The Center for Devices and Radiological Health’s Medical Device Innovation Initiative

May 2006

Over the next decade, medical technology innovations will fundamentally transform the health care and delivery systems, providing new solutions with medical devices that will challenge existing paradigms and revolutionize the way treatments are administered. Already medical innovations that would have been considered the stuff of science fiction just a few years ago are quickly becoming the standard of care. Such advances that the Food and Drug Administration (FDA) has recently approved include drug-eluting stents designed to slowly release a drug to significantly reduce the rate of re-blockage of metal stents inserted into the coronary blood vessels to maintain blood flow to the heart and imaging devices that utilize Computer Aided Detection software to assist radiologists in the detection of cancers.

With the convergence of many scientific and technology breakthroughs, the pace of medical invention is accelerating, inspiring hope for better clinical outcomes with less invasive procedures and shorter recovery times, all in lower cost settings. There are powerful forces at work that are driving rapid fundamental change in healthcare delivery.

New innovations and developments suggest an unfolding pattern of “smart” technologies that integrate engineering and biological approaches, and that enable increasingly precise clinical interventions as well as a progressively decentralized health care delivery system. The FDA is already seeing a steady increase in the number of requests from developers for pre-submission meetings to seek advice on the best approaches for scientific and clinical testing and evaluation of cutting-edge technologies, such as molecular medicines (genetic and proteomic diagnostics and therapeutics) and products developed using nanotechnology.

As these technologies advance, the critical path from promising new science and lab discoveries to applications that treat patients may present greater challenges for both innovative device manufacturers and for the FDA, because the current paradigms for assessing the safety and effectiveness of these products may not be optimal for timely, efficient, and effective product development and premarket review. Similarly, the ability to develop reliable information to more effectively guide clinical practice and inform medical decisions must keep pace with the rapidly increasing complexity of the underlying products.

The FDA’s mission is to protect and promote public health. A critical aspect of this role is to facilitate the public’s timely access to safe and effective innovative medical devices. To continue to meet this objective in the future, we will need to develop better ways to predict earlier in the process which new products are likely to be safe and effective in patients and how to best deploy new technologies to maximize benefits and minimize harm. In particular, we need to ensure that clinical trials, product reviews and approvals, and manufacturing processes are conducted in the most efficient and effective ways. Failure to take appropriate steps now may stifle future innovation and delay patient and practitioner access to important safe and effective devices.

To avoid this outcome, the FDA plans to take proactive steps through an initiative aimed at facilitating technology development: The need to find new ways to move cutting-edge discoveries from the lab bench
into clinical trials; to modernize the clinical trials process so safety and effectiveness can be assessed at the lowest cost, while still protecting human subjects; and to apply the most advanced manufacturing methods from other industries (e.g., semiconductors) to commercialization and use of medical devices, advances that have not been as widely adopted in the medical device industry as in other areas. Much of the foundation for this work has already been laid through additional resources for the device review process provided under the Medical Device User Fee and Modernization Act of 2002 (MDUFMA).

These issues will become more important in the future as industry develops more complex devices and more combination drug/device products, and FDA reviews premarket submissions for these technologies.

Innovation for medical devices differs from innovation for pharmaceuticals. Device innovation includes both giant leaps and incremental changes with life cycles as short as 18 months. Unlike many pharmaceuticals, the effectiveness of such improvements depend on a continuing dialogue between product developers and the ultimate end-users about what works, what doesn't, and what the best solution to problems might look like, because devices generally require the skill of the end-user.

Post-market systems that enable constant learning and feedback not only spur continued innovation but help support best medical practices to ensure safe use of devices with maximum effectiveness. Therefore, opportunities exist to enhance medical device innovation at every phase of the total product life cycle.

To meet these challenges of today and the future, the Center for Devices and Radiological Health (CDRH) is taking new steps to expand its current efforts to foster the development of safe and effective medical devices through a variety of initiatives and regulatory process improvements. Below, we describe the specific actions the FDA’s CDRH plans to take under the Medical Device Innovation Initiative. Following the discussion, we provide a table showing the impact these actions will have on the predictability, timeliness, consistency, transparency and efficiency of the device development and application review process while also helping to reduce regulatory burden. This initiative includes the following efforts:

- Promoting scientific innovation in product development;
- Focusing device research on cutting edge science; and
- Modernizing review of innovative devices.

PROMOTING SCIENTIFIC INNOVATION IN PRODUCT DEVELOPMENT

Provide Regulatory Clarity Through Guidance Development

Guidances can shrink development times and provide clear pathways for novel technologies. In FY06, CDRH has implemented a new process for prioritization of guidance document development to ensure that the Center focuses its efforts on guidances that foster innovation and that promote and protect the public health. By describing regulatory requirements and review procedures in guidance documents, CDRH believes it can increase the consistency and transparency of its review process and provide a clearer pathway for innovators.

These “high priority” guidance documents will be the focus of intense effort by CDRH staff, with the goal of having these draft guidances issued in FY06.

Some of these guidance documents relate to specific innovative medical products. FDA’s own research has found that in areas of medical technology where guidance documents are available to product

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developers, the products often follow smoother development pathways and encounter fewer regulatory hurdles, often owing to more complete submissions.

To address these opportunities, in FY06 FDA intends to release guidance documents for innovative products, such as drug eluting stents, combination device/biologic products for cartilage repair, and genetic and pharmacogenomic tests. The scientific recommendations contained in these documents will not only help guide developers of these specific products but will also serve as a template for other similar combination products currently in the pipeline.

To help expedite and facilitate the development of new technology, FDA intends to release an intercenter guidance document on innovative combination products. This guidance will outline scientific, clinical and technical issues that should be considered early in the development process. We believe the guidance will aid developers by explaining how to leverage existing information on drug, device or biological constituents and by ensuring that development tests are focused on the critical safety and effectiveness issues raised by the combination product.

In the area of in vitro diagnostic devices, FDA intends to release several documents that will provide regulatory clarity as well as more flexibility for product developers. For example, CDRH will develop a guidance document that clarifies the regulatory requirements for analyte specific reagents.

Invest in the Critical Path

In collaboration with outside groups, CDRH is facilitating the availability of innovative medical devices by modernizing the science for developing and evaluating new medical devices, particularly for areas of unmet clinical needs, such as pediatrics, including:

- Guiding the development of anatomically and physiologically-accurate adult and pediatric virtual circulatory systems that can quantify the load and stress forces that cardiovascular and peripheral vascular stent devices can withstand. These models will help assess the safety and effectiveness of new stent designs prior to fabrication, physical testing, animal testing and human trials.

- Developing clinically relevant animal models to improve prediction of toxic effects of medical products on injured tissues in critically ill patients.

- Working with industry and the clinical community to develop a new statistical model for predicting the effectiveness of implanted cardiac stents to measure and improve the long-term safety of these products.

- Evaluating the development of biomarkers and diagnostics and their application to pharmacogenomics (PGx). CDRH and its partners will identify and summarize the issues related to innovation in the development of biomarkers and diagnostics and the perspectives of relevant stakeholders on these issues. The project will help to identify barriers to biomarker development.

- In collaboration with the National Institutes of Health’s National Institute of Child Health and Human Development, CDRH will hold a public workshop to identify new approaches to evaluating new fetal intrapartum monitoring devices,
including the possible development of a large validated test database. This workshop will facilitate the development of a new paradigm for evaluating fetal monitoring devices to stimulate innovation in this field.

- In collaboration with the Juvenile Diabetes Research Foundation, CDRH will work to accelerate development of an artificial pancreas for children (and adults) with diabetes by creating new clinical protocols (based in part on reassessing clinical outcomes from prior research) and improved outcome measures for evaluating the performance of continuous glucose sensors and a closed loop artificial pancreas. This work would also revolutionize diabetes care and management.

- Designing a prospective clinical trial to develop data that will identify better efficacy endpoints for clinical studies evaluating accommodating intraocular lenses. Clinically relevant objective measures will reduce the requirements for subjective testing and will result in more meaningful study findings in less time.

Conduct Stakeholder Outreach and Improving Communications

Effective and on-going communication between FDA, industry, patients and clinicians is essential for fostering medical device innovation and ensuring transparency. CDRH is stepping up its efforts to expand these kinds of interactions, as well as looking for opportunities to increase interactions during product development and premarket review and improve its tools for communicating medical information to consumers and healthcare providers. For example:

- In November 2005, CDRH held a public advisory panel meeting to discuss optimal clinical trial designs for, and ethical issues related to, the evaluation of devices intended to treat pediatric obesity. The recommendations and deliberations of this advisory panel will be used in the development of guidance that will clarify appropriate clinical trial designs for products intended to treat pediatric obesity.

- In January 2006, CDRH conducted a workshop on mechanical circulatory support devices (ventricular assist devices) used in pediatric patients in need of temporary cardiac support. The workshop participants discussed pre-clinical engineering, clinical and regulatory challenges posed by these devices.

Based on the input it receives from these and other interactions with stakeholders, CDRH is undertaking an assessment and improvements upon the manner in which it communicates critical public health information, including public health notifications, and recalls. This effort is aimed at making sure that regulatory actions are accompanied by the most complete and appropriate information for helping patients and providers put actions into medical context and make effective, individualized decisions about the medical products they use.

As one part of this effort, the agency will undertake updating its device recall procedures, to make sure that regulatory actions taken by the agency are communicated in a way that is consistent with good medical decision making.

FOCUSING DEVICE RESEARCH ON CUTTING EDGE SCIENCE
Laboratory Research to Support Efforts to Improve the Device Development Process

CDRH is focusing its laboratory expertise and resources to address challenging scientific issues that arise in considering new medical device technologies. The findings of our research will help inform our regulatory decision-making and, ultimately, help to expedite the availability of products with innovative breakthrough technology.

- For example, CDRH laboratory expertise in experimental and computational fluid dynamics was recently utilized to aid in the evaluation of a post-approval study change for a pediatric left ventricular assist device. The sponsor proposed to make a change to the blood flow path within the pump that could have adversely affected hemolysis and thrombogenesis in the pump such that patient safety and/or device efficacy could have been compromised. It would have been extremely difficult, if not impossible, to validate the design changes using animal or human data. After discussions and a meeting with FDA staff, the sponsor agreed to provide experimental (flow visualization, hemolysis) and analytical (computational fluid dynamics [CFD]) testing to support the design changes. CDRH experts recommended appropriate CFD models to the sponsor and analyzed the results. In this instance, our efforts eliminated the need for the sponsor to perform expensive and time-consuming animal testing and/or clinical testing. The proposed design changes were approved, thus expediting the availability of this innovative device.

- CDRH scientists have played a leading role in the development of new models and methods for the assessment of computer-assisted diagnostic systems. The techniques were first developed during our review of digital mammography systems, and have since been extended to the development of systems for breast cancer screening, lung cancer screening, and CT colonoscopy. CDRH scientists who have developed these methods have played an important role on the review team for applications for these devices. Having these tools and methods available has greatly assisted developers of these innovative imaging and CAD-assist devices.

These and similar actions by our laboratory staff can help reduce the cost and time required to demonstrate the safety and effectiveness of new innovative technologies thereby fostering their development and speeding patient access to these products.

MODERNIZING REVIEW OF INNOVATIVE DEVICES

Implement a Quality Review Program

We have instituted an on-going quality review program for premarket submissions that evaluates the quality of our scientific review in several key scientific areas. The idea is to build on our professional staff expertise to identify and apply best management practices internally to our review processes. CDRH wants to make sure we are doing all we can not only to continue to reduce the time it takes to review new treatments and diagnostics, but also to help product developers get their applications right the first time – to do the R&D work that demonstrates safety and effectiveness as quickly and efficiently as possible.
We have recently completed our first round of quality reviews in the areas of biocompatibility, sterilization and statistical analysis, three cross-cutting areas 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 efficiently assessing the new technological characteristics of these future innovations. This internal review process has pinpointed areas for improvement in the training of our reviewers and the need to develop up-to-date and clear guidance for industry. In the near future, we intend to expand the internal quality review program to additional scientific areas, including software validation.

In addition, we have developed milestones for the review of premarket submissions as well as improved the management and oversight of premarket review to ensure predictability and accountability in the device review process. We believe that continuing and expanding this effort will allow us to improve the quality and efficiency of our reviews, thus ensuring that we consistently ask developers the right questions at the right times and that the right resources are used in the right way to enhance the timeliness and predictability of device review.

Provide Clarity Through Guidance Development

Whereas some guidances, as discussed above, pertain to specific devices, others are cross-cutting or process-oriented, which should facilitate and improve the consistency of the review process.

We plan to develop cross-cutting guidance documents in key scientific areas, such as Bayesian statistical analysis methods for clinical trials. The use of Bayesian statistics for clinical trial design and analysis allows developers to utilize existing information in an efficient and scientifically rigorous manner.

We also intend to release several cross-cutting guidance documents that will greatly aid the process for device development by providing additional regulatory clarity. These include guidance documents for modifications to PMA devices, PMA Annual Reports, Real-time PMA supplements, and a revision of the 510(k) Paradigm guidance document.

In addition, FDA issued a guidance document that addresses the requirements for informed consent for IVD studies that utilize de-identified leftover human specimens. FDA believes that this guidance should reduce the clinical research development time and cost of clinical studies for IVDs, thus expediting the development of innovative diagnostic tests.

Leverage Information Technology Solutions

Now that modern information technology (IT) and information management (IM) have had a fundamental impact on so many parts of our lives, we must leverage that technology to develop a fundamentally better system for helping to protect consumers and assure the safe and effective use of new medical devices. With the aid of modern IT, we can have a much more effective system for easily and quickly spotting potential adverse events and for providing appropriate warnings to doctors and patients. As a result, we should be able to more easily continue learning more about new devices after they’re approved, and continue to provide people with up-to-date information about how to derive the most benefit from the medical products they use.

To these ends, CDRH is undertaking a number of initiatives that leverage the use of IT to improve patient safety and make the development process more efficient. We are developing new IT systems that allow for better monitoring and tracking of premarket submissions and for improved communication and coordination among review members. For example, CDRH has developed a Center-level tracking system...
that helps monitor and manage workload and helps ensure that appropriate scientific expertise is used to review each document.

We are also piloting the use of a web-based software program for our review of PMAs that allows for real-time information sharing and communication among review team members and a central location for document storage and retrieval.

We are encouraging manufacturers to provide electronic copies of premarket submissions and have recently posted information on our web site to guide submitters in preparing these electronic copies. Having electronic copies available will save CDRH resources and will provide review staff with improved search and navigational tools for these documents.

In the area of IVDs, we have developed a software system that allows sponsors to electronically complete and submit premarket notifications [510(k)s]. This electronic submission process will reduce the time and resources expended by industry in preparing 510(k) submissions and will allow for an efficient and timely review.

CDRH is also exploring the future development of integrated, searchable electronic databases that will allow reviewers to identify and use information from applications previously sent to the agency more quickly and efficiently rather than searching through paper records.

Expand Clinical and Scientific Expertise at FDA

With the additional resources from MDUFMA, we are expanding our use of outside experts, through our Medical Device Fellowship Program (MDFP), to help us stay current with the latest technological and clinical advances. For example, over the past several years, we have hired experts in many critical areas, including: Anesthesiology, Brachytherapy, Cardiothoracic Surgery, Electrophysiology, Human Factors Engineering, Neurosurgery, Nephrology, Pediatric Cardiology, Pulmonology, Radiation Oncology and Software Engineering. We believe that utilizing these experts has and will help us expedite the availability of new, cutting edge technology.

• For example, the review team for a first-of-a-kind neuro-interventional device for retrieval of clots in patients suffering from ischemic stroke included a neurosurgeon MDFP fellow. His clinical expertise was invaluable in reviewing and analyzing the results of the clinical study. His recommendations were critical to our decision to approve this device, the first device for retrieval of clots in the neurovasculature.

• In addition, an MDFP fellow who is an expert cardiologist was a key member of the review team for the PMA for the first left ventricular assist device (LVAD) as a permanent implant. The PMA was submitted to demonstrate the safety and effectiveness of an LVAD as a long-term treatment for severe heart failure in patients who are not candidates for heart transplants. The MDFP fellow played a pivotal role in evaluating the clinical safety and effectiveness data and making a determination that the device should be approved for this indication, thus making it accessible to more patients who need it.

As resources permit, we will increase our use of outside experts through the MDFP. With MDUFMA resources CDRH also has hired additional medical specialists, engineers, software experts, and statisticians who are contributing to more timely and predictable reviews of innovative technologies.
### Medical Device Innovation Initiative - Impact on Device Development and Application Review Processes

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