

Driving Biomedical Innovation: Initiatives to Improve Products for Patients

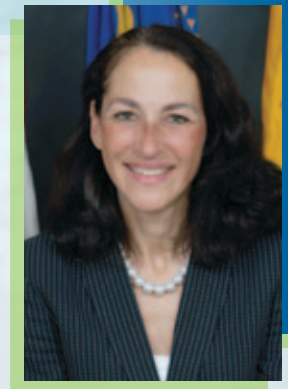


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION

Driving Biomedical Innovation

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When I became Commissioner a little over two years ago, I was struck by the magnitude of the challenge before me. FDA is responsible for ensuring the safety, efficacy, and security of drugs, vaccines and other biological products, medical devices, and certain products that emit radiation, as well as oversight of the safety of our nation's food supply, cosmetics, dietary supplements, animal drugs and feed, and the regulation of tobacco products. In other words, our agency is entrusted with promoting and protecting the health and well-being of anyone who eats, takes an over-the-counter painkiller or prescription drugs, uses a medical device, or has an x-ray. In fact, FDA-regulated products account for approximately 25 cents of every consumer dollar spent in the U.S.



But we also have another important role: promoting the science and innovation it takes to ensure that the nation is fully equipped to address the health challenges we face today and will see in the future. Of course, innovation is not just about new ideas, but about making sure those new ideas truly translate into the products and opportunities people need and count on.

Today we are at a critical moment for innovation. Despite the struggling U.S. economy, American pharmaceutical, biotech, and medical device companies have maintained a competitive advantage in the global marketplace and continue to represent three of the few U.S. manufacturing sectors that maintain a positive trade balance. But there are some signs that the health of these industries may be at increasing risk, jeopardizing a critical piece of our economy and, more importantly, obstructing patients' access to new therapies. Today's medical product pipeline, despite a number of groundbreaking new drugs approved this year, does not have enough new products to sustain the health of the industry in the long-term or address many of the chronic diseases afflicting Americans every day.

While FDA has a strong record of performance, I believe we must redouble our efforts and take proactive steps to be even better. So I've spent countless hours meeting with—and listening to—the various stakeholders in the medical product development ecosystem. We've discussed the challenges ahead for everyone involved, as well as what does and doesn't work in the current FDA regulatory framework. During the course of our internal reviews and discussions with stakeholders, several common themes emerged. In response, we have put together this initiative to outline some important steps we can take to address these issues and drive innovation forward.

Building on existing efforts, such as the groundbreaking Critical Path program introduced in 2004 and the Advancing Regulatory Science Strategic Plan published in August, this agenda focuses on implementing and institutionalizing new programs and reforms within FDA to address the most immediate concerns we've been hearing from stakeholders. It covers everything from streamlining and reforming FDA regulations to creating a new expedited drug development pathway.

This document lays out a brief assessment of the medical product landscape and its current state. The document also outlines how FDA is working to position itself not only as a positive driving force in the ecosystem as a regulator, but also to facilitate medical product innovation. It is important to note that while these are important first steps to address the immediate concerns before us, this is an ongoing initiative at the agency and will be expanded beyond the reforms outlined in this document.

It is clear that our nation is at an important crossroads, where the science before us presents unprecedented opportunities to create new and better medical products and promote better health for the public. But we must act now and work together to capitalize on this groundbreaking science in order to bring safer and more effective treatments to American families and keep our position as the global leader in scientific innovation. I truly believe FDA's innovation initiative will help move us toward this important goal.

A handwritten signature in black ink that reads "Margaret A. Hamburg". The signature is fluid and cursive.

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

Overview



Because of its role as both a regulator and as a public health agency facilitating the development of new, innovative products to meet the needs of patients and the American public, FDA has a unique perspective on the health of the biomedical industries that make up an important sector of the U.S. economy.



Today, advances in science are leading toward a fundamental change in the way medical treatments will be developed and used. Groundbreaking discoveries in complex chemistry and biosynthesis have resulted in promising new approaches for the development of drug candidates, advances in cellular and molecular biologies are creating novel strategies for new biologic therapies such as stem cell-driven products, and cutting-edge electronics, nanotechnology, and advances in materials sciences have revolutionized medical devices. As a result, incredible opportunities await both American companies and patients.

This year, FDA has approved a number of truly novel breakthroughs based on sound science to address critical health needs. These

include several groundbreaking new therapies for devastating diseases, such as the first new treatment for Lupus in fifty years, two new therapies for Hepatitis C, and the first drug ever shown to be effective at treating melanoma.

However, while we have seen an increase in the quality of new drug submissions, there is a concern about a decrease in quantity. The past two decades have been marked by steadily increasing investments in basic research and development, with more than \$95 billion in combined R&D by industry and the National Institutes of Health (NIH) in 2010 alone. And yet, these investments have not translated into a parallel increase in novel products submitted to the Agency for approval. For example, last year the Agency

received the lowest number of applications for novel drugs in nearly two decades.

Additionally, drug companies continue to face increasing development costs, and a number of patents for blockbuster drugs are about to expire, leading to a projected loss of \$114 billion in revenue over the next three years with fewer new products coming down the pipeline to cover the loss of revenue.

Medical device companies are also experiencing their share of challenges. Venture capital for small startup companies has decreased in the recession, and what

investments are being made tend to come at a much later stage of development—leaving many companies and small businesses with limited resources to translate great ideas from workbench to marketplace.

There is no single cause or party responsible for this stagnation in the development of novel medical products. Rather, it reflects a number of factors affecting multiple stages of the development process, such as an uncertain and challenging economic and global marketplace, increasingly complex science and products, and the imperative to ensure the safety and efficacy of innovative medical products.



Medical Product Development Ecosystem

Translating a new idea from a discovery into a medical product is a complex process involving an entire ecosystem consisting of academia, industry, small businesses, payors, physicians, government agencies, and patient and consumer groups. Each member of the ecosystem has an important role to play in bringing a new medical product to market, and each piece of the ecosystem is currently under stress, putting America at risk of losing its competitive edge as the leader in scientific innovation.

It is possible for the U.S. to overcome the challenges ahead, but only by addressing each of the underlying problems. Just as there is no single factor responsible, there is no single solution. Innovation in medical product development transcends a single new drug or a single new device. There is a continuum of concerns that impact the environment for medical product innovation, including intellectual property and patent policies, economic policies, biomedical research and medical technology investments, regulatory reform, and reimbursement policies.

This is a holistic process that involves many different pieces and players. As such, we must all take a comprehensive, integrated approach toward a solution, involving the entire range of relevant players and approaching the ecosystem as a whole. There must be a dialogue among the various stakeholders to identify barriers to progress

and better define what steps need to be taken to overcome these obstacles. By doing this, we can work together toward solutions that truly drive scientific innovation forward. As a nation, we have a unique opportunity to come together to develop an overarching strategy to spur medical product innovation.

FDA has an important role to play in shaping the future of medical breakthroughs by bringing stakeholders together to identify and overcome challenges.



FDA as a Driver of Innovation for Public Health

FDA has an important role to play in shaping the future of medical breakthroughs by bringing stakeholders together to identify and overcome the challenges of product development and assessment. Within FDA, innovation can also be promoted by implementing reforms that adapt to the changing scientific and technological landscape to avoid an unnecessary delay of promising, safe, and effective new treatments for patients.

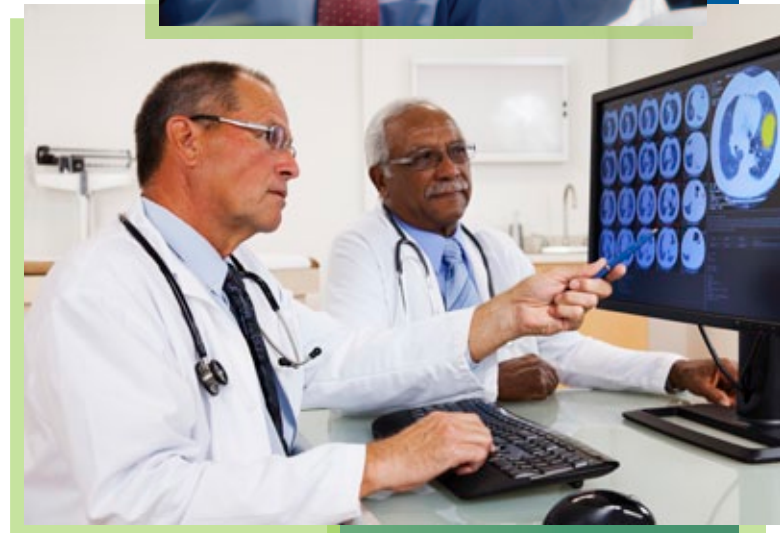
Recognizing the need for action, Commissioner Margaret Hamburg, M.D., set out to develop an FDA Innovation Initiative to place a renewed emphasis on the Agency's role as a driving force behind scientific innovation in America. This

initiative is focused on identifying areas for reform within FDA that will translate to the medical product ecosystem at large.

Understanding that smart reform cannot happen without input from key players, FDA reached out to major stakeholders—the small businesses that serve as the backbone of the medical device and biotech communities, the large corporations developing the next breakthrough drugs to treat disease, the academic researchers whose work leads to new scientific discoveries, and the patients who are directly impacted by the benefits and risks associated with new medical treatments and therapies.

During the course of months of discussions with these groups to identify key areas for improvement, as well as internal analyses of current FDA processes, several common themes emerged. These include:

- The need to do more to inform, engage, and help small businesses navigate the FDA regulatory process.
- The need to adapt current FDA policies and procedures to address the scientific realities and opportunities presented by personalized medicine.
- The need to take advantage of cutting edge information technology and scientific computing to enhance benefits to patients and the American public.
- The need to address regulatory uncertainty within FDA.
- The need to streamline FDA policies and procedures whenever possible.
- The need to develop more efficient regulatory pathways to support devices and diagnostics, including highly innovative devices.
- The need to build regulatory science capacity both within FDA and the broader medical development community.



During the course of months of discussions with stakeholders to identify key areas for improvement, as well as internal analyses of current FDA processes, several common themes emerged.



In response to these themes and recommendations, the Commissioner identified the following major reforms to address the most immediate concerns in each of these areas:

- Rebuilding FDA's small business outreach services.
- Building the infrastructure to drive and support personalized medicine.
- Creating a rapid drug development pathway for targeted therapies.
- Harnessing the potential of data mining and information sharing, while maintaining strong privacy protections.
- Increasing consistency and transparency in the medical device review process.
- Training the next generation of innovators.
- Streamlining and reforming FDA regulations.

As the agency responsible for the approval and regulation of medical products, FDA plays a critical role in American companies' ability to perform and compete in the global marketplace and deliver better products to patients more efficiently. We recognize the importance of maintaining America's presence as a global leader, and we are committed to modernizing our science and regulatory paths to promote innovation. The following blueprint outlines strategies to help reposition the U.S. medical product industry to adapt to the changing scientific landscape and drive innovation forward to provide Americans with cutting edge treatments and therapies that are safe and effective while simultaneously supporting economic growth and development in a critical sector of the economy. [FDA](#)

Rebuilding FDA's Small Business Outreach Services



As noted in President Obama's Strategy for American Innovation, the private sector is the engine of innovation, and much of this innovation begins with small business. This is particularly true within the medical device industry, where small businesses play a crucial role, accounting for more than half of all pipeline products. In the recent history of the biomedical industry, small businesses have built much of the foundation of innovative FDA-approved medical products, including drugs, devices, biologics, and diagnostics, such as the first cell-based therapy for cancer, a mobile cardiac monitoring system, and a rapid screening diagnostic for detecting hyperthyroidism. Many relatively young startup companies are now major players in the pharmaceutical industry.

The private sector is the engine of innovation, and much of this innovation begins with small business.



Small biomedical companies have a unique set of needs compared to their larger counterparts. By nature of their size, small businesses are faced with the challenge of raising capital to bring an idea to fruition. Additionally, most small companies lack the regulatory experience to navigate the complexities of the FDA approval process. A recent survey of 123 companies that utilized the resources provided by the Center for Drug Evaluation and Research (CDER) small

business office found that a majority sought help to navigate all phases of the approval process and to obtain FDA insight into clinical trial design and implementation. Other common topics of interest included how to obtain user fee waivers and how to increase access to FDA consultation and advice. Of the companies surveyed, 85 percent had never before received an FDA approval, and nearly half had fewer than ten employees.

STARTUP AMERICA

Startup America is a White House and interagency initiative to celebrate, inspire, and accelerate high-growth entrepreneurship throughout the nation. President Obama has called upon agencies across the federal government to dramatically increase the success of entrepreneurs by unlocking access to capital, cutting red tape, and accelerating innovation. Many of these policy initiatives will directly benefit biomedical startups, including new funding and mentorship for teams of entrepreneurial scientists, more control over the speed of patent processing, and new funding to bring research from the lab to the marketplace. As part of the program, the Administration hosted roundtable events across the nation and met with more than 1,000 entrepreneurs, investors, and other participants in the entrepreneurial ecosystem. Senior Administration officials, including Commissioner Hamburg, hosted each roundtable, listening to local entrepreneurs explain the barriers they face while starting and growing businesses and offering potential solutions. For more information, visit www.whitehouse.gov/startupamerica.

Many of the challenges faced by the small business community are being broadly addressed through President Obama's Startup America initiative. FDA, which has been working with the administration on Startup America, is addressing the specific needs of small medical product companies through efforts to make the review process easier and more transparent, as well as by providing information that can help businesses prepare for the final phases leading to product approval and marketing.

FDA already has several existing resources to help small businesses succeed, most of which are focused on helping them understand regulatory review requirements, assisting them with finding information regarding FDA law, and pointing them to resources such as guidance documents. Each of the medical product centers

at FDA has an office—such as the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) in the Center for Devices and Radiological Health (CDRH)—dedicated to helping small businesses navigate the Agency and its regulatory approval process.

In addition to addressing the specific questions raised by individual companies—the small business office in CDER alone maintains a listserv of 48,000 companies and fields thousands of inquiries per year—the small business offices also handle common questions through proactive measures, such as monthly webinars and appearances at medical conferences. They are also in the process of developing a small business blog for the FDA website to help increase and enhance engagement with the small business community.

Despite the currently available FDA small business resources, however, many small businesses continue to file applications or materials that do not meet FDA's written and posted requirements, and many are still not prepared for the process of bringing a product to market. Many companies do not seem to take advantage of the small business resources provided by FDA, which may in part be because these efforts are not successfully reaching the intended audience. There is also a perception among some that while FDA staff understand the regulatory process, they do not have a full appreciation of everything a small business must go through to reach the point of submitting an application. The absence of this business

background creates a potential barrier to reaching and assisting small businesses.

After an internal examination of the small business resources at FDA, as well as discussions with small business owners, it became clear that the FDA small business offices—and FDA more broadly—need to enhance their knowledge of what it takes to start and run a small biomedical business, and to ensure that individuals with small business experience can serve as an FDA resource to others. To address these issues FDA will establish a Small Business Liaison program and a Young Entrepreneurs program, and will set up a partnership with the Small Business Administration.



The FDA small business offices need to enhance their knowledge of what it takes to start and run a small biomedical business.

FDA Small Business Liaison Program

FDA plans to establish a Small Business Liaison (SBL) program to assist its small business offices. SBLs will be business people with experience in starting and running biomedical companies, obtaining venture capital funding, and successfully navigating the FDA regulatory process to bring a medical product to market. SBLs will be responsible for establishing and coordinating more effective interactions between the FDA small business offices and domestic and international small medical businesses.

Additionally, SBLs will train FDA staff on how to engage and network with small businesses more effectively, and will provide staff with a

better understanding of the challenges faced by small businesses. This training will help FDA staff better understand the inherent difficulties in running a small business, which will in turn better equip them to hold effective discussions to help small businesses with limited capital make better-informed decisions about their ability to move through the FDA review process given their current resources and potential to raise more capital. In addition, informational seminars and outreach via the SBL program can provide valuable advice for companies at the early stages of product development and help guide their product development planning.



Young Entrepreneurs

Another element of the enhanced small business program at FDA will involve training young entrepreneurs. FDA will offer fellowships for business, engineering, and science students, or other students who may become entrepreneurs, as part of their educational curriculum. The Agency will work with university business schools to establish a four- to six-month internship or training

course within the FDA small business offices to provide future entrepreneurs, venture capitalists, and inventors with first-hand access to information about regulatory review and what it takes to move a product through the FDA approval process. This knowledge base will enhance their effectiveness as future business partners, founders of companies, or investors.

Partnering with the Small Business Administration

FDA is currently engaged in setting up a partnership with the Small Business Administration (SBA) to find innovative, strategic ways to strengthen and support the diverse needs of small businesses. This partnership will be key in assisting small companies to grow and compete in global markets by providing training, counseling, and access to both SBA and FDA resources.

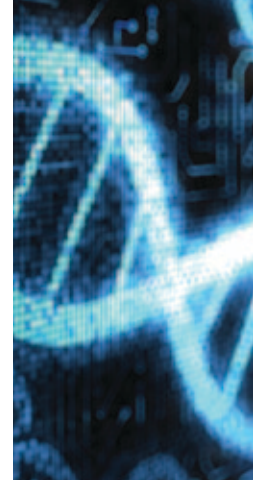
As part of this partnership, we are exploring the feasibility a full range of creative programs, such as an exchange program for SBA and FDA employees. This program would provide cross-educational training to offer SBA staff a better understanding of FDA requirements, and to provide FDA staff with insight into the unique needs of small companies. [FDA](#)

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DRIVING INNOVATION WITHIN FDA

As a science-based agency, FDA employs thousands of the best and brightest in the science, engineering, and medical fields, creating a fertile ground for ideas for new inventions. Federal agencies are allowed to patent inventions made by federal employees for licensure to industry through the Bayh-Dole Act (P.L. 96-517) and the technology transfer activities under the Technology Innovation Act (P.L. 96-480) and related legislation. To enhance these activities, FDA revitalized support for technology transfer by recruiting intellectual property specialists and raising the profile of the program through internal education and relocation of the effort to the Office of the Commissioner. Since these changes, several FDA inventions have been licensed to small businesses and are currently being developed. For instance, the National Center for Toxicological Research recently filed a utility patent application for a variation of an MRI that can distinguish normal brain tissue and eight different brain pathologies to a 95 percent accuracy level, potentially reducing the need for invasive brain biopsies.

Building the Infrastructure to Drive and Support Personalized Medicine



Recent biomedical research breakthroughs, including the sequencing of the human genome and a deeper understanding of the molecular underpinnings of disease, have the potential to transform the treatment of disease and the practice of medicine. One of the most profound changes to medicine is the movement toward tailored therapeutics, or personalized medicine. As defined by the President's Council of Advisors on Science and Technology (PCAST), *personalized medicine* is the tailoring of medical treatments to the individual characteristics of each patient, and the ability to classify individuals into subpopulations based on their susceptibility to a particular disease or their responses to a specific treatment. Personalized medicine therefore has the potential to optimize targeted delivery and dosing of treatments so patients can receive the most benefit with the least amount of risk, cutting out the difficulties of the current trial-and-error process many patients endure to find the correct drug and dose to treat a condition.



FDA INNOVATES: PREDICTING ADVERSE REACTIONS TO DRUGS

Patients respond differently to medicines, and all medicines present the possibility of side effects. Based on the belief that these differences may be based on genetic factors, FDA has been providing scientific and strategic input to the International Serious Adverse Events Consortium (iSAEC) to identify genetic markers that are useful in predicting the risk of drug-related serious adverse events. The iSAEC's initial studies have successfully identified genetic variants associated with drug-related liver toxicity and serious skin rashes. While the majority of iSAEC's genetic findings have been focused on a specific drug instead of across multiple drugs, a number of cross-drug inherited genes are emerging that may provide important insights into the underlying biology leading to a drug-induced serious adverse event.

Realizing the promise of personalized medicine requires a sustained commitment to advancing our understanding of the structure and function of our genomes, the underlying genetic and environmental bases of human disease, and human genomic variations and the ways in which these variations influence disease or responses to therapy. This research also requires a pathway to translate such findings to real world medical products and practices.

Much of the applied regulatory science for evaluating the strategies and outcomes for personalized medicine—such as standards for whole genome sequencing, fully qualified biomarkers (measurable characteristics in

patients), and innovative clinical trial designs and statistics—are still underdeveloped. Additionally, the move toward personalized medicine is resulting in an increasing number of new products that fall within the purview of multiple centers at FDA, creating an additional challenge during the approval process. To address these issues, FDA will continue to take a leadership role on the scientific front and build the infrastructure necessary to support the development of these more personalized targeted therapies, most immediately through investments in regulatory science, clarification of FDA policies, a reorganization of leadership, and engagement of physicians, patients, and their advocacy groups.

FDA will continue to take a leadership role on the scientific front and build the regulatory infrastructure necessary to support the development of these more personalized targeted therapies.

Scientific Leadership: Supporting Personalized Medicine through Regulatory Science

As we continue to expand our understanding of how genomic variations contribute to an individual's disease or response to therapy and gain deeper insights into the mechanisms underlying diseases and disease subtypes, innovative medical product development will increasingly use strategies where diagnostics and drugs are "co-developed," allowing for the diagnostic to guide which patients will be more likely to benefit from the drug and less likely to be at risk for serious side effects.

In order to fully realize the co-development approach, clinical development programs for medical products will require increased

investments in regulatory science. *Regulatory science*, the term used to describe the knowledge, tools, standards, and approaches necessary to assess the safety, efficacy, quality, and performance of FDA-regulated products, will play an important part in addressing the challenges presented by personalized medicine. FDA's regulatory science initiative, as discussed in the Agency's *Advancing Regulatory Science for Public Health* white paper issued in October 2010 and the recently released *Strategic Plan for Regulatory Science*, calls for investments in key scientific areas necessary to promote innovation in personalized medicine.

FDA INNOVATES: STEM CELLS

Human embryonic stem (ES) cells, which hold great promise for providing innovative treatments for a variety of incurable diseases like Alzheimer's, Parkinson's, and diabetes, have the ability to proliferate for an indefinite period of time and can develop into a variety of cell types. However, the mechanism of differentiation, or how cells change from one type to another, and the factors regulating cell development are not completely understood, meaning ES cells may vary when grown in different conditions or may change forms, potentially developing into cancer cells. To address this challenge, scientists at FDA's Center for Biologics Evaluation and Research (CBER), in collaboration with NIH, the National Institute of Standards and Technology (NIST), and academia, are developing new methods to evaluate stem cells using a variety of advanced analytic methods that compare the cells' characteristics when grown in a dish to how they change when placed in an animal. This approach allows scientists to correlate the measurable characteristics of the cells with a desired result, such as the repair of a blocked blood vessel, or with undesired or toxic effects. The knowledge gained from these studies, including the cells' characteristics and how they change, contribute to the development of safe and effective ES cell-based products being evaluated by CBER for humans and will be used to create advanced tools and processes for evaluating how ES cell-based products planned for humans will perform.

Approaches that use novel clinical trial designs and statistics will be crucial. These novel designs will allow for patient selection strategies that identify those patients who will derive the most benefit from a treatment, balancing the need for methodological rigor with the need for more rapid, targeted answers and smaller study populations. Equally important are improved approaches to identify and qualify the performance and quality metrics of biomarkers to ensure that diagnostic tools can be developed and used to guide the selection of therapies.

FDA will continue to invest in these key scientific areas through direct funding efforts and collaborations with other agencies, such as NIH. FDA will also work to expand its efforts through collaborations with other government agencies and academia, as well as through public-private partnerships with industry scientists as collaborative partners to support these efforts.

These novel designs will allow for patient selection strategies that identify those patients who will derive the most benefit from a treatment.



Regulatory Infrastructure: Facilitating Personalized Medicine through FDA Policies and Procedures

Because science alone is not enough to translate personalized medicine from microscope to marketplace, FDA is also developing a series of regulatory policies and procedures to support its fruition. The Agency has received feedback about policies related to personalized medicine from industry groups that regard personalized medicine as one of the most promising avenues for new drugs and other innovative medical products.

During discussions about the future of medical devices in relation to personalized

medicine, representatives of industry specifically requested that FDA address the issue of companion diagnostics, the tests that are used to determine whether a particular therapy may work for a particular patient. In response, FDA issued the draft guidance entitled *In Vitro Companion Diagnostic Devices* on July 12, 2011, to communicate to industry how FDA defines these devices and to assist sponsors in understanding the Agency's perspective on them.



The *In Vitro Companion Diagnostic Devices* guidance addresses several key elements for developing drug/diagnostic products, such as when an in vitro diagnostic test is considered a companion diagnostic and what requirements apply when companion diagnostics are used in clinical trials. It also outlines the steps necessary to obtain FDA approval if a company were to develop a diagnostic that identifies patients with an increased probability of responding to a therapy or an increased risk of adverse reaction to a new or existing therapy, and it specifies the information that must be included in the label of the test and its corresponding therapeutic product. In other words, it seeks to ensure that the tests steering patients toward targeted therapies are accurate and reliable and that the right patients receive the right drug at the right dose, promoting the basic tenets of personalized medicine.

As a follow on to the *In Vitro Companion Diagnostic Devices* guidance, FDA is also developing a draft guidance outlining strategies for clinical trial design and regulatory considerations for co-developing a novel companion diagnostic and therapy simultaneously, where the approval and subsequent use of the therapy would incorporate a requirement for the diagnostic test. This draft guidance includes recommendations for the strategic use of biomarkers for patient selection and screening, as well as clinical trial designs that allow for ethical patient selection strategies. FDA is also producing an internal plan for how it will review applications using co-development strategies for product development to accompany both guidances and ensure the Agency meets the special needs of these types of products in a timely way.

It is fully anticipated that the pathway to personalized medicine will utilize an individual's full genomic sequence, and rapid developments in ultra high throughput genomic sequencing technologies indicate that the era of the personal genome is fast approaching. In order to effectively utilize these new sequencing technologies for clinical applications, appropriate evaluation tools in the form of standards and criteria are needed

to ensure sequencing quality and the accuracy of tests. Though public meetings and direct engagement, FDA is actively seeking input from academia, industry, patients and other stakeholders on validation methodologies, materials, and bioinformatics approaches needed to address these issues and accelerate and support the introduction of innovative sequencing applications.

Promoting personalized medicine means making sure the FDA medical product centers work together as a team to get safe and effective new treatments to patients as quickly as possible.

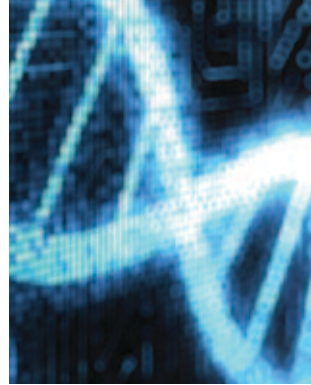
Deputy Commissioner for Medical Products

Promoting personalized medicine not only means having the right policies and science in place, it means making sure the FDA medical product centers work together as a team to get safe and effective new treatments to patients as quickly as possible. Since the primary responsibility for diagnostic approvals lies within CDRH while drugs, biologics and cell-based therapies lie in CDER and CBER, coordination between the Centers for applications incorporating diagnostics as a requirement for therapy use will be necessary.

To spearhead efforts for a seamless integration between the Centers as they

must increasingly work together to promote highly innovative personalized therapies using the latest science and streamlined processes and procedures, the FDA Commissioner appointed a new Deputy Commissioner for Medical Products to oversee and manage the three medical product development centers. The Deputy Commissioner for Medical Products will be responsible for providing overall leadership for the three medical product centers. This person will also be responsible for other programs, such as combination products, where the Centers must work together to establish cross-center programs. [FDA](#)

Expedited Drug Development Pathway



Sometimes during the development of a new drug to treat a serious or life-threatening disease that has few therapeutic options, the new treatment performs much better than standard-of-care in the early trials. While there is general agreement that such a drug should be developed quickly, there is not a common understanding of how to appropriately speed up development while simultaneously gathering adequate evidence about the performance of the product.

Because these patients are selected based on their suspected response to therapy, dramatic responses are in some cases observed in early trials.



During the HIV epidemic in the early 1990s, experts from many fields came together to rapidly work through the science underlying the disease and devise programs for AIDS drug development. The result was a relatively efficient development process and availability of effective anti-HIV drugs.

As we continue to gain an understanding of the mechanisms that underlie diseases at a molecular level, a situation similar to AIDS drug development is emerging in a number of disease areas, including oncology, infections, and genetics. Investigational drugs with the potential to be significant advances over current therapy are being found in early trials.

For example, targeted therapies, such as those used with a diagnostic that classifies patients or predicts responses, are being studied in larger numbers. Trials for targeted therapies frequently use what are known as enrichment strategies to screen and select patients to determine if they are likely to respond to a treatment based on a clinical feature such as the presence of a particular gene mutation or other biomarker. The clinical trials are then performed on this subset of patients, which is often small. Because these patients are selected based on their suspected response to therapy, dramatic responses are in some cases observed in early trials. This effect is similar in tests of anti-infective agents, such as antibiotics that

target a particular bacterium, as well as in genetic disorders where treatment is targeted to address a particular genetic defect.

The early discovery of a potential breakthrough therapy raises ethical and trial design issues. It is important to gain confidence that the effects seen in the early trials are real, and to understand the safety risks of the new drug. On the other hand, from an ethical standpoint, it is important to make sure that people with serious diseases are getting the best possible therapy. In these situations, the clinical trials for the drug's development must be compressed and the evidence about its effects gathered in the most efficient manner possible; however, there is not a good understanding in the biomedical community about how to accomplish this.



Additionally, there are questions surrounding the use of an expedited drug pathway, such as:

- Can FDA, drug developers, and investigators agree on a threshold to determine when a treatment poses “exceptional promise” and should thus be treated in an expedited fashion?
- Can seamless drug development programs be created to utilize natural history data or adaptive trial design concepts to compress drug development time?
- What are the ethical issues involved in identifying a promising intervention? How should the needs of all patients with the disease be balanced against the need for better therapy for an individual?
- Can surrogate outcome measures that could be used for accelerated approval be rapidly identified?
- Can we arrive at a consensus view of the goal of monitoring commitments companies will make once a product is on the market after such a development program, such as scientific expectations and timelines?

To respond to these challenges, FDA will hold a series of scientific meetings with academic investigators, patient groups, drug developers, statistical and methodological experts, and ethicists to achieve a common understanding of steps that can be taken when an investigational drug being studied for a serious disease with no acceptable treatment option shows exceptional promise. CDER will then publish a draft guidance on an expedited development pathway based on the outcome of these meetings.

FDA is also working on two more immediate and related steps toward expedited drug development. First, the Agency is developing a draft guidance on enrichment strategies in clinical drug development. This is a major step forward for speeding progress for targeted

therapies and will lay out many strategies for selecting the patients most likely to benefit from a particular drug. These enrichment strategies are expected to improve the efficiency of clinical trials and serve as a source of expedited drug development.

Second, as a working example of an expedited pathway, CDER will publish a draft guidance on the use of pathologic complete response (pCR)—when no clinical evidence of a disease remains—as a surrogate endpoint for accelerated approval in primary high-risk breast cancer. This guidance will outline a relatively seamless pathway that could be followed from a multi-drug screening trial such as I-SPY 2 to an accelerated approval. This would speed the availability of targeted therapies for breast cancer. [FDA](#)

I-SPY 2

In March 2010, the I-SPY 2 Trial was launched. This is a groundbreaking clinical trial model that will help quickly and efficiently test promising drugs in development for women with high-risk, rapidly growing breast cancers. During the trial, drugs are individually targeted to the biology of each woman's tumor. By applying an innovative trial design, researchers then use data from one set of patients' treatments to decide treatment for future women who join the trial. This will help the researchers learn more quickly which investigational drugs will be most beneficial for women with certain biomarkers.



Harnessing the Potential of Data Mining and Information Sharing



As noted in PCAST's *Report to the President on Health Information Technology*, IT has the potential to transform healthcare and—through innovative capabilities—improve safety and efficiency in the development of new tools for medicine, support new clinical studies for particular interventions that work for different patients, and transform the sharing of health and research data.

The ability to integrate and analyze the data housed at FDA could revolutionize the development of new patient treatments.



FDA currently houses the largest known repository of clinical data (all of which is de-identified to protect patients' privacy), including all the safety, efficacy, and performance information that has been submitted to the Agency for new products, as well as an increasing volume of post-market safety surveillance data. The ability to integrate and analyze these data could revolutionize the development of new patient treatments and allow us to address fundamental scientific questions about how different types of patients respond to therapy. It would also provide an enhanced

knowledge of disease parameters—such as meaningful measures of disease progression and biomarkers of safety and drug responses that can only be gained by analyses of large, pooled data sets—and would allow a determination of ineffective products earlier in the development process.

Additionally, the ability to share information in a public forum about why products fail, without compromising proprietary information, presents the potential to save companies millions of dollars by preventing duplication of failure. FDA sometimes sees

applications from multiple companies for the same or similar products. Although we may have reason to believe that such a product is likely to fail or that trial design endpoints will not provide necessary information based on a previous application from another company, we are currently unable to share this information. As a result, companies may pour resources into the development of products

that FDA knows could be dead ends.

To harness the potential of information sharing and data mining, FDA is rebuilding its IT and data analytic capabilities and establishing science enclaves that will allow for the analysis of large, complex datasets while maintaining proprietary data protections and protecting patients' information.

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Scientific Computing and the Science Enclaves at FDA

Historically, the vast majority of FDA de-identified clinical trial data has gone un-mined because of the inability to combine data from disparate sources and the lack of computing power and tools to perform such complex analyses. However the advent of new technologies, such as the ability to convert data from flat files or other formats like paper into data that can be placed in flexible relational database models, dramatic increases in supercomputing power, and the development of new mathematical tools and approaches for analyzing large integrated data sets, has radically changed this situation. Furthermore, innovations in computational methods, including many available as open-source, have created an explosion of

statistical and mathematical models that can be exploited to mine data in numerous ways to enable scientists to analyze large complex biological and clinical data sets.

The FDA scientific computing model provides an environment where communities of scientists, known as enclaves, can come together to analyze large, integrated data sets and address important questions confronting clinical medicine. These communities will be project-based and driven by a specific set of questions that will be asked of a dataset. Each enclave is defined by its participants, datasets, and sets of interrogations to be performed on the data. Enclaves may be comprised of internal FDA scientists and reviewers working

together or outside collaborators working with FDA scientists under an appropriate set of security controls to protect the sensitive and proprietary data of patients and sponsors, respectively. Engagement of industry sponsors as part of community building will be vigorously pursued, leveraging expertise from the companies that submitted the data in a public-private partnership model.

The scientific computing environment will also provide a dedicated infrastructure for application development and software testing for FDA scientists and reviewers. This will allow FDA staff to develop new applications to improve review, monitoring, and business processes in an environment separate from where regulatory review data is assessed. Additionally, the scientific computing environment will be used to evaluate novel software developed outside of FDA and to rapidly incorporate innovative developments in support of FDA regulatory reviews. This ability to “test drive” new applications outside the regulatory review environment has the potential to shorten traditional FDA development cycles and facilitate the adoption of new software that can enhance quality,

efficiency, and accuracy of FDA regulatory reviews, as well as streamline the adaptation of new higher-powered analytical tools into FDA review and research efforts.

The ability to integrate large data sets across multiple clinical trials, post-market surveillance data, and pre-clinical data will enable FDA to generate new insights into a variety of important issues confronting medical product development and use. Examples of such insights include the identification of patient subsets who do or do not respond to a specific therapy during a clinical trial, which has the potential to drive personalized medicine; identification of patient subsets with differential safety profiles, efficacy, or side effects related to age or gender; evaluations of standard of care; analyses of disease progression; assessment of current endpoints based on aggregated data; and potential to generate better endpoints and insight into placebo effects. This work, which will address broader scientific issues, is intended to impact whole product classes and therapeutic areas and will be central to driving innovations in medical product development and basic research.





Modernizing the FDA IT Infrastructure to Support Scientific Computing

FDA is currently embarking on a landmark IT modernization effort. Information Computing Technologies for the Twenty-First Century (ICT21) is a major initiative that lays the foundation for the modernization of the FDA's aging IT infrastructure and core computing capabilities. The first phase of the ICT21 effort was completed in April 2011 and resulted in the consolidation of FDA's many disparate systems into two modern data centers and the virtualization of over ninety percent of FDA data.

The first phase of the ICT21 Program anticipates the Data Center Consolidation strategy which was subsequently outlined in White House Chief Information Officer Vivek Kundra's *25 Point Implementation Plan to Reform Federal Information Technology Management*. The purpose of the Data Center Consolidation strategy is to enable rapid migration to a Cloud First policy, using cloud computing technologies to maximize capacity. At its core, a cloud strategy reduces computing to a utility and enables the end user to have simplified, rapid, on-demand access to computing resources.



Building an Infrastructure for Patient-Centered Outcomes Research

FDA is also currently developing the policies, standards, infrastructure, and tools for clinical study data to enable analyses across multiple studies. These investments form the core infrastructure needed to build out a clinical data repository, which can then be expanded and seamlessly linked to other data sources, such as pre-clinical pharmacology and toxicology data or post-market safety surveillance clinical data. Additionally, FDA has launched the Partnerships in Comparative

Effectiveness Science (PACES) program to support the development of new mathematical methods to support patient-centered outcomes research. PACES provides funds to pilot out the technical, infrastructure, scientific and legal constructs that will be used as foundations for science computing communities involving FDA scientists and data. These activities will support scientifically sound assessments of medical interventions consistent with FDA's public health responsibilities.

FDA INNOVATES: VIRTUAL PATIENT

Medical device design is highly iterative, and the ability to test novel designs within computer models constructed from digital images of diseased and normal human anatomy could greatly reduce the cost, time, and risk to patients normally involved in producing a new medical device. FDA is in the process of developing a Virtual Physiological Patient—a collection of functional computer models including both normal human anatomy and diseased tissues. These models, which are being developed in partnership with stakeholders, will be made publicly available for medical device companies. Once fully developed, the Virtual Physiological Patient may allow personalization of medical devices so a device can be redesigned to suit an individual patient's anatomy, physiology, and disease state.

Opportunities through Public-Private Partnerships

FDA is also creating a framework for building collaborative scientific computing communities through public-private partnerships. These public-private partnerships incorporate multiple medical product development companies and will be invaluable for enhancing new leads for drug discovery and development, diagnostic and device development and refinement, and the most efficacious use of products in the real world environment. Additionally, building communities where industry and FDA scientists are working collaboratively to address complex data problem solving will enhance external communications between product sponsors

and FDA staff around general product classes and scientific principles. The importance of improved communication cannot be underestimated. These projects may not only result in deeper understanding of diseases and their treatments, but may also lead to a generation of new standards that can be used for regulatory review, resulting in a reduction in scientific uncertainty. Enhanced communications can also help facilitate a better understanding of scientific thinking on both sides, thereby enhancing future sponsor-FDA review discussions; incorporation of academic researchers into these data analyses communities will drive new lines of academic investigation. [FDA](#)



The Future of Medical Devices

Earlier this year, FDA announced plans to increase consistency and clarity in the medical device review process—including our standards for safety and effectiveness—and encourage innovation within the medical device community. These reforms—which included 25 actions that CDRH, the Agency’s medical device center, will take in 2011 to improve the predictability, consistency, and transparency of its premarket review programs—are an important first step to encourage innovation and address some of the barriers that can impede a product’s timely progress to market while assuring that devices are both safe and effective. These actions were designed to increase the ability of innovating companies to attract investors, estimate costs, and bring safe and effective products to market more quickly.

CDRH will reduce product review times and increase consistency in the review process.

Following continued discussions with the medical device community, FDA is moving forward with several new actions through the CDRH Medical Device Innovation Initiative to help accelerate and reduce the time and cost of development, assessment, and review of

innovative medical devices. By establishing a new expedited review pathway, providing better training and incentives to staff, and offering increased clarity to industry, CDRH will reduce product review times and increase consistency in the review process.

New Expedited Review Program

Under the current framework at FDA, pioneering treatments and diagnostics are typically reviewed under the premarket authorization (PMA) pathway, which is often time-consuming and costly. To help prevent unnecessary delays, the Agency recently created a new, expedited review program called the Innovation Pathway that will provide a more streamlined path to market for important technologies. Under this program, CDRH will commit time and

resources earlier in the product development process so scientific issues and regulatory hurdles can be identified early on and unnecessary delays can be avoided. Clinical trial protocols will be developed by the sponsor and CDRH through an interactive process and have flexibility built in to allow for repeat testing and redesign, which will reduce the cost and time of development and ensure an efficient review.



Understanding Emerging Technologies

The ability to effectively identify, anticipate, and respond to technological innovation and scientific breakthroughs is particularly challenging in the medical device realm because of the tendency of these devices to emerge and evolve rapidly. To increase FDA's preparedness in this area, CDRH will identify emerging trends in science and technology by enhancing its current horizon scanning methodology, an approach that incorporates information from a broad range of sources, such as reviewing important scientific

literature and accounting for public health needs, seeking input from manufacturers and other stakeholders, and considering technologies funded by other government agencies. In addition, CDRH, in an effort to enhance its scientific capabilities, is in the process of developing a Network of Experts to serve as a resource to address scientific questions and provide better understanding of emerging technologies in fields where FDA reviewers may not be immediately familiar.

CDRH ENTREPRENEURS-IN-RESIDENCE

FDA's Center for Devices and Radiological Health is participating in a pilot agency program sponsored by the White House Office of Science and Technology Policy that brings innovation experts into federal agencies to collaborate on improving business models that will empower positive change, including economic growth, job creation, and leadership in innovation technology. The EIR program allows CDRH to engage with more than a dozen outside experts who bring state-of-the-art thinking in business process and medical device innovation, decision science, and information technology. Five of these entrepreneurial experts will work alongside staff and management to build an early working version of the Innovation Pathway program, a priority premarket review program whose principal focus is on technologies that demonstrate the potential to revolutionize disease treatment, diagnosis, or health care delivery and that target unmet medical needs (see page 29).

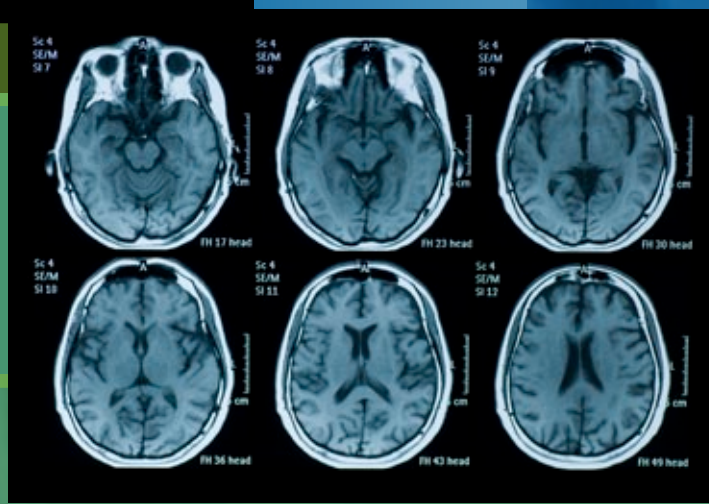
The Reviewer Certification Program will provide new staff with training on the fundamental review principles and practices that are essential at CDRH.

Increasing Consistency through Improved Training

To help increase consistency between review teams for medical devices, all new reviewers are now required to participate in a Reviewer Certification Program. This program will provide new staff with training on the fundamental review principles and practices that are essential at CDRH.

The Agency is also developing an Experiential Learning Program that will

provide staff with real-world training experiences as they visit manufacturers, research and health care facilities, and academic institutions. This will allow staff to see devices while they are being manufactured, as well as during actual clinical use. This comprehensive understanding of the device technology and use will inform the review process in a meaningful way.



Providing Additional Clarity to Industry

Companies often rely on FDA's written guidances to clarify key elements of the medical device development pathway and ensure they are providing FDA with the necessary information to determine a product's safety and effectiveness. CDRH is developing a series of additional guidances to address important questions by industry in certain areas. These include: a guidance to streamline the de novo process (released on September 30, 2011), which can facilitate the development and review of innovative, lower-risk devices;

a guidance on first-in-human studies that will describe the circumstances under which such studies can occur earlier in the development pathway and allow for iterative changes to the device without having to apply for a new Investigational Device Exemption; a guidance on criteria for approving and not approving clinical trials, including feasibility studies and pivotal trials; and a guidance (released on August 15, 2011) on the factors used in making benefit-risk determinations for device approval and clearance. [FDA](#)

Training the Next Generation of Innovators



One of the challenges of the current state of the U.S. economy is the availability of jobs, including those in the biomedical enterprise, that require highly technical and practical knowledge and expertise. Many of these jobs remain unfilled, even in a time of significant unemployment, because there are not enough qualified candidates with the necessary skill sets to fill them. Because of the nature of the work performed at FDA, there is an opportunity to provide these important skill sets to early- and mid-career professionals—both to bring top talent into the Agency and to equip up-and-coming professionals in the private sector with the experience and knowledge they need to develop innovative new treatments and therapies for American patients.

FDA's new Future Innovators program will bring practical regulatory science and policy training together to meet the scientific and technological demands of the 21st century.



Building on the success of FDA's Commissioner's Fellowship program, a competitive two-year program that provides on-the-job training for early- and mid-career scientists and health professionals, FDA is designing a new Future Innovators Program that will bring practical regulatory science

and policy training together to meet the scientific and technological demands of the 21st century. Under this competitive program, FDA will hire qualified candidates who show outstanding promise in their fields for a short-term position within the Agency.

These candidates will receive hands-on training across multiple disciplines, including regulatory affairs, manufacturing, diagnostics, computational science, biomedical device engineering, and design and development of complex therapeutics such as cell-based therapies. These Future Innovators will benefit the Agency by providing outside expertise and perspectives, while they, in turn, will be provided with highly marketable skills and knowledge that will equip them for highly technical jobs in a variety of fields, such as the biotechnology/pharmaceutical industry, diagnostic or device companies, the public health sector, academia, non-profits, health care administration and delivery,

manufacturing, and consulting. In addition, the retention of some Future Innovators will help ensure a pool of highly trained personnel to sustain the Agency as the current workforce turns over or retires.

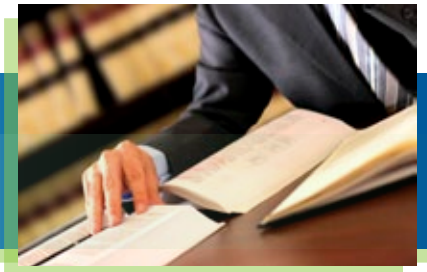
The Agency plans to create this program by working with the Reagan-Udall Foundation, a non-profit organization affiliated with FDA, to enhance its existing fellowship program. Overall, FDA believes it can serve as a rich job training ground to help develop qualified candidates for these important but often unfilled positions, thereby expanding and enhancing a U.S.-based, highly-trained technical workforce. [FDA](#)




Improving FDA Regulations



In addition to developing new programs to adapt to the changing scientific landscape and ensure the safety, efficacy, and timely approval of new treatments and therapies for patients, FDA is also taking proactive steps to reform its existing regulations. Early this year, President Obama issued Executive Order (EO) 13563, outlining his plan for creating a 21st-century regulatory system that is simpler and smarter and that protects the health and safety of the American people in a pragmatic and cost-effective way. One goal of EO 13563 is to target existing rules to increase flexibility and remove regulations that are outdated, unnecessary, excessively burdensome, inefficient, or in conflict with other rules. Based on feedback from our partners in industry and academia and other stakeholders, and under the direction of the Commissioner, the Agency is currently reviewing its regulations to identify burdensome, unclear, obsolete, ineffective, or inefficient regulations. A list of regulations already under review at FDA is posted at <http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm257692.htm>. The Agency also issued a Federal Register notice in April 2011 soliciting stakeholder input on additional rules that could be improved.



In addition, FDA has been revising rules to spur innovation and access to care as result of its existing retrospective review activities. For example, earlier this year, the Agency issued a final rule modernizing the requirements for constituent materials in biological products and has just proposed a rule to

update and make more flexible the sterility test requirement for biological products. The proposed rule will allow greater innovation by industry to identify more rapid and sensitive means to evaluate biological products for sterility that may save both time and cost in lot release testing. 

Conclusion



Recent advances in science and technology have created unlimited potential for how medical treatments will be developed and used. But to truly realize this potential, we must act now—not only for the health of our nation’s public, but for a critical piece of the economy as well.

The steps outlined in this document will be an important driving force in quickly getting the safest and most effective treatments to market to help protect the public health.



This document is a blueprint stemming from extensive engagement with all of the major stakeholders— from leaders in industry to academic researchers to small businesses to patients. While it outlines immediate steps that FDA will take as an Agency to adapt to the changing landscape and drive American biomedical innovation forward, it is just a starting point.

As an agency, FDA will continue to engage the biomedical community to assess and reassess the ecosystem and identify additional areas for improvement. The future of medical treatment is full of opportunities for patients and industry alike, and the steps outlined in this document will position FDA to be an important driving force in quickly getting the safest and most effective treatments to market to help protect the public health. [FDA](#)



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION