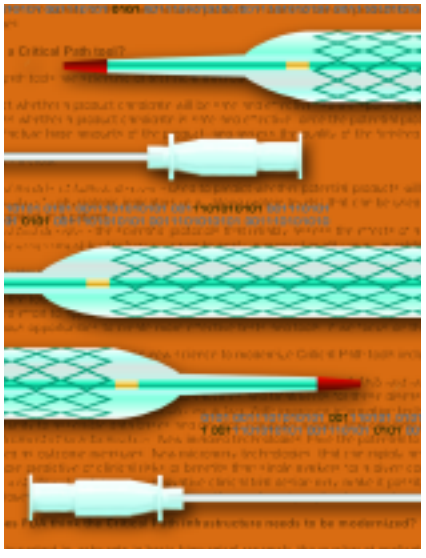

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Jules T. Mitchel, Vanessa Hays, Mary Shatzoff, and Glen Park

The Critical Path Initiative Meets Medical Devices

Interaction is high on FDA's list of ways to improve the development & review process for technologies.

The advancement of new technologies and their adoption by the clinical community poses a challenge to regulators. The regulatory community is charged with ensuring safety and effectiveness and comes under criticism when problems ensue. Likewise, if patient and physician access to an important new therapy is delayed, regulators are the object of criticism by a highly educated and increasingly sophisticated consumer.

In an effort to stay ahead of a new generation of technologies that range from genomics, cellular therapies, and combination products—where the divide between drugs, biologics, and devices is progressively growing smaller—the FDA has introduced the Critical Path Initiative (CPI).[1]

Moving forward

The CPI is an FDA modernization effort to identify and prioritize challenging product development issues, as well as to identify novel solutions. The CPI, which began in 2004, has identified "opportunities" for collaboration between the FDA, industry, academia, and patients. These issues are all covered on the FDA's Critical Path Web site (http://www.fda.gov/oc/initiatives/criticalpath/).

The primary goal of the CPI is to ensure that basic scientific discoveries move rapidly into new and better medical treatments, and that new tools and approaches are implemented to facilitate the evaluation of safety and effectiveness. Thus, the CPI is meant to provide practical means for continuous product development, so that as new scientific information is revealed, sponsors and FDA can consider it continually, allowing for a more rapid adoption of a new product or technology.

As is often the case with efforts to develop new or improved regulatory means of scientific discovery, the CPI is also defined by what it is not. For example, it is not meant to replace existing regula-

tory structure, but rather fine tune it and allow for more timely and precise scientific examination.

From discovery to market

With the number of submissions for novel compounds down since the mid-1990s (see Figure 1), it is time to look for novel ways to expedite safe drug, biologic, and device development.

The Critical Path is expected to promote early interaction between FDA and the device industry and advance product innovation.

Time and cost are key factors considered by FDA when reviewing and approving new products, and the CPI's job is to consider "least burdensome" requirements.

To accomplish the CPI's goals, FDA is planning to work closely with the pharmaceutical, biotechnology, and medical device industries, as well as with the medical and scientific communities.

The CPI is a future-looking program. In order for the CPI to be meaningful, product developers must have new tools to progress effectively along a multidimensional critical path that leads from discovery, or design concept, to commercialization. Three main areas in the FDA's critical path include:

- assessment of safety through multiple development stages
- demonstration of clinical utility (i.e., will the product benefit the specific people to whom the therapy is targeted)
- demonstration of industrialization (i.e., can the laboratory concept or prototype be produced commercially).

Table 1 provides a summary of the dimensions of the CPI.

CPI's impact on devices

Innovation for medical devices differs from pharmaceuticals. In contrast with drug development, the time from concept to market for a device can take as little as 18 months. In addition, unlike many pharmaceuticals, which are purely driven by clinical need, devices generally require the skill of the end-user. Therefore, the ultimate effectiveness of device innovations, such as a new spine implant, depends on continuous interaction between the industry and consumers.

In May 2006 the Center for Devices and Radiological Health (CDRH) announced[2] it was launching the Medical Device Innovation Initiative[3] to make new medical devices available more quickly for patients. The initiative will attempt to expand current efforts to promote scientific innovation in product development, focus device research on cutting-edge science, modernize the review of innovative devices, and facilitate a least burdensome approach to clinical trials. According to FDA, the initiative should promote early interaction between the agency and the device industry, and should optimize review times and foster innovation.

The CPI is meant to build on CDRH's strong commitment to basic science as well as the additional resources provided under the Medical Device User Fee and Modernization Act of 2002.[4] It is not meant to repackage old ideas in a new wrapping. The success of the program will depend on whether it has the commitment from FDA management and is able to provide useful regulatory solutions for the agency's scientific staff. Of course, a number of uncertainties remain.

Decline in Novel Compound Submissions

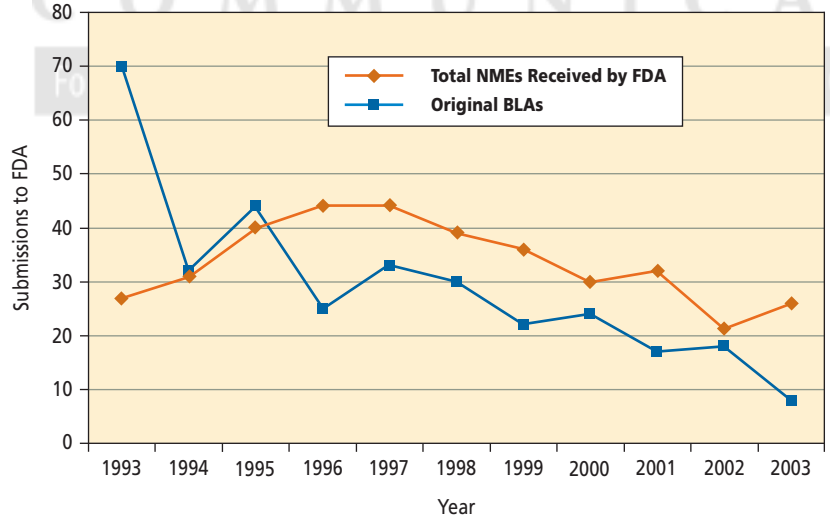

Figure 1. Ten-year trends in major drug and biological product submissions to FDA.

Product safety

Currently, safety issues may be detected during a clinical trial or after a product is on the market. With advances in technology, however, the current way of assessing safety may not be sufficient for cutting-edge medical devices such as drug-eluting stents and imaging devices used to detect cancer. The FDA's aim is to develop reliable methods that will identify significant safety problems early in the development process, ensure the safety of participants in clinical trials, and protect and facilitate the progress of new technologies.

The Critical Path Initiative: A Future-Looking Program

Dimension	Definition	Examples of Activities
Assessing Safety	Show that a product is adequately safe for each stage of development	■ **Preclinical:** Show that a product is safe enough for early human testing. Eliminate products with safety problems early. ■ **Clinical:** Show that a product is safe enough for commercial distribution.
Demonstrating Medical Utility	Show that the product benefits people	■ **Preclinical:** Select appropriate design (devices) or candidate (drugs) with high probability of effectiveness. ■ **Clinical:** Show effectiveness in people
Industrialization	Go from laboratory concept or prototype to a commercial product	■ Design a high-quality product • Physical design • Characterization • Specifications
		■ Develop mass production capacity • Manufacturing scale-up • Quality control

*Adapted from: Innovation Stagnation: Challenges and Opportunities on the Critical Path to New Medical Products. U.S. Department of Health and Human Services Food and Drug Administration, March 2004.[3]

Table 1: The three dimensions of the Critical Path Initiative: safety, medical utility, and industrialization.

Quality review program

FDA wants to expedite applications for sponsors so the research and development necessary for demonstrating safety and effectiveness is done as quickly and efficiently as possible, and the time it takes to review new treatments and diagnostics is reduced. The FDA has recently completed the first round of quality reviews in the areas of biocompatibility, sterilization, and statistical analysis—three areas for potential cost and time savings that are common to many medical device submissions. For example, establishing the safety of new materials for use in implants or in combination drug–device products is paramount to the efficient assessment of new technological characteristics of novel devices.

FDA's internal review process has identified areas for improvement in training reviewers and the need for up-to-date and clear guidance for industry. In the near future, FDA intends to expand the internal quality review program to additional scientific areas, including software validation. In addition, FDA has developed milestones for the review and evaluation of premarket submissions to ensure consistency, predictability, and accountability in the device review process.

Efforts to improve

Guidances. The FDA plans to develop guidance documents in key scientific areas that will provide additional regulatory clarity, including modifications for PMA (premarket approval) devices, PMA annual reports, real-time PMA supplements, innovative combination product submissions, in vitro diagnostic device submissions, and revision of the 510(k) Paradigm guidance document.[5] These guidance documents should increase the consistency and efficiency of the review process and give clear guidance for product development.

Knowledge enhancements. Since medical innovation is rapidly expanding, the FDA must review an increasing number of industry requests for guidance on developing new technologies. In an effort to manage these requests, the agency is working to enhance its infrastructure and resources.

Two initiatives the FDA has taken to manage industry expectations is to employ outside experts through the Medical Device Fellowship Program and increase its staff with additional experts. These experts will help enhance FDA's capabilities to remain knowledgeable about new technological and clinical advances and to meet the expectations for timely and predictable reviews of innovative technologies.

Another initiative that the FDA has taken is to use its own laboratories to perform research to support new medical device technologies. This initiative by the FDA may reduce industry resources necessary to demonstrate the safety and effectiveness of new technologies.

Outreach programs. Since effective and on-going communication between FDA, industry, patients, and clinicians is essential for fostering medical device innovation and ensuring transparency, CDRH is looking for opportunities to improve interactions during product development and premarket review and to improve its tools for communicating medical information to consumers and practitioners.

Based on the input it receives from these communities, CDRH will undertake an assessment to improve the manner in which it communicates critical public health information and recalls. This effort is aimed at making sure that regula-

tory actions are accompanied by the most complete and appropriate information so that individualized treatment decisions can be made about the medical products. As part of this effort, CDRH is updating its device recall procedures to make sure that regulatory actions are communicated in a way that is consistent with good medical practice.

The Critical Path. FDA is planning to help sponsors develop medical devices in the areas of unmet clinical needs, including pediatrics. For example, the FDA plans to guide the development of new models to assess the safety and effectiveness of new stent designs, innovative toxicology animal models on injured tissues, new efficacy and safety statistical models for implanted cardiac stents, and biomarkers and diagnostics and their application to pharmacogenomics.

Information technology

The FDA is working to leverage information technology (IT) and develop better systems to protect consumers and assure the safe and effective use of new medical devices. With the use of new Web-based registries and postmarketing surveillance tools, it should be easier to learn about new devices postlaunch and provide up-to-date information about how to derive the most benefit from medical products.

The FDA is also developing new IT systems that allow for better monitoring and tracking of regulatory submissions. It is piloting the use of Web-based software for PMA review, which makes real-time information sharing and communication among review team members possible, and creates a central location for document storage and retrieval. In addition, FDA is encouraging manufacturers to file electronic submissions, and provides information on its Web site about it.[6]

FDA will employ new Web-based systems to make the review process for devices more efficient.

A new free software tool, CeSub eSubmitter (CDRH electronic Submissions), evolved as a result of two very successful pilot programs: eLaser and Turbo 510(k).[6] CeSub eSubmitter allows sponsors to electronically:

- complete and submit 510(k) premarket notification applications to the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)
- submit information for a variety of radiation safety Product Reports and Annual Reports for radiation emitting products to the Radiological Health Program.

The agency is continuing to evaluate new electronic databases to facilitate the application process.

Discussion & conclusion

In the very near future, innovations in medical technology will fundamentally transform health care and delivery systems, providing new solutions that will challenge existing paradigms and revolutionize the way treatments are administered. The FDA has clearly indicated a desire to be a partner in the development of these new and emerging technologies.

As these technologies advance, the critical paths from concept to market present greater challenges for both innovative device manufacturers and the FDA. Since current review methods for assessing the safety and effectiveness of these products may not be sufficient, development and review processes must change. The evolving CPI program is a means for the agency to better use its resources to bring efficiency to the review process for emerging technologies, and close the developing gap between the practice of medicine and the practice of regulation.

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Jules T. Mitchel,* *MBA, PhD, is president of Target Health Inc., 261 Madison Avenue, 24th Floor, New York, NY 10016, email: Julesmitchel@targethealth.com.* **Vanessa Hays**, *BS, JD, is manager, regulatory affairs,* **Mary Shatzoff**, *MS, is senior manager, regulatory affairs, RAC, and* **Glen Park**, *PharmD, is senior director, clinical and regulatory affairs, with Target Health Inc.*

**To whom all correspondence should be addressed.*