Engineering Improvements in Endovascular Devices

Design and Validation

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ABSTRACT: Advances in endovascular treatment of vascular disease have focused on basic and translational research of vascular disease and endovascular devices. Clinical trials serve to establish the safety and efficacy of engineering advances that incorporate this research. Recent position statements by the Food and Drug Administration (FDA) emphasize that research into conducting these trials in a timely and cost-effective manner (critical path research) is as important to patient care as the engineering advances themselves. This article reviews the recent FDA documents discussing critical path research, highlighting those topics that the FDA emphasizes. Several directions of translational research in which engineering advances may contribute to enhanced device design and improved patient care are reviewed.

KEYWORDS: critical path research; endografts; Food and Drug Administration (FDA)

INTRODUCTION

The endograft revolution is upon us. As we evaluate third and fourth generation devices for treating abdominal aortic aneurysms, wrestle with endoleaks, and debate how rigorously to follow device IFUs in treating the patient with marginal anatomy, it is tempting to think that engineering advances will solve our problems. However, when we are speaking of how to treat an aneurysm, our problems become our patients' problems. Several recent Food and Drug Administration (FDA) documents serve to remind us that the world of devices is more complicated than searching for engineering improvements. Basic science advances are a small part of adding a new device to the daily inventory of the interventionalist. While chemical engineering no doubt has much to

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Ann. N.Y. Acad. Sci. 1085: 213–223 (2006).
doi: 10.1196/annals.1383.021

contribute to endograft technology, a more pressing question is: What is the probability that a chemical (or other) engineering improvement will find its way into a new device on the shelf?

CRITICAL PATH RESEARCH

The first of these FDA documents is a report from March 2004, Challenge and Opportunity on the Critical Path to New Medical Products.[1] According to the FDA, the applied sciences needed for product development have lagged advances in the basic sciences. Furthermore, there has not been "enough validated work towards showing how the safety and effectiveness of new products can be demonstrated faster, with more certainty, and at lower costs." Finally, the path of a device to market is "long, costly . . . inefficient," and, we may add, unsure. In support of these observations, the FDA presented evidence of steadily increasing financial outlays by the pharmaceutical R&D enterprises and the FDA (FIG. 1), and declining submissions of new molecular entities and biologics license applications (FIG. 2). Other data from the FDA web site show similar trends in submissions of original PMAs, IDEs, and HDEs (FIG. 3) and 510(k)s (FIG. 4).[2] While a comparable figure for device failure is not available, 75% of the cumulative research and development costs of new drugs are due to failure of the drug to meet safety or efficacy standards.[3] The

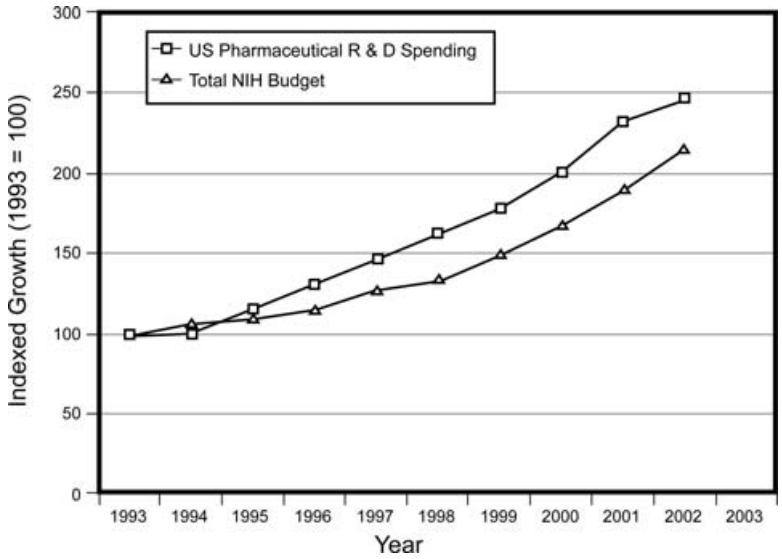

FIGURE 1. Graph showing increasing expenditure by pharmaceutical companies and the FDA for drug development (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html).

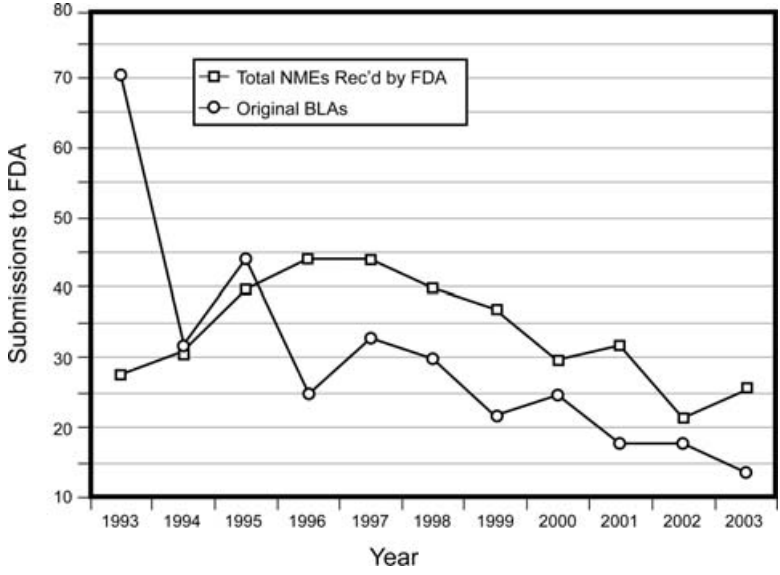

FIGURE 2. Graph showing declining submissions of new molecular entities and biologics license applications (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html).

research model discussed in the FDA Critical Path report focuses separately on basic sciences research, translational research, and what the FDA calls "critical path research" (FIG. 4). The presentations in this symposium have been in the categories of basic sciences and translational research. Before taking up the charge of this presentation, namely surveying engineering advances that will improve endovascular treatment of aneurysms, which comprise another facet of translational research, it is worthwhile looking in greater detail at the FDA discussion of critical path research.

The FDA lists six areas of critical path research, four of which (TABLE 1) are pertinent to the medical and economical environment affecting development of current medical devices.[4] From a list of 66 specific topics within these four areas, 18 (27%) are pertinent to endovascular treatment of aneurysms (TABLES 2–5). The list is not exhaustive. Recent experience in conducting U.S. device trials has highlighted additional challenges and opportunities for improvement (TABLE 6). These challenges affected the Wallgraft trial for treatment of arterial pseudoaneurysms and numerous endograft trials for treatment of aortic aneurysm.

Recently, at the 2006 Centennial FDA Science Forum, a group of FDA staff, industry representatives, and university investigators met " . . . [to discuss] how emerging science and technology can be effectively applied in support of the FDA's public health mission, [and] . . . to revisit the investment in regulatory science and communicate not only the tangible results of that investment, but highlight the process by which that original commitment to high quality

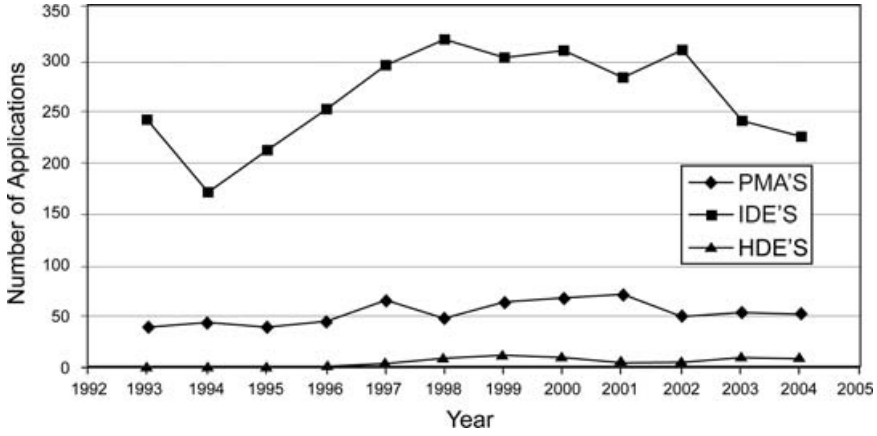

FIGURE 3. Graph showing declining submissions of original PMAs, IDEs, and HDEs adapted from web site (as of May 3, 2006) http://www.fda.gov/cdrh/annual/fy2004/ode/part3.html.

scientific achievement will translate into the future of science at [the] FDA."[5] From a list of 24 break-out sessions in this forum, eight (33%) discussed topics relevant to critical path research in medical device development (TABLE 7). To give the reader the flavor of the conference, some of these topics are listed in TABLE 8; for the sake of brevity, the presenter and parent institution have been omitted, but are available on the web site.

To summarize these recent discussions of critical path research, approximately one-third of the effort has been devoted to topics directly relevant to medical device development. Success in streamlining the path from device

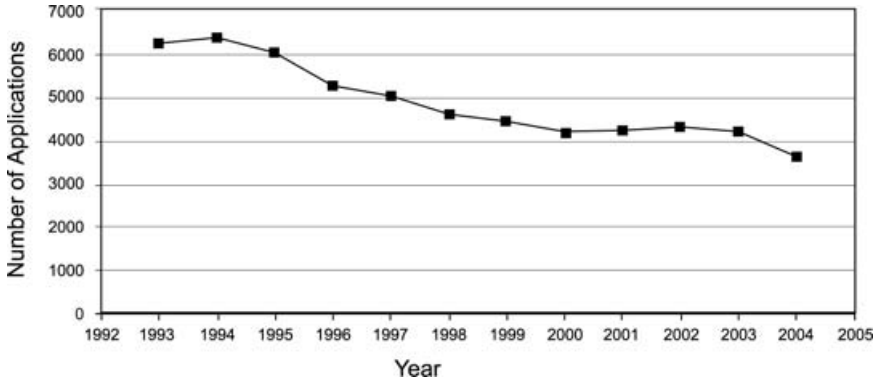

FIGURE 4. Graph showing declining submissions of 510(k)s adapted from web site (as of May 3, 2006) http://www.fda.gov/cdrh/annual/fy2004/ode/part3.html.[2]

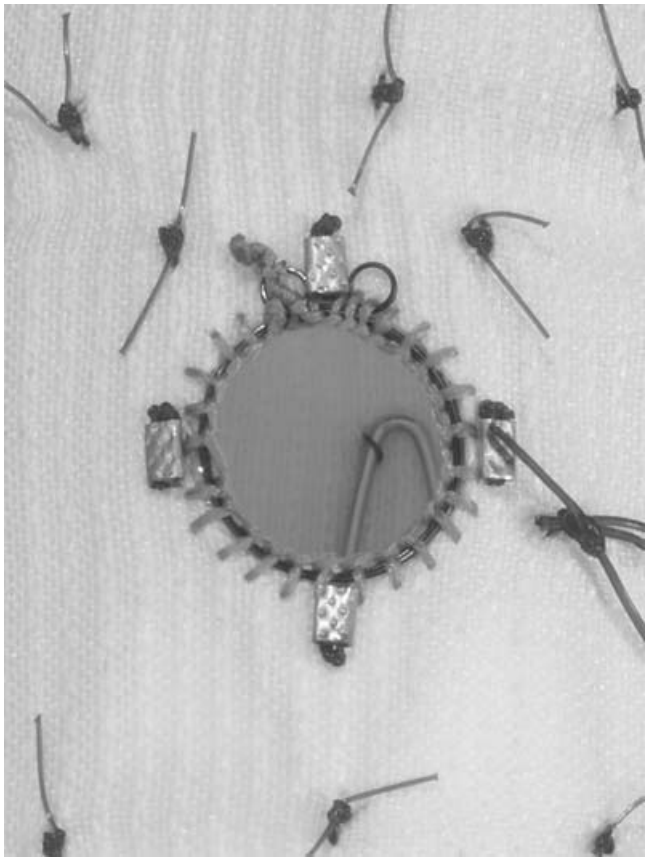

FIGURE 5. Detail of fenestrated endograft showing nitinol-reinforced fenestration, radio-opaque markers, and securing sutures in this hand-sewn device.

design to implantation is critical for economic, scientific, and medical reasons.

ENGINEERING OPPORTUNITIES IN ENDOVASCULAR TREATMENT OF ANEURYSMS

Many speakers at this symposium have reported on exciting developments in understanding the biology, hemodynamics, and treatment of aneurysms. The remainder of this presentation is to illustrate additional areas of opportunity where engineering solutions can benefit treatment of patients with aortic aneurysms.

TABLE 1. Critical path opportunities list

1. Better evaluation tools
2. Streamlining clinical trials
3. Harnessing bioinformatics
4. Moving manufacturing into the 21st century

COMPUTER-AIDED DESIGN AND COMPUTER-AIDED MANUFACTURE (CADCAM)

Fenestrated and branched endografts are under clinical trial at a few U.S. institutions. Successful development will obviously increase the population of aneurysm patients who are candidates for endografts. Yet, because of natural variation in branch vessel anatomy as well as because of distortions in branch artery anatomy imposed by the elongation and kinking of the aneurysmal aorta, considerable variation in aortic and arterial anatomy is encountered in clinical practice. The manufacturers of the test device have elected to accommodate this anatomic variation by means of an endograft built to individual patient specification. The anatomical details of a given aneurysm and design of the matching endograft can be specified with great precision by means of several commercial rendering-software packages. A company spokesman estimated (in a personal communication) that building such a device required 20 h of labor by hand (FIG. 5). The device is, therefore, built with the help of computer-aided design and, literally, manufactured; it is a child of the 21st and 19th centuries. The real cost of building such a device is proprietary information. The 20 h of hand labor severely limits turnaround between device specification and shipping. Clearly, however, to extend the benefit of this device to a larger group of patients, to allow emergency use of the device on patients presenting with symptomatic aneurysms, and to extend use of the device to patients with marginal anatomy, it will be necessary to replace manual fabrication with computer-aided manufacture.

TABLE 2. Better tools for evaluating medical innovations*

6. Surrogate outcomes for cardiovascular drug eluting stents
7. Circulating biomarkers in cardiovascular diseases
22. Using medical imaging as a product development tool
23. Imaging biomarkers in cardiovascular disease
29. Imaging implanted devices
30. Improving extrapolation from animal data to human experience

*Numbers correspond to itemized list in the Critical Path document.

TABLE 3. Streamlining clinical trials*

34. Design of active controlled trials
36. Use of prior experience of accumulated information in trial design
44. Development of data standards
45. Consensus on standards for case report forms

*Numbers correspond to itemized list in the Critical Path document.

MICRO-ELECTRO-MECHANICAL SYSTEMS (MEMS)

According to a web site dedicated to this technology, micro-electro-mechanical systems (MEMS) comprise "the integration of mechanical elements, sensors, actuators, and electronics on a common silicon substrate through microfabrication technology."[6] One realization of this technology is the pressure sensor, marketed by CardioMEMS, Inc., designed to be implanted in the aneurysm sac after deployment of an aortic endograft. The device itself is several centimeters long. The "micro" in the name refers to the manufacturing technique used in fabricating the induction coil of the sensor. The resonant frequency of the device is determined by the ambient pressure. By interrogating the device externally and measuring the frequency of induced signal, the pressure in the sac surrounding the sensor can be determined.

In designing systems such as this, several constraints have to be considered. The actuator, which in this case is pressure within the aneurysm sac, must be a surrogate that reliably predicts the desired (or undesirable) endpoint. Implicit in choosing sac-pressure as a surrogate for a stable treated aorta are the following assumptions: rising sac pressure predicts an unstable aneurysm in time to treat the patient, and a single sac pressure is representative of pressure throughout the aneurysm sac. The second assumption is equivalent to treating the sac as a single compartment filled with a liquid. The clinical experience with the device will settle the question whether these assumptions are adequate for reliable patient follow-up, and what pressure change within the sac is clinically significant.

Actuators responding to shear stress or temperature could be developed if needed. All these devices have to be enclosed in a biocompatible package.

TABLE 4. Harnessing bioinformatics*

47. Virtual control groups in clinical trials
49. Multiple complex therapies
50. Modeling device performance
51. Clinical trial simulation
52. Failure analysis

*Numbers correspond to itemized list in the Critical Path document.

TABLE 5. Moving manufacturing into the 21st century*

61. Device interaction with blood flow
62. Development of a biocompatibility database
66. Characterizing and qualifying nanotechnologies

*Numbers correspond to itemized list in the Critical Path document.

This packaging requirement does not interfere with measuring ambient pressure using the technique of the CardioMEMS device, which transduces minute physical deformations of the gap between the membranes. However, a sensor that responded to levels of a protein or other molecular species needs to interact with its medium without eliciting an allergic, antigenic, foreign-body, or nonspecific inflammatory reaction that might interfere with sampling of its biochemical environment.

Extensions of the MEMS technology include Micro-Optical-Electro-Mechanical Systems (MOEMS) and Nano-Electro-Mechanical Systems (NEMS). As noted above, the CardioMEMS EndoSure™ Wireless AAA Pressure Measurement System is a macrodevice that is constructed using microtechniques. It is a macrosensor, and, when implanted, sits side-by-side with the endograft, a macrodevice. But it is clear, from examples in the space and automobile industries, that sensors can be incorporated in the construction of a device such as an airbag accelerometer, fuel tank sensor, or tire pressure monitor. An endograft so constructed would have, embedded in its construction, micro or nanodevices that monitored surrogates for device integrity and aneurysm stability.

ARTIFICIAL ARTERIES

Vascular graft material is needed for coronary artery and lower extremity bypasses, dialysis conduits, and repair of abdominal aortic aneurysms. The diameter of these conduits ranges from 3 mm to 10 mm for arterial bypasses and dialysis grafts, to 15–40 mm for aortic grafts. The ideal conduit resists thrombosis and infection, does not incite an inflammatory or antigenic response, and responds to vasoactive stimuli. It should have compliance, resistance to

TABLE 6. Challenges to conducting device trials in high risk medical conditions

1. Design of a device trial when the test device removes clinical equipoise relative to standard treatment
2. Execution of a device trial when the test device is available commercially for a different indication, and off-label treatment of the test condition competes with the trial for patient accrual
3. Execution of a device trial when a new device competes with approved devices for patient accrual

TABLE 7. FDA 2006 Centennial science forum: Breakout sessions[a]

1. FDA science at the centennial: History and perspective
2. Seafood safety: From algae to aquaculture
3. Preparing for and preventing a modern plague: Focus on avian flu
4. **Nanotechnology**
5. **Clinical trials & statistics: A glance at the past and present & a look to the future**
6. Omics along the critical path to new medical products
7. Body marking: Tattoos, permanent make-up and laser removal
8. **Partnering on the critical path to new products**
9. Rapid detection of multiple pathogens
10. Bioinformatics
11. **Risk-based inspections and surveillance**
12. Personalized medicine
13. Obesity
14. Bringing home biomarkers: Science, regulation and common sense
15. Current challenges in the treatment of parasitic diseases in humans and animals
16. **Combination products**
17. **Advances and frontiers in using records databases for surveillance of medical products**
18. Pediatric experience with the FDA: Where we have been and where we are going
19. Public health preparedness
20. Blood and tissue safety
21. Public health during natural disasters: The FDA Katrina-Rita experience
22. **Minimally invasive devices**
23. **Managing uncertainty in risk assessment: Probabilistic approaches**
24. Novel approaches to cancer therapy and monitoring

[a]Sessions in bold font discuss Critical Path research relevant to medical device development.

kinking, and tensile strength similar to native vessels. For use as a surgical implant, it should be easy to process and handle, capable of holding sutures without tearing, and available in a suitable range of diameters and lengths.

Synthetic conduits like Dacron and PTFE have limited patency, especially for smaller diameters and longer lengths. They may kink if extended across joints of the upper or lower extremity. The patient's own vessels present a limited source of autologous vascular "grafts," including the great saphenous vein, radial and internal mammary artery, and superficial veins in the forearm used *in situ* in an arteriovenous shunt for dialysis access. Medicare figures from 1996 suggest significant potential application of a biological graft that combines the advantages of the autologous material to the availability of the synthetic graft. Per 1,000 Medicare enrollees in 1996, there were 6.5 coronary artery bypass procedures (70% using the internal mammary artery), 2.0 infrainguinal bypass procedures (39% using synthetic conduits), 1.6 major amputations, and 1.6 initial vascular access procedures for hemodialysis (83% using synthetic conduits).[7] Several centers have been exploring ways to construct biological implants.[8,9] These efforts have resulted in successful implants in nonprimate mammals but not, to my knowledge, in humans. This work has obvious importance in this era of growing prevalence of patients with type II

TABLE 8. FDA 2006 Centennial science forum: Focus on devices

1. Quantum dots: Emerging applications in biology, imaging and medicine
2. The toxicology of nanomaterials: Size, number and surface as determinants of toxicity
3. Preclinical characterization of nanomaterials intended for cancer diagnostics and therapeutics
4. From microscopy toward nanoscopy and nanobiosensing: How to break the diffraction barrier in subwavelength nanoscale
5. A history of clinical trials from post Harris Kefauver, 1962 , to present
6. The future of clinical trials – informatics
7. The future of clinical trials – clinical medicine
8. The future of clinical trials – industry
9. CPath Institute – Cross-validation of genomic biomarkers and the community pharmacy program for drug safety
10. Imaging as a Biomarker – FDG-PET in non-Hodgkin's lymphoma
11. Numerical models and tools – "The virtual family"
12. Utilization of FDA's ECG warehouse for monitoring cardiac safety in medical product development
13. Case study: Cordis cypher sirolimus-eluting stent
14. Case study: Boston scientific taxus paclitaxel-eluting stent
15. Regulatory challenges
16. Drug-eluting stents: Pharmaceutical challenges
17. Beyond drug-eluting stents: The next frontier in drug delivery
18. Drug safety in the Department of Veterans Affairs
19. Frontiers in surveillance of medical devices
20. Prompt, active identification of ADR signals using population-based data
21. Medications – adverse events, unanticipated benefits and what to do about them – the Indiana experience
22. Optical coherence tomography for detection of atherosclerotic plaque
23. High intensity focused ultrasound surgery and extracorporeal shock wave therapy
24. Recent advances in medical imaging
25. Image-guided surgery and drug therapy

diabetes, in whom coronary, lower extremity, and dialysis conduits are needed. A smaller group of patients in whom biological grafts might be used are those with abdominal aortic aneurysms (1.09 repairs per 1,000 Medicare enrollees[7]), where autologous biological graft might offer advantages over fabric for composite endografts in reducing endoleaks and inducing perigraft thrombosis and aneurysm shrinkage.

CONCLUSION

There is no shortage of engineering challenges in endovascular treatment of aneurysm and other vascular disease. Focusing specifically on treatment of aortic aneurysms, these include MEMS and related technologies for smart devices to monitor device integrity and complications, artificial vascular tissue as biofabrics for endografts or branch artery prostheses, and biocompatible coatings for stents, valves, and vascular access devices. However, in the excitement

of exploring these technical paths of research, the vascular community must keep in mind the sobering reminder from the FDA: IND applications are diminishing, and costs are expanding. Critical path research, as outlined above, while less glamorous than basic or translational research, may actually benefit more patients sooner.

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