote that it will eventually be dismissed outright.”

Singapore Respondent 12 – Industry Lab Researcher 2

- “while the case-by-case chances are slim of [contamination and exposure] happening after drug disposal, our current experience with other pharmaceutical drugs and their improper disposal forces us to consider the likely possibility that these novel drugs may reach the environment unintentionally.”

Singapore Respondent 13 – Academia Lab Researcher 6

- “we have to be wary of side-effects […], there could be something new here that produces harms to humans in a manner that is very debilitating or even fatal in very small numbers of cases.”

Singapore Respondent 14 – Academia Social Scientist 4

- “generally emerging, but the attitude we take away is that our research is important and risk is handled internally though internal review boards and other university governance regimes.”
- “there is a belief here that we can learn much from the West’s experience in regulating synthetic biology”
- “understand the possibilities that the technology may yield, and recruit talent to pursue such goals.”

Singapore Respondent 15 – Academia Social Scientist 5

- “the ability of synthetic biology to produce drugs and vaccines for neglected tropical diseases will pressure innovators to move quickly”
- “such review boards and self-governance would help us air on the side of caution by looking for potential concerns, while avoiding burdensome and potentially unnecessary regulation.”

Singapore Respondent 16 – Industry Social Scientist 1

- “these review boards are scientifically competent and can more directly review health risk of this developing technology.”

Appendix 2

Lexicon of Terms to Frame Quotations

Synthetic biology novel health risk (generally speaking),

"technology uncertainty"

"Efficacy – ability to survive outside of containment"

"Efficacy – ability to be controlled"

"Horizontal gene transfer"

"Data limitations"

"Scientific capacity/capabilities"

"novel vs conventional risk"

Synthetic biology novel health risk (pharmaceuticals),

"probiotics"

"Biosafety"

"Biosecurity"

"Pharmaceuticals – General Comments"

"Mutation *in vivo"*

"Environmental fate/end-of-life risk"

"Pre-clinical trial risk/Lab Safety"

"General Development"

Emerging technology regulation,

"internal oversight"

"external oversight"

"Commercialization"

"Incremental/Hardening regulation"

"Adaptive regulation"

"Regulatory Reform"

"Precautionary Principle"

"Proaction"

(iv) differences in cultural risk perception

"Risk Tolerance"

"Government Structures"

"Global Development/Risk Concerns"

Appendix 3

Interview Protocol

Instructions

Thank you for your interest in my PhD dissertation research project entitled *Synthetic Biology Risk Governance for Pharmaceuticals*. Your assistance is extremely helpful in this research project, and your input will be kept anonymous at all times.

Below are a list of questions regarding general synthetic biology/genetic engineering risk and governance methods to address those risks. Your opinions, judgment, and/or advice will be requested to answer these questions in any way you deem reasonable. As this is an 'unstructured' interview, you may add any information to each response you believe is helpful. The only request is that you focus your answers on emerging biotechnology risk, with synthetic biology or genetic engineering as a primary focus. A main point of interest in this project is the impact that synthetic biology research will have on new pharmaceuticals, particularly the novel risks that will emerge due to the use of this emerging technological method. As such, any discussion related to synthetic biology or genetic engineering and pharmaceuticals is particularly beneficial, although your opinion on synthetic biology/genetic engineering and risk generally speaking is quite welcome.

Your interview timeframe is fluid, and may be conducted between 20 minutes and 3 hours based upon your availability. If you do not feel comfortable answering a question, you may ask to skip. If you have a question, you may ask for clarification at any point of the interview.

Purpose & Confidentiality Statement

The purpose of this study is to assess several elements of synthetic biology risk governance amongst subject experts. Specifically, information from these interviews will be used to acquire information regarding the types of risks imposed by the use of synthetic biology or genetic engineering in various technologies (particularly pharmaceuticals), the differences in risk perception of synthetic biology products across culture, and general discussion of risk management options and recommendations for synthetic biology and genetic engineering research and development going forward. For any questions or comments, please feel free to ask your interviewer or contact the primary investigator.

If you agree, your interview will be recorded and notes will be taken throughout your discussion with the interviewer. These recordings and notes will remain with Benjamin Trump, and will not be disseminated to any other source. Any identifying information related to you will be removed, and you will be referenced to a randomly assigned code by which your interview will be referenced from in the future. No identifying information connecting you to your statements made in this interview will be made without your express and written permission. You may choose to terminate the interview at any

time, for any reason. In addition, you may ask for further information to follow-up with the progress of this study by emailing the primary investigator (bdtrump@umich.edu).

Again, thank you for your participation in this project!

Best Regards,
Benjamin Trump
PhD Student, University of Michigan
Department of Health Management and Policy, School of Public Health

Questions

Demographic Questions:

1) Can you state your background with genetic engineering or synthetic biology, or your general familiarity with the subject (emerging technology and biotechnology)?

2) What is your general opinion of the subject? Where do you see the field going in the next year? Five-Ten years? Can scientists and engineers safely build and genetically reprogram bacteria cells for a biomedical purpose?

3) Is there an application of genetic engineering or synthetic biology that particularly excites you? One that worries you?

4) What do you see as being particularly beneficial about the technology? What do you see as being potentially risk-inducing? Is there anything unique about these considerations?

Synthetic Biology General Risk Questions:

1) When you think of synthetic biology, what is meant about risk?

2) Is there anything that makes risks within synthetic biology development unique?

3) Looking at specific categories of synthetic biology risk discussed in literature, what concerns do you have related to the technology's biosafety?

4) Are there particular areas of concern relative to biosafety that may have more substantial or lasting risk? Who or what is particularly at risk of such negative consequences?

5) Looking at synthetic biology biosecurity concerns as noted in the literature, what concerns do you have about the dual-use nature of the technology?

6) What factors could increase the possibility of synthetic biology being deliberately used in a harmful manner? What factors may decrease that possibility?

7) What other risk considerations do you have that should be noted as important to consider relative to synthetic biology and risk?

Synthetic Biology Pharmaceutical Risk Questions:

1) Based upon discussion above, what are your thoughts regarding the use of synthetic biology to facilitate pharmaceutical production? What types of products do you see as arising from such research?

2) When do you think such products might enter clinical testing? What about eventual commercialization?

3) What are the specific biosafety considerations that should be considered? What about biosecurity?

4) Think about the life cycle of a pharmaceutical product (Research – Manufacturing – Consumption – End-of-Life Disposal). What types of risk might arise at each life cycle stage for a conventional pharmaceutical? What about with a synthetic biology-derived option?

5) What is the effect that exposure to novel genetic information would have to lab researchers? Workers? Consumers? The environment? Think about considerations you noted above of biosafety and biosecurity here.

6) Of the risks discussed, which are most consequential? Which are most likely to occur?

How Should We Deal With These Risks:

1) What are the regulatory capabilities currently available to govern synthetic biology? What are the regulatory agencies? What are the regulations or laws? Other options?

2) Based on your answer above, should any new steps be taken to govern synthetic biology production? Formal regulation? What about self-governance?

3) Would you have any concerns if genetically engineered, synthetic biology-derived pharmaceutical were produced in a country other than your own to be sold in your local markets? If so, what could alleviate these concerns?

4) Any other thoughts about synthetic biology governance in your country?

Outgoing Control:

1) What is your general opinion of genetic engineering/synthetic biology? How about its applications to pharmaceuticals?

2) Is there anything in particular that excites you about genetic engineering/synthetic biology? Worries you?

Any Outgoing Comments?

Additional Information

Definitions:

Synthetic Biology – the design and construction of biological devices and systems for useful purposes. It combines biology and engineering, thus often overlapping with bioengineering and biomedical engineering. It encompasses a variety of different approaches, methodologies, and disciplines with a focus on engineering biology and biotechnology.

Synthetic biologists approach the creation of new biological systems from different perspectives, focusing on finding how life works (the origin of life) or how to use it to benefit society. The former focus includes the approach of biology, inserting man-made DNA into a living cell; and chemistry, working on gene synthesis as an extension of synthetic chemistry. The latter focus includes engineering, building the new biological system as a platform for various technologies; and rewriting, rebuilding the natural systems to provide the engineered surrogates.

Among other things, a primary difference between synthetic biology and genetic engineering is that synthetic biology is based on the intentional and total redesign of artificial biological systems, rather than on a replacement or modification of a single gene or collection of genes in an existing and living host cell.

Synthetic biology is a maturing scientific discipline that combines science and engineering in order to design and build novel biological functions and systems. This includes the design and construction of new biological parts, devices, and systems (e.g., tumor-seeking microbes for cancer treatment), as well as the re-design of existing, natural biological systems for useful purposes (e.g., photosynthetic systems to produce energy). As envisioned by SynBERC, synthetic biology is perhaps best defined by some of its hallmark characteristics: predictable, off-the-shelf parts and devices with standard connections, robust biological chassis (such as yeast and E. coli) that readily accept those parts and devices, standards for assembling components into increasingly sophisticated and functional systems and open-source availability and development of parts, devices, and chassis (SynBerc 2013).

Genetic Engineering: the direct manipulation of an organism's genome using biotechnology. New DNA may be inserted in the host genome by first isolating and copying the genetic material of interest using molecular cloning methods to generate a DNA sequence, or by synthesizing the DNA, and then inserting this construct into the host organism. Genes may be removed, or "knocked out", using a nuclease. Gene targeting is a different technique that uses homologous recombination to change an endogenous gene, and can be used to delete a gene, remove exons, add a gene, or introduce point mutations.

An organism that is generated through genetic engineering is considered to be a genetically modified organism (GMO).

Governance – all processes of governing, whether undertaken by a government, market, business, or network, whether over a family, tribe, formal or informal organization or territory and whether through laws, norms, power or language. It relates to processes and decisions that seek to define actions, grant power, execute and implement policy, and verify performance.

Risk – the potential of losing something of value, weighed against the potential to gain something of value. Values (such as physical health, social status, emotional well-being or financial wealth) can be gained or lost when taking risk resulting from a given action, activity and/or inaction, foreseen or unforeseen. Risk can also be defined as the intentional interaction with uncertainty.

Biosafety- The prevention of large-scale loss of biological integrity in the form of potential risks to human and environmental health. For this context, such events are generally not intentionally caused.

Biosecurity- The prevention of the deliberate misuse of synthetic biology capabilities by a nefarious agent as with a bioterrorist. Such concerns arise from the technology's 'dual use' concerns, where it may be utilized either to drive scientific innovation as with medicine, or be used to deliberately cause harm in the form of an engineered virus or bacterial agent.

Data Retention:
Any raw information (information not coded for anonymity) will be send to the primary investigator – Benjamin Trump – and will remain in his sole possession, to not be distributed publically or privately. This data will be coded by the primary investigator for anonymity and aggregated with other responses, and kept for Benjamin's research use for his dissertation. No identifying information of any kind will be retained or used for the publication of any research results without the express permission of the individual interview respondent.

After you have responded to this interview, your views will be aggregated with the responses of other scientific experts. Together, this expert interview will form the foundation for further risk assessment and will be summarized in a PhD dissertation and potential journal articles. Your responses to this questionnaire will be treated confidentially at all times. Any notes or identifying information collected in the interview is for the interviewer's coding only, and will not be distributed or made available to any other person than the primary investigator (Benjamin Trump – bdtrump@umich.edu).

Appendix 4:

Qualitative Methods Available to Test Variations of Government Regulation of Emerging Technologies

1.1 Introduction

Qualitative methods serve as tools to derive context-rich information from interviewed individuals, archived information, and various other sources (Denzin and Lincoln 1994; Creswell 2012). Such methods may be used to amplify or contextualize findings from quantitative research, or work by themselves to offer insight into specific research problems (Creswell and Clark 2007; Berg et al 2004). Such context may include insight into complex social behaviors or activities as well as generating explanations for ongoing beliefs or actions that are not obvious or attainable within strictly quantitative research (Creswell 2012; Creswell and Clark 2007). In essence, the narratives and findings provided through activities like subject expert interviews and narrative analysis help interested parties approach research questions by answering the 'why' or 'how' of a research topic that is not as easily covered via quantitative analysis (Berg et al 2004; Taylor et al 2015).

Such methods have been discussed by Linkov et al (2008) and Bates et al (2015) as an avenue to understand the potential risks and benefits of emerging technologies which lack quantitative data to measure such variables. A specific application of this includes synthetic biology, where Kelle (2009), Carter et al (2014), and Roberts et al (2015) represent some of the published literature that have used narrative analysis and expert interviews gain insight into the technology's risks within an environment of high uncertainty. In this way, qualitative methods provide two key benefits to those looking to review the process of synthetic biology product development, including (i) serving as a source of information to overcome data limitations associated with these novel products, and (ii) providing approaches to gauge expertise and

intuition of subject experts, particularly for those areas that are difficult to quantify (Silverman 2013; Lewis 2015; Gibson and Brown 2009; Daiute 2013).

Given that qualitative approaches may serve as helpful tools for researchers to assess technological risks and regulatory needs, this Chapter seeks to unpack the specific methods that might be used to drive such research. To accomplish this task, the following sections include a general introduction and overview to the most common methodological and theoretical frameworks (respectively) that are utilized by qualitative researchers.

Specific to emerging technology regulation in general and synthetic biology in particular, several reasons exist with respect to why interview-driven qualitative research methods are both necessary and useful for many research ventures. Among others, these include:

i) The lack of robust quantitative data for technologies such as synthetic biology with limited to no fully developed applications, as well as the need for more context-rich assessment to guide regulatory decision making (Bates et al 2015; Roberts et al 2015),

ii) Limited insight and understanding regarding the types of risk that may realistically arise through the life cycle of synthetic biology products (Kelle 2009; Roberts et al 2015; Bates et al 2015),

iii) Incomplete understanding and limited context regarding the ability and efficacy of various regulatory options to adequately resolve the risks associated with these technologies (Carter et al 2014; Allan et al 2015; Church et al 2014), and

iv) A need to engage in horizon scanning for future technologies and understand the challenges they may pose to regulatory structures moving forward (Bates et al 2015; Carter et al 2014; Roberts et al 2015).

Given the context-rich and experientially-driven dataset derived from subject experts and other qualitative sources, qualitative methods may serve as one option to acquire, organize, and analyze risk-based information regarding synthetic biology research and development (Cannella and Lincoln 2015; Vincent et al 2015).

The chapter begins in Section 1.2 by discussing the more commonly used qualitative methods as defined by Creswell (2012), Denzin and Lincoln (1994), Berg et al (2004), Giacomini (2010), and Taylor et al (2015), among others. Some of these approaches, particularly with

narrative analysis and expert interviews, have already been used in within literature pertaining to synthetic biology regulation (Carter et al 2014; Bates et al 2015; Kelle 2009; Roberts et al 2015). Next in Section 1.3, the chapter discusses the collection of methods that may be applicable to such research, with the aim of indicating the various strengths and weaknesses the individual methods possess with respect to knowledge acquisition and information analysis for research centered on synthetic biology risk regulation. Section 1.4 then builds from this discussion by reviewing the philosophies driving qualitative research and the use of the methods introduced in Section 1.3. Lastly, Section 1.5 offers extensions into mixed-methods research, where qualitative methods may be used to complement quantitative analysis.

1.2 Overview: Qualitative Methods for Synthetic Biology Research

While still limited in discussion, several scholars have already made use of qualitative methods to assess synthetic biology health risks (Starkbaum et al 2015; Breitling et al 2015; Kelle 2009; Bates et al 2015; Roberts et al 2015). These approaches range from open-ended and exploratory in nature where the researcher seeks to gain general feedback regarding synthetic biology risk and benefit to more focused and quantitative with respect to a particular application or group of anticipated synthetic biology products and their associated risks and benefits.

Maurer et al (2006) serves as the earliest known example of interviews being used to guide discussion of risk and security issues related to the process of synthetic biology development. Specifically, their report sought to review the perceptions of biosafety and biosecurity risk amongst synthetic biologists (n=24) to identify where, if at all, synthetic biology affects traditional biosafety and biosecurity concerns within the process of product development. The overall goal of this research was to drive community-based policy options to govern synthetic biology research at the Synthetic Biology 2.0 Conference, where it was presented and discussed amongst participants and signaled areas that may require further regulation beyond existing regulatory capabilities.

Kelle (2009) serves as one of the earliest deliberate pieces of published scholarship that utilized expert interviews directed towards reviewing national regulatory capabilities of

synthetic biology development. Specifically, Kelle (2009) sought to construct a narrative regarding the awareness of subject experts in Europe on the developing synthetic biology hard and soft law related to biosafety and biosecurity, respectively. Specifically, Kelle interviewed 20 European subject experts via purposeful sampling between June and October 2007, and reviewed their perceptions and understanding of dual-use issues related to synthetic biology research as outlined by the Fink Committee (see Chapter 3). Information from these interviews was general in nature, where Kelle (2009) only indicated the general level of awareness that a given interview subject noted with specific laws, regulations, and guidance related to synthetic biology biosecurity and biosafety. Kelle (2009)'s approach is a relatively early case where qualitative information from semi-structured interviews is derived from a general perspective, where the interviewer used feedback from respondents to inform general perceptions of subject experts with respect to one element of synthetic biology regulation. A limitation here is that interview discussion focused primarily on biosecurity issues, yet Kelle's example demonstrates how interview-driven research may yield expert insight on a topic with limited context and understanding. Kelle's findings were further disseminated in a 2007 SynBioSafe Report and reviewed in SB 3.0 in Zurich, Switzerland (see more discussion on the SB Conference Series in Chapter 3). Further, Kelle's approach was used to drive SynBioSafe's regulatory assessment of synthetic biology in Europe, where such discussion was further included in the European Scientific Committees Opinions on Synthetic Biology (2014; 2015a;2015b).

From a mixed-methods perspective, Roberts et al (2015) made use of 4 rounds of open-ended subject expert interviews and surveys to gain insight into regulatory discussion of four synthetic biology products in particular, and general regulatory discussion of the technology in particular (research described in Roberts et al 2015 will be discussed in detail in the 'Interview Protocol and Methodology' section below). Round One was deliberately open-ended in nature, where the researchers listed by Roberts et al (2015) asked for general feedback and insight by 45 experts in the United States and Europe regarding their opinions of synthetic biology regulation. Input from Round 1 was used to focus questions related to Rounds 2-4, where surveys were deployed to gain further perspective of synthetic biology regulation for a variety of technological applications. This specific example presented by Roberts et al (2015) indicates

the potential for multiple qualitative methods and information collection approaches (expert interviews and content analysis alongside ordinal survey design) to drive scholarship on synthetic biology regulatory research, although the project was not explicitly geared towards advancing qualitative methods for synthetic biology research. Roberts et al's research was presented in the Society for Risk Analysis' World Congress in 2015 (Singapore), with final dissemination intended for the Alfred P. Sloan Foundation and the Society for Risk Analysis in late 2016.

Another example of synthetic biology literature that utilized qualitative methods to populate quantitative models includes Bates et al (2015). Specifically, Bates et al make use of semi-structured interviews and surveys to acquire information that informs their criteria weights and risk scores for their Multi-Criteria Decision Analysis (explained in detail below in 'Using Qualitative Methods to Populate Quantitative Models'). At the onset, Bates et al conducted a small number of semi-structured interviews (n=19), and asked each expert questions related to their perception of synthetic biology risks, benefits, and governance requirements for the case of environmental bioremediation. Overall, Bates et al demonstrates how qualitative approaches to acquire risk and benefit information related to synthetic biology can populate quantitative decision models related to regulate the process of synthetic biology product development, with this particular case focusing on comparing and evaluating the different conventional and emerging technologies geared towards environmental remediation.

Starkbaum et al (2015) took a different approach by reviewing perceptions of risk and regulatory needs by members of the lay public. Focusing on citizens of Austria and Germany (n=69), the authors utilized focus group information from lay citizens to identify areas that respondents noted concern of. These areas include, among others, biosecurity and the potential for bioterror, biosafety concerns and unintentional exposure, and general harms to animals and the environment. Starkbaum et al (2015) complemented such discussion by asking focus groups about the potential benefits of synthetic biology. The three areas of discussion noted as being favorable to respondents include insect control, vaccine development and production, and the maturation of viable biofuel. Starkbaum et al's example indicates how narrative analysis and interviews for synthetic biology risk regulation can branch out beyond

subject experts such as with lay perception of the technology, where such findings can inform particular areas of public concern that may not be readily known by regulators.

2.3 Qualitative Methods Beneficial to Synthetic Biology Research

The literature noted above serves as the major categories of qualitative methods applicable to synthetic biology research. Building off of such discussion, this section discusses the methodological options used by qualitative researchers to investigate and test theories. Among the various tools available, Hennink et al (2010), Creswell (2012), Creswell (2013), Denzin and Lincoln (1994), Taylor et al (2015), Giacomini (2010), and many others reference five approaches that are frequently used as both tools for information gathering as well as information assessment. These include:

1) narrative research,
2) phenomenology,
3) grounded theory,
4) ethnography, and
5) case studies.

1.3.1 Narrative Research

Narrative research and narrative analysis has a history of longstanding use in qualitative research since the early 20th Century (Riessman 1993; Taylor et al 2015). The term serves as an umbrella term for the acquisition, organization, and analysis of human knowledge and experience in a context-rich manner, and includes tools such as (Clandinin and Connelly 2000): individual and collective stories, journal entries and log statements, field notes and letters, interviews (both amongst subject experts and within general members of a population), photos, and various historical artifacts where written or oral communication is sparse. Using the information gathered from these approaches, it must next be filtered, organized, and analyzed in order to make it useful for the purpose of addressing a research question from a qualitative perspective.

Green and Thorogood (2013), Garner and Scott (2013), and Silverman (2013) state that narrative analysis offers the flexibility needed to conduct comparative research on subjects that are inherently difficult to quantify or lack context. Vincent et al (2015) further notes that such flexibility is helpful for technologies involving health risks that are uncertain or potentially novel in nature – something that may apply for synthetic biology (Engelhard 2016). This derives from the ability of a researcher to gain written and/or oral feedback from targeted respondents on subjects that may not be easily studied via quantitative approaches, or may have uncertain risks or implications (Tesch 2013; Garner and Scott 2013).

For oral and written feedback, transcripts of discourse produced via discussions with interview subjects or within written logs, diaries, and field notes generally serve as the source of raw data for a narrative analysis approach (Coffey and Atkinson 1996; Tesch 2013). Subsequent analysis of these transcripts is performed to separate the information deemed 'useful' for the predetermined research question from the 'irrelevant' or 'unhelpful' (Polkinghorne 1995; Tonkiss 2004). Once the 'useful' information is acquired, researchers must next utilize a tool to organize this information in a meaningful manner, keeping in mind that these organizational tools need to both be in line with the theoretical and philosophical framework adopted by the researcher (described further below) as well as the particular research question that the narrative information is intended to address (Kohlbacher 2006; Creswell 2013).

Organizationally, such approaches include thematic organization (Labrov 1972; Braun and Clarke 2006), comparative subject assessment of a single narrative (Bruner 1991), chronological organization (Polkinghorne 1995), and discourse-driven organization (Riessman 1993). For starters, thematic organization often seeks to understand the effect of specific events upon communities, where 'useful' interview information is organized around the Who, What, Where, and Why regarding the event's impact upon individual and collective behavior and beliefs (Smith 2000; Labrov 1972). Next, comparative assessment of a single narrative seeks to understand how individuals both within and across social and professional groups understand a single idea, principle, or object (Bruner 1991), where the important takeaway from such analysis includes reviewing the different perceptions and discussions used by

interview subjects, and seeking to understand how and why these differences of interpretation occur. Chronological organization (Polkinghorne 1995; Merriam 2002) is similar to thematic organization, yet instead of organizing interview feedback into different 'themes', the qualitative analyst seeks to derive a chronological beginning, middle, and end of the collective narrative derived from texts and interviews, and is favorited by those conducting qualitative historical assessment (Feldman et al 2004; Cortazzi 2014). Lastly, discourse-driven organization places heavy importance upon the language that a speaker uses to frame and understand a given issue, leaving researchers to organize interview feedback into separate sections and reviewing those sections for unique pieces of discourse separately as well as describing how these different sections connect with one another in particular (Feldman et al 2004; Riessman 1993). Regardless of the organizational and analytic approach chosen, the ultimate objective of these organizational tools within qualitative research is to group interview, textual, and artifact-driven information into groups based upon their shared traits and draw inferences and conclusions regarding their similarities and differences (Cortazzi 2014; Polkinghorne 1995).

With respect to individual and collective interviews, the consolidated criteria for reporting qualitative research (COREQ) checklist is one tool available to guide narrative analysis with live subject interviews (Tong et al 2007; Neale and West 2015). Dividing the checklist into three domains, COREQ requires researchers to (i) note the role of the researcher upon and within the research question and environment, (ii) address concerns of study design to note potential flaws within the interview process and help strengthen such areas of potential weakness, and (iii) offer suggestions for interview analysis and facilitate the ability to transform qualitative information derived from interviews and focus groups into useful information pertinent to the given research question (Tong et al 2007; Lasch et al 2010). The COREQ requirements as noted by Tong et al (2007) are included below in Table 14.

Item	*Consideration*
Domain 1: Research team and reflexivity	
Personal Characteristics	
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?
2. Credentials	What were the researcher's credentials?
3. Occupation	What was their occupation at the time of the study?
4. Gender	Was the researcher male or female?

5. Experience and training	What experience or training did the researcher have?
Relationship with participants	
6. Relationship established	Was a relationship established prior to study commencement?
7. Participant knowledge of the interviewer	What did the participants know about the researcher?
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator?
Domain 2: study design	
Theoretical framework	
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis
Participant selection	
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email
12. Sample size	How many participants were in the study?
13. Non-participation	How many people refused to participate or dropped out?
Setting	
14. Setting of data collection	Where was the data collected?
15. Presence of non-participants	Was anyone else present besides the participants and researchers?
16. Description of sample	What are the important characteristics of the sample?
Data collection	
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?
20. Field notes	Were field notes made during and/or after the interview or focus group?
21. Duration	What was the duration of the interviews or focus group?
22. Data saturation	Was data saturation discussed?
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?
Domain 3: analysis and findings	
Data analysis	
24. Number of data coders	How many data coders coded the data?
25. Description of the coding tree	Did authors provide a description of the coding tree?
26. Derivation of themes	Were themes identified in advance or derived from the data?
27. Software	What software, if applicable, was used to manage the data?
28. Participant checking	Did participants provide feedback on the findings?
Reporting	
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings?
30. Data and findings consistent	Was there consistency between the data presented and the findings?
31. Clarity of major themes	Were major themes clearly presented in the findings?
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?

Table 14. COREQ Requirements Discussed in Tong et al (2007)

Domain 1 serves as a 'credentials check' of the given researcher, where questions here force the researcher to consider their ability to conduct interviews on a given research area alongside the relationship they may have with interview subjects both before and during the research process. Domain 2 focuses more on evaluating the study design, where researchers are forced to consider their methodological theory and organizing principles, sampling techniques, and data collection methods used throughout the study. Lastly, Domain 3 helps the researcher take a systematic approach to classify and analyze their data, check for themes in discussion, and note potential biases or issues that may complicate or derail their research argument. Overall, the COREQ checklist can be a helpful launch point for practitioners of narrative analysis and for those making use of interviews and focus groups by helping them address potential concerns before, during, and after research, although it remains the responsibility of the researcher to honestly fill out the checklist and resolve concerns raised by checklist in a manner that reduces considerations of bias and strengthens information regarding how the research process was carried out (Tong et al 2007).

Narrative analysis has also been used as an approach to gather and assess information for use within quantitative methods (Vaismoradi 2013; Snowden 2010; Teddlie and Tashakkori 2009), such as with decision analysis (Linkov et al 2012; Bates et al 2015). For such cases, researchers seek to review transcripts, narratives, and textual evidence using content analysis (Castro et al 2010; Hesse-Biber and Leavy 2010; Mohan et al 2012; Linkov et al 2012; Bates et al 2015) to derive quantitative trends or statistical markers pertaining to the interview subject's perceptions of the given research questions, including indications of the general frequency that certain terms or phrases arise alongside discussion of the relative magnitude or importance of certain factors relative to decision assessment. Such use of qualitative methods for to drive qualitative assessment can use an amalgam of expert interviews, surveys, and textual analysis from literature, yet ultimately most research ventures in this vein seek to derive quantitative markers from such qualitative methods to drive tools such as with decision support systems and traditional methods of risk analysis (Snowden 2010; Linkov et al 2012; Linkov et al 2014). Methodologically, this often requires researchers to rely upon more quantitative content analysis and less qualitative discourse analysis, where content analysis enables researchers to

derive quantitative trends in interview transcripts while discourse analysis is better saved for situations where more context-rich sources of information are helpful for research projects with more uncertainty and fewer quantitative capabilities available to resolve such uncertainty (Sandelowsi 2000; Kohlbacher 2006).

As will be noted in Chapter 3, this dissertation made specific use of discourse analysis to review comments by subject experts from three case areas regarding the risks and regulatory requirements needed for synthetic biology development. Generally, speaking, discourse analysis as an approach to analyze written or verbal comments in order to better understand how interview subjects make knowledge claims (Wooffitt 2005). Rather than focusing on specific word choice within interview or written discussion, discourse analysis instead seeks to review how language is used to represent ideas. In other words, discourse analysts seek to understand the meaning behind language used by writers and speakers to communicate specific ideas (Wooffitt 2005; Potter 1996).

1.3.2 Phenomenology

As with narrative analysis, phenomenology is an approach with extensive use since the early 20th Century. According to Creswell (2009), phenomenology "is a strategy of inquiry in which the researcher identifies the essence of human experiences about a phenomenon as described by participants." This framework drives practitioners of phenomenology to adopt particular methods towards information acquisition and analysis, with particular emphasis on individual and group interviews along with discourse analysis (Smith 2007; Giorgi 1997; Starks and Trinidad 2007). Specifically, phenomenological research tends to focus on small numbers of interview subjects over extended periods of time with the goal of understanding patterns of behavior along with perceptions of how such individuals come to understand, perceive, and make opinions of various facts, objects, or events (Moustakas 1994; Giorgi 1997). Philosophically, phenomenologists seek to distance themselves from their research, and instead seek to organize and analyze interview findings in a manner that reduces interpretive bias where possible (Nieswiadomy 1993; Groenewald 2004). Such interviews may be chronological or thematic in nature, although phenomenological approaches often utilize discourse-driven

approaches that seek to 'construct a story' regarding interviewee opinions, beliefs, and behaviors before, during, and after a triggering event (Giorgi 1997; Creswell 2009). Phenomenological research may also include secondary data in lieu of direct interviews such as the case of Latour (1993), which sought to understand why Louis Pasteur's theories on microbes and bacterial behavior were accepted in an uneven and politically-driven manner. However, the challenge within such cases as with Latour (1993) is that it is difficult to gain an unbiased view via secondhand accounts of how an event was understood, interpreted, and acted upon by individuals and communities – making it difficult to 'construct a story' regarding how the triggering event as with Pasteur's discoveries were absorbed in 19th Century France.

Phenomenological research is a mainstay for sociology, where it is used by researchers to gain insight into specific moments and experiences through multiple perspectives of affected individuals (Menon et al 2014). One example here includes Latour (1993), who utilized a phenomenological approach to investigate the scientific and social debates of Pasteur's discoveries of the microbe in 19th Century France. Another example includes the work of Eric Voegelin, who sought to investigate interstate violence of the 20th Century from the perspective of societal interpretations of religion, politics, and history (Voegelin 1995). The method has been applied to various sociological and philosophical works, yet a common linkage here includes the investigation of differing social perceptions and accounts for certain events that are shaped and defined by collective social understanding (Creswell 2009).

1.3.3 Grounded Theory

Practitioners of grounded theory seek to formulate new theories through an organization and analysis of data (Martin and Turner). Further, grounded theory differs strongly from other forms of research, which generally identify a theory at the onset of study and seek to use data and evidence to strengthen or weaken that theory (Glaser and Strauss 2009; Allan 2003). In this way, grounded theory is more geared towards developing new theories rather than testing existing assumptions or opinions, making it more applicable for research upon less structured or certain topics (Creswell 2009). Relying less on literature and secondary analysis and more on interviews, grounded theory often involves a system approach to acquiring,

organizing, and analyzing interview transcripts and discourse (Corbin and Strauss 2008; Creswell 2009). Specifically, these general steps include (i) generating categories of interview information, (ii) choosing one of these identified categories and describing it theoretically, and (iii) describe an analytical and/or causal story that links the various categories denoted in step 1. Such a process may not be easily manipulated for use to inform or populate quantitative methods, but can be useful for advancing theory for areas of limited or incomplete understanding of human behavior or actions (Morse et al 2009).

Grounded theory has common use within sociology, psychology, and certain applications in business (Pettigrew 2000). For psychology, grounded theory is noted by Smith et al (1995) as an approach that can utilize the interpretive nature of psychological research on human cognition and assessment where existing theories are limited or not applicable. Further, Stray et al (2016) note applications of grounded theory in business studies, where the investigators researched organizational practices such as 'stand up meetings' in order to improve organizational cohesion and information-sharing by employees. Regardless of discipline, proponents of grounded theory seek to make use of available interpretive data to derive new theory, rather than test existing theory within various case studies (Pettigrew 2000).

1.3.4 Ethnography

Ethnographic research centers on the study of cultural groups within their local and natural environments over one or more years (Berg et al 2004; Silverman 2010; Creswell 2009). The purpose of such research is for the researcher to use this extensive observational period to be able to discuss and reflect the opinions, beliefs, and actions of the observed society, indicating that field observation and research is almost a default necessity (Blomberg 1993; Denzin and Lincoln 2009). Data collected within an ethnographic research project is generally observational in nature, including a mixture of individual and collective group interviews over the period of several months to years (Silverman 2010; Creswell 2009; Creswell 2012). Due to the context-rich requirements of ethnographic research, methodological considerations here tend to favor discourse-driven approaches that are more subjective in nature and are generally not amenable to being transformed for use in a quantitative model (Creswell 2012; Riessman

1993). Further, ethnographic approaches, interview protocols, and research questions may evolve over time as a response to the researcher's experiences in the field over an extended period (Lewis 2015; LeCompte and Schensul 1999). The main constant within this process is the reliance by ethnographers upon interview-driven research, where extensive interview responses over the course of several months are deemed necessary in order to made strong claims about the observed group's behavior, beliefs, and actions (Lewis 2015; LeCompte and Schensul 1999; Creswell 2009).

Ethnography serves as a commonly-used approach for scholars in anthropology and science technology, and society (STS) studies who seek to better understand the customs and interactions of peoples and cultures (Wolf 2012). This is particularly true for anthropologists, who utilize ethnographic approaches to immerse themselves in different cultures over an extended period of time (generally, at least one year or more) (Bernard 2011). Within such research, anthropologists and sociologists seek to use direct subject interviews as well as secondary analysis of text to gain perspective on the values, thought processes, and beliefs of local people within a target society (Bernard 2011; Wolf 2012). One example of this includes David Maybury-Lewis' *The Savage and the Innocent* (Maybury-Lewis 1988), who sought to apply ethnographic research to study the indigenous peoples of central Brazil. Another example includes Mary Douglas' *The World of Goods* (Douglas 2002), which sought to gain perspective on consumers and consumption – specifically on why consumers save in certain situations, spend in others, and value quality when considering a purchase.

Relative to emerging technology regulation, ethnographic approaches may help describe cultural or social influences of a technology's regulation that are inherently difficult to quantify (Anders 2005; Barry 2001). Such research may help explain cultural influences on technology regulation within one or multiple countries (Anders 2005; Barry 2001). In this regard, ethnographic research may provide helpful to understand elements of local risk cultures as described in Chapter 1, where such risk cultures are difficult to quantify and are driven by the political, social, and institutional factors unique to a given society (Kelemen 2011; Lash 2000; Jasanoff 1986).

1.3.5 Case Studies

Case study research seeks to explore a contemporary phenomenon at a specific place and time (Travers 2001; Stake 1995; Creswell 2012). Within a given case study, explicitly outlining the geographic location of observation alongside the given time period of analysis is of paramount importance to researchers, where the 'case' is how the observed phenomenon occurs and impacts stakeholders within these dimensions (Travers 2001; Stake 1995). Such research is helpful to address research questions regarding how a new or little understood event occurs and impacts a community – particularly if the phenomenon in question is in its early stages or is otherwise ongoing (Baxter and Jack 2008; Creswell 2009). Specifically, Yin (2013) outlines that case study research is preferred in situations including: (i) When, how or why questions are being asked, (ii) When the researcher has little control over events, (iii) When the focus is on a contemporary phenomenon. Further, Yin (2013) stresses the importance for case study researchers to utilize multiple sources of information, including both primary and secondary data, in order to reinforce and triangulate conclusions derived from the case study (Dibb and Meadows 2001). While not a necessary precondition, Creswell (2009) argues that most case study research seeks to use findings from the case to be generalized to similar situations, where the primary and secondary data may be used to better understand how certain circumstances influence human behavior and beliefs. Case study research may also be longitudinal in nature (Leonard-Barton 1990), yet this may be financially or temporally prohibitive for the researcher (Travers 2001; Creswell 2009). Overall, case studies may include both individual and collective interviews, literature reviews, historiography and ethnography, and any other qualitative approaches deemed useful by the researcher, making this particular process more flexible and methodologically inclusive based upon the needs of a given research question and the types of information available for a particular evaluation context (Denzin and Lincoln 1994; Creswell 2009; Creswell 2012).

Case studies serve as a central method of choice for comparative politics and policy. Within such studies, cases allow comparative researchers to test proposed theories using applied examples in the real world – particularly the characteristics and behaviors of States. Further, findings from case study research allow comparative researchers to draw empirical

connections regarding how, for example, a State's institutional and political structure contributes to differing characteristics in its domestic or foreign policies (Eckstein 2000). One example of such research includes Theda Skocpol's *States and Social Revolutions* (Skocpol 1979), which sought to explain how political revolutions with similar characteristics took place in the differing contexts of France, Russia, and China.

These five methodological approaches serve as some of the more popular techniques available for researchers to conduct qualitative research. Selection of a particular approach is dependent on both the type of information available to researchers along with the research questions that may or may not be addressed, leaving some options more capable of answering certain questions than others. A further point of consideration includes the methodological and philosophical opinions and beliefs held by researchers as they conduct their work, where certain methods are more favored than others (Giacomini 2010). Keeping these qualitative methods in mind, some of the more popular philosophical frameworks for qualitative research are discussed below.

1.3.6 Philosophical Research Frameworks in Qualitative Methods

It is important to note here that each of the philosophical research theories and frameworks alongside the methods to elicit qualitative information all assume that its users follow a general research process that outlines research questions, develops theories, contains a general plan to acquire and subsequently analyze collected information, and interpreting findings to offer some insight into the research question at hand (Denzin and Lincoln 1994; Silverman 2010; Giacomini 2010; Creswell 2012). Philosophical frameworks are particularly important with respect to analyzing qualitative information (Silverman 2010; Creswell 2012; Giacomini 2010; Polkinghorne 1995), where the philosophical leanings of the researcher may cause them to use certain organizational tools and analytical techniques (described above) to answer their research questions based upon their expert judgment. Theory and philosophy directly influence how this research process is carried out (Lewis 2015; Giacomini 2010; Creswell 2012; Alvesson 2009), yet the following research stages are generally carried out regardless of the technique and philosophy utilized (Denzin and Lincoln 1994; Creswell 2012):

1) The researcher is required to understand their role and capabilities to collect information and robustly analyze said information for a targeted research question,
2) The researcher applies theory to the research question, often deriving from philosophical underpinnings or expectations from experience or personal belief,
3) The researcher identifies a research method to collect and analyze information to test the theory and hypothesis developed in Step 2,
4) The researcher uses the research method and design to collect and analyze such information, and
5) The researcher aggregates, discusses, and otherwise interprets findings from analysis to discuss the robustness and strength of their predefined theories to describe a pattern or behavior relevant to their research question and/or discuss causal implications related to the ability of one factor to influence a change in another.

Below, Section 2.4 discusses the philosophical frameworks and subsequent methodologies that form and advance qualitative research through the general research process noted above and found within the work of Denzin and Lincoln (1994), Silverman (2010), Creswell (2012), Creswell (2013), Alvesson (2009), and others. These philosophical frameworks and methods are pulled from various sources in scholarly literature, with a shared basis in that they primarily discuss either how to conduct valuable qualitative research, or explain how such research may fit within the purview of quantitative or mixed-methods research processes. Though it is not the purpose of this dissertation to advocate for a particular method or research philosophy for research pertaining to synthetic biology risk regulation (or indeed any other emerging technology), the following sections do indicate the strong variety of methods available to conduct such research, and indicates the general types of research questions that may be best suited for one particular method or another.

1.4 Theory and Philosophy Driving Qualitative Research

Given the discussion of specific qualitative methods above, a further consideration for prospective users of qualitative methods includes the methodological philosophies that

influence how and when such methods are used (Silverman 2010; Giacomini 2010; Creswell 2012; Denzin and Lincoln 1994). In other words, this section seeks to describe the common theoretical and philosophical options utilized by qualitative researchers to review the relationships between concepts.

Huff (2008) asserts that developing and understanding philosophy and theory behind any research project is important due to the ability of such theory to drive the formulation and scope of research questions, to elucidate the types of information needed to answer such research questions, and to understand the biases and personal assumptions made by researchers that may skew findings towards one avenue or another. Such theories and philosophies are inherently embedded within qualitative research that influences researchers to use specific methodologies and seek to address particular types of research questions (Patton 2005; Denzin and Lincoln 2011), making understanding a researcher's philosophical leanings an important task in order to understand their views of a given research question, the methods available to the researcher under such a mindset, and also the analytical tools and reasoning deployed by the researcher to utilize their acquired information to provide greater understanding to a particular research question (Bryman 2006; Silverman 2010; Giacomini 2010; Creswell 2012).

Giacomini (2010) outlines three general axes by which qualitative health research may be evaluated (see Figure 22 below), including:

i. **Ontological**, the nature of reality, or the ability of research findings to be found empirically (Blackburn 1996),
ii. **Epistemological**, what counts as knowledge, or concerns of how phenomena come to be understood and known (Guba and Lincoln 1994), and
iii. **Values**, or a researcher's position on whether morals and principles are present and reflected within scientific fact, alongside beliefs of how to control for bias from such values.

Further unpacking Figure 22 below, Creswell (2012) and Lewis (2015) adopt a similar approach and understanding of research philosophy and theory, although differs from Giacomini (2010) by further defining the 'Values' axis as axiological (the role of values within

qualitative research), and adding a fourth axis dubbed 'Methodological' (the procedures of qualitative research). Specific to the 'Methodological' axis, Creswell (2012) states that qualitative research is an inherently inductive enterprise, such research is heavily shaped by "a researcher's experience in collecting and analyzing […] data", where research questions within a given venture may even change in the midst of a given research inquiry in an effort to better focus research questions in a manner more appropriate for a given series of questions or research problems. Further, when such changes occur, Snape and Spencer (2003), Hesse-Biber and Leavy (2010), and Creswell (2012) state that a qualitative researcher's data collection strategy must also shift to match the change in scope.

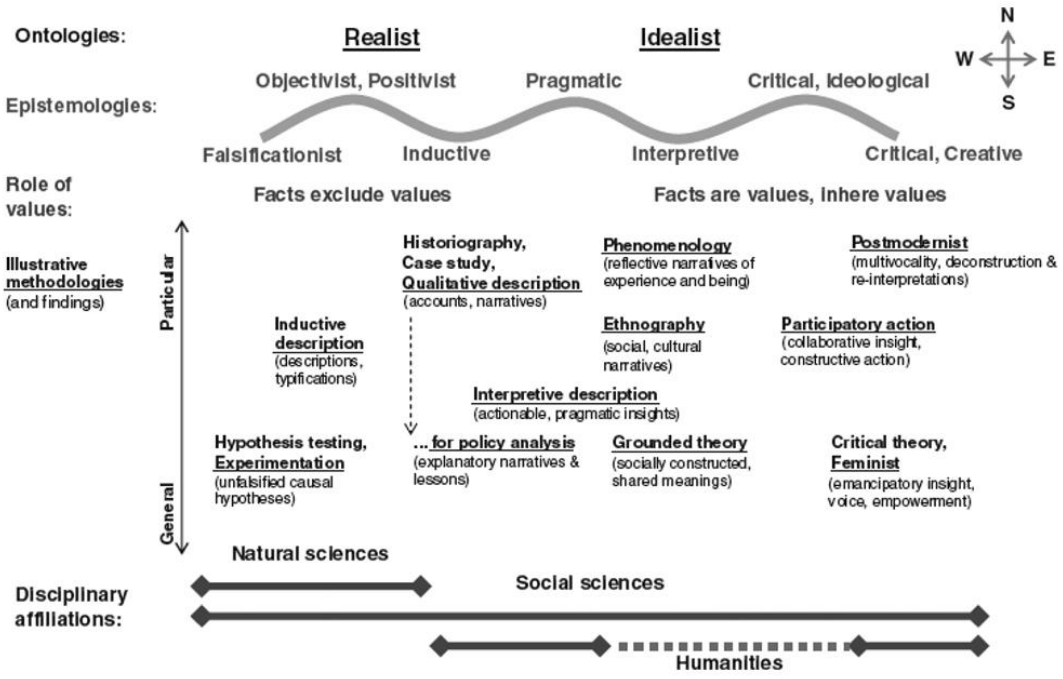

Figure 22. Health research traditions, by ontological & epistemological neighborhood (in Giacomini 2010)

As discussed by Guba and Lincoln (1994), Giacomini (2010), Denzin and Lincoln (2011), and Creswell (2012), the philosophical frameworks prescribed to by a given qualitative researcher influences their perspective and views upon conducting research, including their selection of methods to address a particular research question. Given this notion, this subsection denotes the various qualitative methods and approaches that may be useful and

applicable for research on synthetic biology regulation, where such methods are categorized based upon the philosophical and theoretical leanings and preferences of the given qualitative researcher.

Collectively, Guba and Lincoln (1994), Snape and Spencer (2003), Giacomini (2010) and Creswell (2012) collectively claim that ontology, epistemology, values, and methodology comprise the major philosophical assumptions that are intrinsically used and adopted within qualitative research. These assumptions also drive the adoption of a particular interpretive framework (Silverman 2010; Snape and Spencer 2003; Creswell 2012), which more specifically drives a researcher's selection of methodology and analysis. Specific to this point, Creswell (2012) and Lewis (2015) identify four such interpretive theories whose selection depends strongly upon the philosophical beliefs and approaches that a qualitative researcher takes, including:

i. Postpositivism
ii. Social Constructivism
iii. Pragmatism
iv. Critical Theories

Below includes discussion of the first four philosophical frameworks presented by Creswell (2012), Lewis (2015), Silverman (2010) Alvesson (2009) and others, and describe the methodological selections often prescribed and carried out by practitioners in their given field. Where research pertaining to synthetic biology regulation is driven by a need to better understand the potential risks and uncertainties facing the technology's developmental trajectory alongside the potential limitations of existing regulatory frameworks to resolve such novel risks for specific product categories (Carter et al 2014; Bates et al 2015; Mohan et al 2012), the Critical Theories category is omitted for discussion, where Fay (1987) claims that such research is primarily concerned with "empowering human beings to transcend the constraints placed on them by race, class, and gender." Instead, the first three frameworks denoted by Creswell (2012), Lewis (2015), and Silverman (2010) are more capable of answering qualitative research questions related to synthetic biology regulation due to their more general focus upon reviewing human perceptions and behavior for a variety of applications such as with

perceptions of risk amidst technology development. Within these four approaches, Denzin and Lincoln (1994), Snape and Spencer (2003), and Creswell (2012) do note that while qualitative scholarship does not necessarily need to directly describe the method and approach used, being transparent about the philosophical framework that underpins such qualitative research does help indicate the theoretical and methodological connections available for use by the research to address a given research question while also informing upon the type of information that a qualitative researcher may be able to generate using their arsenal of approaches.

1.4.1 Postpositivism

For a postpositivist researcher, qualitative research inherently embraces a reality where the opinions, beliefs, and experiences of a researcher can directly influence what is being observed within their frame of study, contributing to imperfect and probabilistically-defined perceptions of reality (Robson 2002). In this way, knowledge is neither universal nor unassailable, but instead tentative and subject to inquiry that may falsify or reject such knowledge in response to evidence to the contrary (Phillips and Burbules 2000). Giacomini (2010) contends that certain knowledge and claims are rendered true by trying yet failing to disprove the principles of such knowledge upon repeated inquiry, and that such postpositivist research is among the more deductive of the approaches chosen by qualitative researchers. Likewise, Guba and Lincoln (1994), Prasad (2005), and Creswell (2012) state that post-positivists in health research often come from backgrounds within quantitative research, where such researchers often make use of multiple techniques of data analysis and seek to refine their approaches with computer simulation and modeling to assist with rigorous analysis of qualitative inputs.

Drawing upon the work of Robson (2002), Creswell (2012), and Phillips and Burbules (2000), it can be said that postpositivist methodologies are generally deductive and possess a general goal of creating new knowledge and rigorously testing such knowledge for potential avenues of falsification. Where the principle of ‘falsification’ is an important tenet within postpositivist research, Giacomini (2010) states that qualitative postpositivist research must do more than assert that a hypothesis is “not untrue”, but instead test the hypothesis as if it were true and

determine if any logical faults or challenges subsequently arise (Chalmers 1999). Under such conditions, Ryan (2006) claims that postpositivists are directly engaged with (i) the concept of discourse, (ii) the concern with power, (iii) the value of narrative, and (iv) the need to be reflexive. Methods within this framework tend to take on an experimental design framework with pre- and post-test measures of attitudes derived from surveys and interviews, where the researcher utilizes an instrument that measures such attitudes on a predefined scale (Chalmers 1999; Prasad 2005). Such methods often use statistical analysis within the codification of discourse and/or content analysis with interview contacts, where discussant response is reviewed with computational software to test a hypothesis using a pre-post assessment to review the effect of a given treatment upon interviewee responses (Prasad 2005; Creswell 2013; Alvesson 2009). Where possible, retesting and assessment should be conducted in an attempt to falsify the given hypothesis established for a particular research question (Taylor et al 2015; Creswell 2013; Ryan 2006).

1.4.2 Social Constructivism

Social constructivism is inherently focused upon the concept that where reality is not naturally given or objectively defined, it is instead derived based upon the subjective perceptions of humanity alongside the perceptions of an individual given their participation and interactions with a particular group (Crotty 1998; Lincoln and Guba 2000). Alvesson (2009) states that such research is rooted within older phenomenological studies, where information is derived as individuals describe their experiences (Moustakas 1994). Further for Taylor et al (2015) and Alvesson (2009), social constructivism is centered on the idea that "We create within our social relations all the time new habits and routines in our actions, as well as new categories in our observing of others and their actions." Through social interaction, institutions arise out of shared habits and routines that, over time, become perceived as both external and objective objects (Berger and Luckmann 1966; Taylor et al 2015).

Creswell (2012) states that research that utilizes social constructivism is generally inductive in nature, where researchers generate theories of action in the process of research rather than base initial research on a foundational theory. In this view, social constructivists

seek to gain an understanding of a research question's complexity (as opposed to narrowing inquiry onto a small number of defined concepts or variables for measurement), and include as many experiences and views of individuals as possible to gain subjective perspective regarding the experiences of these individuals within a given situation of social activity and institutional development (Crotty 1998; Creswell 2012). Then, the researcher would generally acknowledge their own social constructions of the given research question, and 'interpret' their findings based upon their own social experiences and history (Taylor et al 2015; Lewis 2015; Alvesson 2009; Creswell 2012; Creswell 2013).

As a theory, social constructivism seeks to approach qualitative research in a manner that enables a broad and general focus so that those stakeholders and participants asked for their input for a particular research question can construct their own meaning of a given situation based upon their existing knowledge and experiences (Taylor et al 2015; Creswell 2012; Alvesson 2009). Such frameworks often arise through the use of open-ended interviews, where a social constructivist researcher would review discourse from an interview for particular markers regarding what a given respondent would say or do within a given situation (Guba and Lincoln 1994; Creswell 2012; Creswell 2013). Methods commonly used to further such research include discourse analysis from interviews, ethnographic observation of individuals and communities to understand social dynamics and constructions for a given activity, and reviews of written and published material to analyze text for shared meanings and constructions by individuals within and across given social groups (Taylor et al 2015; Silverman 2010; Creswell 2012; Creswell 2013). Overall, the social constructivist researcher seeks to deploy an "inductive method of emergent ideas through consensus", where discourse from live interview subjects or texts would collectively inform knowledge on behaviors or beliefs regarding a given activity or institution (Attride-Stirling 2001; Creswell 2012; Alvesson 2009; Taylor et al 2015).

1.4.3 Pragmatism

Of the various philosophical and theoretical approaches available to qualitative researchers, pragmatism may serve as the one example that is implicit within most qualitative research projects (Rossman and Wilson 1985; Patton 1990; Cherryholmes 1992). Specifically,

researchers within this category seek to utilize “what works” for a given research context, with a general goal of solving research problems that may not normally be defined by a specific method or approach (Patton 1990). In this way, pragmatism is inherently focused upon producing useful and valid research outcomes (Creswell 2012; Patton 1990; Cherryholmes 1992), where “the important aspect of research is the problems being studied and questions asked about this problem” (Creswell 2012).

In this vein, Cherryholmes (1992) and Murphy (1990) conclude that pragmatist researchers are free to select any method that addresses the given research questions and needs of a particular situation. Ideally, a pragmatist researcher would likely use multiple qualitative methods for a given research application (Creswell 2012), with one such example including the use of quantitative surveys and content analysis alongside qualitative interviews and focus groups by ethnographers (LeCompte and Schensul 1999; Yin 2010). One of the few constants in this research stream is the need for researchers to acknowledge the impact of their own beliefs and values within the research design and information gathering process, where such views may inherently bias research analysis and eventual discussion (Creswell 2012).

Methodologically, pragmatist researchers utilize both inductive and deductive approaches to research based upon both the availability of information alongside the appropriateness of different tools to analyze and assess such information to address a given research question (Patton 1990; Cherryholmes 1992; Creswell 2012). Deductive tools may be similar to those utilized by postpositivist researchers, and include surveys and content analysis that would help populate quantitative assessment models for research. Similarly, inductive tools may be similar to those utilized by constructivists and postmodernists, with more open-ended interviews and focus groups to gain greater understanding of individual and/or subject expert responses to given research questions (Creswell 2012). Overall, qualitative researchers utilizing a pragmatist approach are less bound to any particular approach or philosophy (Patton 1990), and emphasize the practicality of tools within given situations instead of abiding by any singular approach to inform theory, philosophy, and general approach to qualitative methods.

1.5. Using Qualitative Methods to Populate Quantitative Models

Aside from the methodological options (2.3) and philosophical frameworks (2.4) noted above, the use of qualitative methods has also been demonstrated as useful tools to inform decision context (Bates et al 2015; Roberts et al 2015; Mohan et al 2012). Findings from qualitative research can be utilized within quantitative methods by (i) converting qualitative interview feedback along an ordinal scale to substitute for missing or unavailable quantitative data (Roberts et al 2015; Bates et al 2015), (ii) acquiring subject expert insight to offer generalized assessments of risk such as with surveys, questionnaires, or long-form responses (MacKay et al 2013; Linkov et al 2009; Linkov et al 2012), or (iii) developing qualitative scenarios to describe exposure scenarios for emerging materials (Zalk et al 2009; Brouwer 2009).

Where such methods may traditionally utilize quantitative data to generate risk-driven analysis, qualitative information may also be used to populate these models. This is accomplished through a variety of means such as with ordinal survey design as an extension of expert interviews or with a quantification of recurring interview terms in content analysis in a manner in line with postpositivist research. This subsection includes two particular approaches which can process and utilize information from qualitative information acquisition exercises, including (i) Bayesian Approaches and (ii) Multi-Criteria Decision Methods.

1.5.1 Bayesian Analysis

Experimental design is a central element of quantitative research methods, and helps yield quantitatively defensible research findings that are verified via statistical analysis (Chaloner and Verdinelli 1995). However, such experimental design is also resource intensive, and can be challenged from the perspective of experimental validity in the presence of uncertainty and limitations of available data to drive statistical inference (Chaloner and Verdinelli 1995; Ryan 2014). Within such situations, Bayesian experimental design includes an amalgam of existing knowledge related to the research experiment alongside considerations of the various uncertainties in of the experimental observations and inputs (Chaloner and Verdinelli 1995; Ryan 2014; DasGupta 1996). In this way, Bayesian experimental approaches are useful for decision making under uncertainty, where a single decision point may be used by which to drive statistical assessment, and prior distribution of available data points is used to

update and evaluate that single data point (Ryan 2014; Chaloner and Verdinelli 1995; Lindley 1972). This is the principle of Bayesian inference, which drives Bayesian experimental design and seeks to make use of "posterior predictive distribution" to conduct predictive inference and ultimately predict the distribution of a new, uncertain, and previously unobserved data point for a given dataset (Ryan et al 2014).

Bayesian approaches are useful tools to drive quantitative assessment when certain factors within the experiment lack concrete information, where such situations would complicate more traditional experimental design (DasGupta 1996; Chaloner and Verdinelli 1995). Such an approach has already been demonstrated for systems biology (Wilkinson 2007; Jha et al 2009), where Bayesian methods are helpful for addressing measurement error or 'noise' within data related to computational systems biology, genetics, bioinformatics, and similar related fields. Within such a framework, qualitative information has been discussed as being helpful to "[inform the] distribution describing plausible potential values for parameters" (Voils et al 2009), particularly for cases where acquiring information about the parameter distribution is unethical or exceedingly troublesome (Roberts et al 2002). Such qualitative information may derive from literature reviews or interview information, yet must be robust and ideally may be triangulated from a variety of sources to improve distribution reliability (Voils et al 2009).

1.5.2 Multi-Criteria Decision Methods

While many decision analytic methodologies are data intensive and require robust sources of objective information to conduct their analyses, one particular branch of such methods known as Multi-Criteria Decision Analysis (MCDA) has an extensive scholarly history of utilize qualitative and quantitative information alike to inform decision making (Linkov et al 2009; Tervonen et al 2009; Belton and Stewart 1999; Paruccini 1994; Funtowicz et al 1990; Matos and Miranda 1989). Where cases of emerging technologies such as with nanotechnology and synthetic biology are generally lacking of substantial objective data, the use of qualitative opinion and subject expert beliefs regarding the potential risks and benefits is necessary and helpful in order to inform policy decisions related to how the technology should be regulated

and governed (Mohan et al 2012; Bates et al 2015; Linkov et al 2013). Transparent decision analytical tools such as MCDA make this task possible in the immediate term, where qualitative information is used in place of quantitative data to guide the decision analytic process. Using MCDA, expert opinion and judgment may be aggregated in a formal and quantitative manner, ultimately affording its user the potential to make value judgments and tradeoffs based upon the perceived risks and benefits of the technology.

Multi-Criteria Decision Methods have been applied in various ways to emerging technologies risk assessment and governance scholarship, specifically within the purview of utilizing qualitative methods (expert interviews, qualitative surveys, scorecards, literature reviews, and content and discourse analysis) to populate models that guide decision making. Specific examples include general nanomaterial risk assessment (Tervonen et al 2009; Linkov et al 2008), life cycle approaches to reviewing health risk and liability concerns of nanoparticles (Mohan et al 2012), assessing respective risk and benefit options of synthetic biology and nanoparticles for environmental remediation (Bates et al 2015), guiding synthetic biology regulation and policymaking for specific compounds (Roberts et al 2015), and advancing decision making for emerging technologies under high risk and uncertainty (Linkov et al 2013). The versatility afforded by MCDA derives from the ability of a decision analyst to quantify findings from interviews and surveys with experts to inform the criteria weights and/or alternative scores within a decision model, allowing for a transparent view regarding how certain decision factors such as risk, cost, and benefit influence regulatory outcomes related to technology development and eventual commercialization (Bates et al 2015; Roberts et al 2015). Such frameworks and decision aids have been adopted by the US Army Corps of Engineers for the environmental risk assessment of nanotechnology, and are currently being discussed as options to address risks of synthetic biology (Bates et al 2015; Bates et al 2015).

Methodologically, the qualitative methods used for MCDA applications tend to make use of ordinal surveys with Likert and Likert-like scales (Bates et al 2015), although semi-structured interviews have been utilized to inform parameters of general technological risk across a product's life cycle (Roberts et al 2015). Regardless of the information acquisition process, the overall goal is to transform qualitative information into quantitative input for the

decision model of choice (Linkov et al 2013; Mohan et al 2012), making this approach generally in line with postpositivist approaches that seek to quantify as much as possible qualitative information for risk-based output that can be processed by computer programs such as described by Yatsalo et al (2010) and Yatsalo et al (2016). Such a transformation requires the qualitative researcher to be able to acquire information that is amenable to numerical codes, limiting the qualitative methods available for such research limited to those that can be derived using ordinal scales or could be subject to some quantification of interview data as with content analysis.

1.6 The General Strengths and Weaknesses of Such Methods

Given the various philosophical frameworks and methods available for qualitative research, selecting the proper approach for a given research venture requires the qualitative researcher to consider the various strengths and weaknesses that a given method possesses. With respect to both the collection and analysis of qualitative information, no single method is optimal in all situations and for all applications (Silverman 2010; Taylor et al 2015; Giacomini 2010; Creswell 2009; Creswell 2012). Instead, the qualitative researcher must determine several factors, including (Taylor et al 2015; Alvesson 2009; Giacomini 2010; Yin 2010; Creswell 2012):

1) What purpose does the method serve for the research question at hand? To generate new knowledge and theory, to view individual and/or collective opinion on an event, or to test existing theory?
2) Is there an expectation that my qualitative research will have to populate a quantitative metric or model?
3) How can I acquire the information needed to address my research question?
4) What limitations may I face within the information gathering process?

The first two questions are inherently concerned with the researcher's philosophical leanings alongside perceptions of how the qualitative findings derived from such work will be applied to a given research question. To help guide this effort, reviewing the COREQ checklist (Tong et al 2007) can help researchers break down their research questions into various inputs

and methodological considerations, although substantial consideration of what those methods are is important to ensure such research is successful (Lewis 2015; Giacomini 2010). Further, the researcher must consider their own philosophical leanings within the context of scholarly research (Ponterotto 2005; Creswell 2012; Giacomini 2010), and how those beliefs and opinions affect their ability to conduct research for the given question. These issues are not as easily resolved, and instead requires substantial inquiry by the researcher into their scholarly field to determine their intended role within a particular community. This community could advocate for qualitative methods as an ends by themselves (Alvesson 2009), or contend that such methods may best be used to facilitate quantitative methodologies where larger datasets are elusive or difficult to obtain (Neuman 2005; Creswell 2012; Giacomini 2010).

Question 3 is a methodological consideration that may be assisted through the use of a checklist such as with COREQ (Tong et al 2007). Understanding the role and abilities of the researcher upon a given question can help indicate the tools and skills available to conduct research, particularly related to the gathering of information from interviews or focus groups. This may be further facilitated by a thorough understanding of published scholarly literature related to the research question at hand (Yin 2009; Bates et al 2015), where the researcher may identify past strategies for successful information gathering within their field or identify strategies to organize their interview protocols around important and unresolved research areas. A thorough literature review, alongside the assistance of an interview preparedness checklist as with COREQ, will likely help the researcher structure their qualitative search, organization, and assessment approaches, and reduce potential bias that could arise within the scope of such research (Tong et al 2007).

Lastly, Question 4 requires an honest appraisal by the researcher regarding the limitations of the capabilities to conduct certain research and answer particular research questions. As with assistance regarding the construction of interviews and the acquisition of qualitative information, a helpful first step here would be to consult a methodological checklist such as COREQ (if the qualitative approach includes interviews) may indicate potential methodological concerns that may arise during the research process (Tong et al 2007). However, such a checklist will not necessarily address all of the specific contextual and field-

specific issues that may complicate qualitative research within the given field, forcing the researcher to determine the methodological constraints exhibited by their approach. This could include the need to account for concerns related to not receiving ideal feedback from interview subjects, having difficulties gaining access to such subjects, or concern that the interview subjects acquired do not offer a robust sample of contacts that can offer generalizable feedback the given research question. Rectifying these concerns may take considerable effort, but may be rectified through stratified sampling and use of professional networks to branch outwards to identify further contacts, conducting a thorough literature review to both identify potential research contacts and/or streams of discourse ripe for questioning, and thoroughly classifying interview contacts based upon their demographic, professional, intellectual, vocational, and other criteria (Bates et al 2015; Creswell 2007; Yin 2009). Such strategies that may allow a qualitative researcher and interviewer to compare responses across such criteria to compare and contrast responses, and offer descriptive information regarding the types of respondents available within the qualitative study (Bates et al 2015; Linkov et al 2012).

Overall, qualitative methods can both offer valuable insight into a given research question individually or also by acquiring information to populate quantitative methods and analysis (Neuman 2005). Method selection depends largely upon the philosophical framework preferred by the researcher along with the researcher's level of comfort and expertise with various qualitative approaches, ranging from narrative analysis to ethnography to case studies (Ponterotto 2005). For cases where quantitative information is limited due to ethical, financial, or technological reasons, qualitative methods (either within the context of information acquisition to populate such quantitative methods or individually as an approach to acquire context-rich input for a given research area) may help a researcher overcome such limitations by turning to individual and collective interviews, literature reviews, artifact analysis, and several other tools discussed above (Neuman 2005; Duffy 1987).

1.6 Criticisms and Prejudices of Qualitative Methods

Despite the promise and flexibility that qualitative methods provide to researchers, such methods have been criticized due to the subjective nature of subsequent research findings

(Sandelowski 1986; Borman et al 1986). Specifically, some writers as Borman et al have argued that such methods produce results that do not rigorously and objectively test theoretical propositions given that measurement and analysis are undertaken using subjective schemes for the coding and interpretation of data. Other scholars such as with King et al (1994) insinuate that qualitative research may overcome such concerns, but only by mimicking quantitative methodological processes to test scientific inferences. Among others, such suggestions by King et al (1994) include an affinity for larger sample sizes, the need to stress study operationalization and repeatability, and concerns related to avoiding endogeneity and multicollinearity.

Researchers should be mindful of such arguments raised against qualitative methods, and take steps to protect against such concerns by seeking to remove bias in the selection of cases and interpretation of data (Creswell 2012; Giacomini 2010). However, such concerns should be countered with an understanding that qualitative methods have multiple potential benefits to facilitate research on synthetic biology development under high uncertainty and potential risk, including (i) the ability, where necessary and helpful, to utilize qualitative data within quantitative methods, and (ii) the improved context and understanding of perceived technological risks and benefits that are inherently difficult to quantify (Schultze and Avital 2011).

1.7 Discussion

Qualitative research is a rich and robust field with various methods and approaches used by stakeholders to elicit and process information. These methods are diverse based upon their information needs and analytic capabilities, and have specific contexts that make certain methods more appropriate for a given research context than others, and are ultimately useful based upon whether the method can acquire information and derive findings from such information in a manner useful and relevant to stakeholders. In this way, qualitative methods seek to offer a richer assessment of a research question than currently exists, where common approaches such as with subject expert interviews, ethnographic research, historical/literature assessment, and content/discourse analysis can all help researchers better understand the

context where a research problem exists alongside the options available to alleviate, resolve, or simply better understand the context of that problem (Creswell 2010; Giacomini 2010). Synthetic biology research is no different, where a qualitative researcher must be mindful of the emerging nature of the technology (i.e. the uncertainty regarding the field's potential for novel risk and benefit) alongside the given context that information is acquired in (i.e. what is the cultural or vocational background of the individual or group offering input into the qualitative research process).

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