Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products

U.S. Department of Health and Human Services,

Food and Drug Administration

As required by FDASIA, Section 1124

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Introduction

This report, entitled "Strategy and Implementation Plan for Advancing Regulatory Science," responds to the requirements of section 1124 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144), which specifies that the Secretary of Health and Human Services "shall develop a strategy and implementation plan for advancing regulatory science for medical products in order to promote the public health and advance innovation in regulatory decision-making." The organization of this document is based on the five requirements for the plan listed in § 1124(b). In section I we fulfill the first requirement, which states that we shall "identify a clear vision of the fundamental role of efficient, consistent, and predictable science-based decisions …with respect to medical products." The next section, "Priorities and Challenges in Regulatory Science," fulfills requirements 2 and 3, which direct the Food and Drug Administration (FDA) to identify the regulatory science priorities of FDA with respect to decision making about medical products and the scientific gaps that impede the timely introduction of safe and effective products. In the third section, entitled "Advancing Regulatory Science: Adressing Priorities and Gaps," we describe and provide examples of how FDA advances regulatory science through its internal scientific activities and external collaborations to address the previously identified priorities and gaps. This section serves as helpful background for the next section, where we describe "how the Food and Drug Administration will ensure that advances in regulatory science for medical products are adopted" (requirement 5), again providing illustrative examples. Finally, in Section V we identify "clear, measurable metrics" by which progress on these priorities and gaps will be measured and new science adopted (requirement 4).

Section 1124 also requires that each of the four annual user fee performance reports submitted to Congress for each of fiscal years 2014 and 2016 include a report that describes progress on (1) advancing the priorities and gaps identified in this plan, (2) integrating and adopting advances in regulatory science, and (3) addressing our regulatory science commitments under the four user fee agreements.[1] This plan includes a description of the metrics we will use for these future reports.

[1] The Prescription Drug User Fee Agreement (PDUFA), the Generic Drug User Fee Agreement (GDUFA), the Biosimilar User Fee Agreement (BsUFA), and the Medical Device User Fee Agreement (MDUFA).

I. A Vision for Regulatory Science and Decision-making

Summary Statement:

The role of regulatory science[2] with respect to medical products is to develop the knowledge, methods, standards, and tools needed to increase the certainty and consistency of regulatory decisions and improve the translation of basic discoveries to viable medical products. The fundamental goal is to ensure availability of medical products with proven efficacy and safety that are manufactured with consistently high quality and monitored postapproval to ensure their safety during real-world use. Regulatory decisions must be informed by the best available scientific evidence and supported by reasoning that is transparent and free of bias. The science that supports these decisions must constantly advance to adapt to changes in the kinds of products we oversee, advances in our understanding of health and disease, emerging technologies, and new statutory requirements and policies. It must also be proactive and anticipate and prepare for future public health challenges.

FDA will continue to work to establish and validate our regulatory science priorities, ensure the quality of our regulatory science activities, and clearly articulate the impact these efforts have on our regulatory mission and on public health.

A. The Framework for Regulatory Decision-making

FDA's regulatory decision making operates within a framework of law, science, and policy. The legal structure is provided by statute, which defines the broad regulatory requirements, goals, authorities, and boundaries, and by regulation, which provides more detailed requirements and procedures for compliance with statutory requirements. Because laws and regulations often cannot prescribe detailed requirements to keep pace with rapid advances in science, they typically establish general standards without mandating the scientific approaches that would best be applied to implementing the law.

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[2] FDA has defined regulatory science as "the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products." *Advancing Regulatory Science*, U.S. Food and Drug Administration, http://www.fda.gov/scienceResearch/specialtopics/RegulatoryScience.

Science establishes, to the extent possible, objective facts that are germane to a regulatory decision. With agreement about underlying facts, there is a greater likelihood of achieving consensus about the scientific interpretation or implications of those facts; this, in turn, can promote more consistent and objective regulatory decision making.

Policy brings additional concerns to bear, including resource constraints, emerging public health needs, the likely impact of an action or decision, and in some cases, historical precedents. For example, in deciding whether to allow a company's medical product to remain on the market despite compliance issues, we will consider not only the law and science, but also whether there is a compelling public health need for the product, whether there are other sources for the product, and whether the risks associated with the compliance issue can be managed.

B. Regulatory Science in the Medical Product Life cycle

FDA advances the public health by applying scientific standards to assess the safety, efficacy, and quality of medical products throughout the product lifecycle. When serious problems emerge in the product development process, our scientists can help address them by bringing them to the attention of the scientific community, or by conducting or collaborating on relevant research. During clinical testing, our scientists provide important scientific feedback on trial designs and endpoints and conduct ongoing reviews of emerging data on safety, efficacy, and product quality. When a marketing application is received, data submitted by the medical product sponsor are evaluated against the established scientific standards. After marketing, the safety of the product is further evaluated based on adverse event reports and other information. In short, regulatory science drives FDA decision making—across the product lifecycle, we work with the scientific community to set the clinical and technical standards used in product development and product review.

FDA stated its vision for regulatory science in our August 2011 "Strategic Plan for Regulatory Science" as follows:

> "FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community."

C. Moving Regulatory Science Forward

Regulatory decision making by FDA relies on having the best available science to reduce uncertainty and improve the likelihood that the approved medical product is both safe and effective. However the "best available science" may not be adequate to ensure certainty for every regulatory decision that needs to be made. There are, inescapably, significant gaps in our scientific knowledge of existing products and our understanding of how they should best be regulated (see Section II). Long-standing challenges, such as how to better predict safety and efficacy in the real world, persist and are the focus of continued regulatory science efforts. Layered on existing scientific gaps are uncertainties that arise from evolving product types, new therapeutic indications, updated assessment tools, or evolving statutory requirements.

In the course of reviewing multiple regulatory applications, FDA reviewers see a range in the quantity and quality of supporting data, the methods of analysis that have been applied to that data, and in the scientific interpretation of the results. In evaluating a product, all the information, knowledge, or methods needed to optimally assess safety and quality of the product may not be known or available at the time of a regulatory submission to the Agency. As the science underlying a particular regulatory requirement or new technology is developed and refined, often through analysis of accumulated data from many regulatory submissions or other research, the knowledge gained can enhance implementation or application of regulations, and it can be communicated to industry through guidance and revised standards. The new knowledge is also integrated into internal training requirements and regulatory review procedures and standards. Development of the regulatory science brings convergence of scientific opinion and corresponding improvements in the scientific quality of regulatory submissions and the consistency and objectivity of regulatory evaluation. ***The added knowledge reduces uncertainty, resulting in greater predictability and efficiency in the process for both submitters and reviewers.***

The efficiency and consistency of regulatory decisions are also enhanced by establishing reference materials, test panels, and standards for methods and data submission. For example, consistent interpretation of analytical test results requires a method that not only accurately measures the intended endpoint, but does so reliably across laboratories and over time. Similarly, the manipulation and analysis of the huge volume of data required for review of a regulatory submission can be made more efficient and consistent by clearly defined standards for data fields and standard definitions of what those fields represent.

We provide examples below of how regulatory science develops in the context of new legislation and emerging science to guide regulatory decision-making.

Clinical Trials for Medical Products

The Kefauver-Harris Amendments of 1962[3] introduced a requirement that there be "substantial evidence of effectiveness" for new drugs as demonstrated by "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."[4] It was then up to FDA to set the standards for trials by providing guidance on what constitutes an "adequate and controlled investigation" and what would be considered "substantial evidence of effectiveness." Early submissions to FDA under the new statute varied greatly, and regulatory decisions were made without the benefit of a mature scientific understanding of optimal trial design or data interpretation. Gradually, as the number of clinical trial submissions increased, FDA and the clinical trial community gained an enhanced understanding of the critical attributes needed to define an "adequate and controlled investigation," and also refined the trial designs, statistical methods, and clinical endpoints needed to determine "effectiveness." Approaches to clinical evaluations have continued to evolve and diversify into multiple forms, with specialized statistical methods and trial designs being developed that are appropriate for specific product classes and clinical conditions, and products targeted to specific patient populations.

A similar evolution occurred in clinical trials for devices, starting with the Medical Device Amendments of 1976,[5] which required that there be a "reasonable assurance of safety and effectiveness" based on valid scientific evidence for a medical device[6]. Similarly, under the changing legal framework for the "bioequivalence" of generic drugs, FDA continues to incorporate current science into guidance documents targeted to specific generic drugs.

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[3] Kefauver Harris Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

[4] Section 505(d) of the Food, Drug, and Cosmetic Act, 21 U.S.C. 355(d).

[5] Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539.

[6] Section 515(d) of the Food, Drug, and Cosmetic Act, 21 U.S.C. 360e(d).

Development of a Pathway for Review of Biosimilars

Basic research in a variety of disciplines related to the life sciences has led to a profusion of products created by biologic processes that may be complex mixtures of proteins, nucleic acids, or other biomolecules, or living tissues and cells. Title VII of the Patient Protection Affordability and Accountability Act of 2010[7] required FDA to develop a new regulatory framework for review of "biosimilar" and "interchangeable" biologic products, analogous to what is required for generic drugs. The law defines *biosimilarity* to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." FDA is in the process of working with industry and academia to develop the initial science needed to establish requirements for evaluation of these products. In the recently released FDA draft guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*,[8] we delineate a stepwise process for collecting scientific data about the candidate biosimilar. Steps include evaluating the extent to which there is residual uncertainty about the biosimilarity and identifying next steps needed to address that uncertainty. Regulatory decision-making with respect to biosimilar license applications will become more straightforward as more data emerge from products regulated under this pathway, and as methods become available to reduce the uncertainty regarding the biosimilarity of the product to the reference product.

An active regulatory science program, including research, is critical if FDA and its partners are to fill current knowledge gaps in medical product development and review and meet newly emerging challenges associated with applying advances in the biomedical sciences to improving public health. The goal of this research is to have the best available scientific data, knowledge, methods, and tools to reduce uncertainty and increase the consistency of regulatory decision-making.

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[7] Public Law 111-148, 124 Stat. 119.

[8] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

II. Priorities and Challenges in Regulatory Science

A. Priorities for Regulatory Science for Medical Products

The regulatory science priorities and gaps relevant to this Strategy and Implementation Plan for Regulatory Science for Medical Products are consistent with, and drawn from, the Agency's Strategic Plan for Regulatory Science, which was published in August 2011. The Strategic Plan defined eight priority areas of regulatory science based on identified gaps where new or enhanced engagement is essential to the continued success of FDA's public health and regulatory mission. The three FDA Centers responsible for the approval of medical products for human use – the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Drug Evaluation and Research (CDER) -- with the strategic leadership and support of the Office of the Chief Scientist, leverage the expertise at other components of FDA— the National Center for Toxicological Research, the Office of Orphan Product Development, the Office of Combination Products and the Office of Counterterrorism and Emerging Threats—to address the implementation strategies identified within the priority areas relevant to their mission. The eight priority areas identified in the Strategic Plan for Regulatory Science,are as follows:

1. Modernize Toxicology to Enhance Product Safety
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes
3. Support New Approaches to Improve Product Manufacturing and Quality
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health[9]
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

These priority areas, all of which except number 6 are related to medical products, are where new or enhanced engagement in regulatory science research is essential to advancing FDA's regulatory mission. They address cross-cutting needs and

[9] Priority area 6 does not apply to medical products and is not addressed in this plan. Throughout this plan, numbering of priorities will remain consistent with the numbering in the Strategic Plan for Regulatory Science.

opportunities that typically extend across several product areas where benefits and engagement from regulatory science successes will enhance the development evaluation and health outcomes related to multiple products and populations. FDA's Strategy and Implementation Plan for Regulatory Science for Medical Products is designed to allow the Agency to meet today's public health needs and to be fully prepared for the challenges and opportunities of tomorrow to help harness revolutions in science that can be translated into products that help make and keep our nation both safe and healthy.

B. Challenges for Regulatory Science for Medical Products

The complexity of FDA's regulatory science portfolio is growing rapidly, in large part due to scientific challenges inherent in evaluating a new generation of products based on quickly evolving science and technology. Adding to the complexity are the realities of an expanding global economy that requires FDA to evaluate and manage risks associated with a vast array and volume of regulatory data, products, and ingredients produced in a multitude of global locations. New drugs, biologics, and medical devices are increasingly complex in their development, manufacture, and evaluation. Medical products may contain a complicated array of ingredients and components, all sourced from shifting global commodities markets and often of uncertain provenance. In addition, improved information technology capacity provides opportunities to harness the substantial data resources both within and external to FDA for regulatory decision-making.

The challenges of modern product development and globalization underscore the critical importance of modernizing and advancing regulatory science to match advances in basic and applied science and technology. The Strategic Plan for Regulatory Science provides a detailed compilation of areas where progress in regulatory science is needed. This section summarizes gaps relevant to medical products and adds challenges related to new programs and expectations outlined in the user fee programs (PDUFA, GDUFA, BsUFA and MDUFA) authorized in FDASIA.

Priority Area #1: Modernize Toxicology to Enhance Product Safety

> Preclinical testing has served a fundamental role in characterizing the potential risks associated with new FDA-regulated products. However, serious and sometimes rare and unexpected adverse events may be observed in clinical trials or postapproval, suggesting that critical gaps exist in our understanding of the relationship between human responses and animal toxicology findings. We will work to develop and assess markers obtained through in-life sampling and non-invasive methods, like state-of-the-art imaging modalities, which can be used to measure response or toxicity associated with medical products in both animal and human studies. These

approaches enhance the translational potential of nonclinical testing, while enabling sequential monitoring, with a goal of reducing the number of animals needed.

New and improved toxicology models are essential to provide relevant safety information for vaccine antigens and adjuvants, biologics, cell and gene therapies, and nanoparticles. Development of cell and tissue-based models, including organ specific toxicity models that may better predict human toxicity, must continue to be a priority.

Computer models of physiologically based pharmacokinetic systems are important supplementary tools to experimental models. As more is learned about toxicity mechanisms and pathways, there are opportunities for advanced computational analyses and models to facilitate more effective translation of nonclinical findings to clinical settings. Implementation of new scientific approaches, including the use of bioinformatics, multiscale and level modeling, and integration of diverse sources of toxicological data will be pursued. Such approaches may help flag potential unwanted effects of drugs, biologics, and devices, including immunogenicity, for further evaluation and monitoring. The predictive accuracy of toxicology models and safety assays must be rigorously validated to define their reliability and limitations.

Priority #2: Stimulate Innovation in Clinical Evaluations & Personalized Medicine to Improve Product Development and Patient Outcomes

Clinical development programs for medical products are dependent on the availability of appropriate clinical trial design and analysis methods as well as related tools, such as biomarkers and other endpoints considered in the assessment of efficacy and safety. Significant progress in understanding how genomic variations alter an individual's response to medical therapies is supporting improvements in the clinical use of existing therapeutics, while expanding opportunities for co-development of therapies and tests that can be used to tailor treatment to individual patients (personalized medicine). Development of personalized therapies would be facilitated by tools to assess therapeutics along with their companion diagnostics. Additional in-house infrastructure and expertise is needed to support the receipt, analysis, and interpretation of genomic data for regulatory decision-making.

Clinical trials represent a significant investment of time and resources, and enhancing their efficiency requires continual refinement of designs and statistical analysis methods, including enrichment strategies adaptive designs and, for device trials, Bayesian approaches. Special challenges around designs that target defined populations or small numbers (e.g. those for orphan diseases) must be addressed. Best practices and standard approaches for benefit-risk assessments and meta-analysis

methods for safety analyses must also to be established. The development of modeling and simulation methods, often leveraging data from previous clinical development programs, can enhance trial design and dose selection in late-phase trials, as well as provide predictive information about the performance of generic drugs. For generic drugs, modeling and simulation can support the use of alternative in vitro equivalence studies that can accelerate access to generic drugs. For device development, a credible strategy of computational modeling and simulation could substantially augment animal, bench, and human models and potentially streamline the regulatory review process for many products.

Identifying and qualifying biomarkers, patient-reported outcomes, and other study endpoints that are clinically meaningful remains a challenge. In addition, the analytical methods used to measure biological response, whether they involve physiologic, imaging, genomic, or traditional lab tests, must be accurate and consistent across analytical platforms and laboratories.

Generic drugs, which account for 80% of dispensed prescriptions, pose a number of scientific challenges related to their clinical evaluation. We are working to evaluate approaches to assessing the bioequivalence of topical drugs, such as creams and patches, inhaled drugs (e.g. asthma medications), and drugs that have a local site of action in the gastrointestinal tract. In all these cases, the straightforward measures of blood levels that support bioequivalence for systemically active drugs cannot be used. The evaluation of therapeutic equivalence (defined as the ability to undertake successful generic substitution) is an emerging challenge. Patient factors and usability should be integrated into the review of generic products to establish equivalence standards that will ensure successful substitution. Examples include adaptive equivalence standards that take into account the therapeutic index and tighten standards when needed, consideration of human factors and performance of drug device combinations, and the impact of dosage form factors, including size, shape, and hardness, on patient acceptance of generic products.

Overcoming the challenges facing medical product development and clinical evaluation requires collaborative approaches that involve companies, academia, and government expertise and resources. Expanding opportunities to develop joint solutions through the use of consortia, public-private partnerships, and other collaborative mechanisms are needed.

Priority Area #3: Support New Approaches to Improve Product Manufacturing and Quality

Application of novel science and technologies is leading to new methods of manufacturing and to innovative products that are often complex. To foster these innovations, FDA conducts research – in collaboration with industry and academia – to assess how these new technologies affect product safety, efficacy, and quality, and to use the information to inform development of regulatory policy relevant to these innovations. In addition, analytical technologies are rapidly changing, leading to dramatic improvements in sensitivity, resolution, and precision in the determination of product structure and the detection of contaminants.

To enhance development and evaluation of novel products and improved manufacturing methods, efforts to promote the adoption of state-of-the-art manufacturing strategies, such as quality by design, process analytical technology, and continuous manufacturing, must continue. These approaches may require sophisticated statistical methods for successful implementation. For small molecules, including generic drugs, we will pursue methods for evaluating the in vitro performance characteristics of complex dosage forms, enhance our understanding of the relationship between in vitro and in vivo characteristics, and introduce screening approaches to assess the quality of drug ingredients.

For biologics, improved product quality and manufacturing requires developing the assays and technology to monitor and control critical product quality attributes that can affect efficacy and safety. For example, for influenza vaccines, this would include faster methods to develop seed stocks and reference reagents and to perform tests for potency and sterility to allow for more rapid response in pandemics, as well as evaluating the safety of new production methods, such as use of mammalian cell substrates to propagate new influenza strains for vaccine development. For all medical products, rapid and accurate methods for assessing sterility are also critical to reduce the risk of microbial contamination.

Assessing the quality of finished medical products is becoming increasingly complex, as products such as targeted therapies, combination products, biologics, generic versions of complex dosage forms, and biosimilars represent a growing proportion of regulatory submissions. Advanced analytic technologies, such as nuclear magnetic resonance, high-throughput sequencing, and high resolution mass spectrometry, need to be evaluated for characterizing biologics and biosimilars. New assays that might provide high throughput and cost-effective alternatives to measure product quality attributes, as well as reference materials, panels, and standards are needed to facilitate

adoption of new methods. Advanced analytical technologies also open the pathway to generic versions of products that are complex mixtures of active ingredients.

The safety and effectiveness of medical devices depend on a number of factors, including design, manufacture, quality assurance, packaging, labeling, storage, installation, and servicing. Unlike many other products regulated by FDA, medical devices often contain hundreds of complex components and systems, all of which must work together. Research in this area focuses on improving the initial product design and manufacturing processes.

Priority Area #4: Ensure FDA Readiness to Evaluate Innovative Emerging Technologies

We are at a critical moment when advances in science are leading toward fundamental changes in the way medical treatments and diagnostics are being developed and used. Groundbreaking discoveries in complex chemistry and biosynthesis promise to yield new drug and biologics candidates, and cutting-edge electronics, nanotechnology, and materials science have revolutionized medical devices. Emerging fields such as gene therapy, cell therapy, tissue engineering, nanotechnology, high-throughput sequencing, optogenetics, high-intensity focused ultrasound, and information technology are also yielding innovative approaches to improve our health. Ongoing advances in genomic technologies such as high-throughput sequencing are presenting new challenges to FDA related to the data volume and computing infrastructure.

Evaluation of medical products developed and/or produced with emerging technologies will require multidisciplinary tools and approaches to fully characterize products and assess product quality, product safety, sterility and clinical safety and efficacy. For example, tissue-engineered medical products, and more broadly, those developed through the multi-disciplinary field of regenerative medicine, are often combination products composed of two or more regulated components (e.g., biologic and device, biologic and drug, etc.). Evaluation of stem cell-derived products that will undergo differentiation either as part of the manufacturing process or after clinical introduction into a patient requires a complex systems biology approach to understand the biological processes and attributes that are critical to measure during manufacture, in nonclinical models, and to monitor in the study subject. The components may have been developed with disparate manufacturing techniques and controls, and interactions among the components may impact product quality during clinical use. Other areas of challenge include assessment of complex drug delivery systems, drug-device combination products, and generic versions of drugs with complex formulations or delivery systems to determine comparability to innovator products.

In the rapidly evolving and complex arena of devices and combination products, developing a framework for qualifying medical device development tools (MDDT) such as clinical outcome assessments, biomarkers, and nonclinical assessment models will provide a clear path forward for evaluation and qualification for use by multiple medical device sponsors. As previously noted, solving the complex challenges related to the development and evaluation of medical products resulting from emerging technologies requires a multisector, multi-disciplinary collaborative approach. One opportunity is to work with external partners, such as the Medical Device Innovation Consortium (MDIC), a public-private partnership for medical device regulatory science, to leverage the expertise and resources of industry, government, and non-profits to develop tools to drive innovation.

Priority Area #5: Harness Diverse Data Through Information Sciences to Improve Health Outcomes

FDA receives a vast amount of information from a variety of sources, including product submissions, inspection reports, adverse event reports, de-identified patient data from health care providers, and results from surveys and basic scientific research. Successful integration and analysis of data from these disparate sources would provide knowledge and insight not possible from any one source alone.

Opportunities to address knowledge gaps include developing new approaches and data sources for postmarket surveillance. Challenges include identifying and assessing appropriate postmarket data sources and appropriate data standards for sectors that are not productively captured in major databases, including data on generic drugs and drugs dispensed and administered in doctors' offices, such as oncology drugs. Medical device postmarket surveillance presents unique problems compared to drugs and biologics due to the greater diversity and complexity of medical devices, the iterative nature of medical product development, the learning curve associated with technology adoption, and the relatively short product life cycle. Regulatory scientists must also develop better ways to manage unstructured text data in adverse event reports using new text mining tools. In addition to integrating data on patient outcomes, the predictive safety assessment tools should meld postmarket data with other sources of information, such as clinical trial data and information on potential adverse event pathways. Methods such as semantic text mining that can reliably retrieve information from textual sources such as the scientific literature and case report forms must also be developed and refined. There may also be opportunities to leverage smart phone technologies to enhance communication regarding medical product performance from, as well as to, medical professionals and patients.

Handling the receipt, storage, retrieval, analysis, and visualization of increasingly voluminous and complex data is a continual challenge. As clinical trial designs have evolved, with newly emerging biomarkers and endpoints, and as novel data types are being collected for exploratory purposes, the amount and complexity of the data have increased. In addition, genomic and other omic data are being evaluated or considered for evaluation. These types of data may require huge amounts of memory and new analysis and visualization tools. To manage and process these data efficiently, data standards will have to be universally applied, and FDA scientists will need to develop an enterprise-wide information model that is both robust and flexible enough to accommodate scientific data from multiple sources. This will minimize the need to retool information systems and analysis tools as the volume and complexity of the scientific data grow.

The continuing increase in the volume and complexity of data, while posing technical challenges, also offers opportunities for synthesizing new knowledge from seemingly disparate data sources. To realize this will require fresh approaches to data mining and modeling.

Note: Priority Area #6, Implement a New Prevention-Focused Food Safety System to Protect Public Health, is not related to medical products.

Priority Area #7: Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security

Medical countermeasures, or MCMs, are drugs, biologics (including vaccines), devices (including diagnostic tests and personal protective equipment), and other equipment and supplies for response to public health emergencies involving chemical, biological, radiological, or nuclear (CBRN) threat agents or naturally occurring infectious threats such as pandemic influenza. The range of MCMs required to rapidly and effectively respond to identified threats is not yet fully developed. Moreover, once an event is detected, there is limited capability to develop new MCMs rapidly in response to new or emerging threats, and only limited capacity to ramp up production of some existing MCMs. As with all medical products, FDA's regulatory assessment of MCMs for approval, clearance, or licensure is data-driven and thus MCMs face the same challenges as other medical products with respect to developing the data to support regulatory decision-making. Accordingly, advances in all of FDA's regulatory science priority areas may apply to MCM development; however, there are also challenges related to MCM development and regulatory review that are unique to MCM products that necessitate MCM-focused regulatory science efforts. For example, for many of the diseases or conditions for which MCMs are being developed, it is not ethical or feasible to conduct efficacy studies in humans.

Instead, the Animal Rule[10] provides a development pathway for drugs and biologics such that efficacy studies are performed in animals and the results extrapolated to humans, while safety is still established through human studies. In addition, children can participate in clinical trials only when the research is ethically sound and will provide a direct benefit to them. For MCMs being developed for use in children, FDA often relies on the extrapolation of data from adult populations and, where appropriate and if available, pediatric animal models for the approval or licensure of pediatric use information.

FDA's MCM regulatory science program, which is composed of both intramural and extramural components, is focused on animal model development and qualification; the identification and qualification of biomarkers for safety and efficacy; the use of protein engineering to stabilize vaccine proteins; developing methods to assess MCM product quality and related product release assays; the validation of next−generation in vitro diagnostics platforms; the assessment of the performance of emergency medical equipment; and the tracking and evaluation of the safety and clinical benefit of MCMs during public health emergencies.

Priority Area #8: Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

One way that FDA protects the public from harm and promotes public health is by ensuring easy public access to sound information. This is accomplished by setting and enforcing high standards for product information to ensure that labels are accurate, and advertising about these products is clear, truthful, and not misleading. FDA also seeks to provide clear information about how to use products to promote health or reduce harm so consumers and health professionals can make informed decisions, and FDA communicates new or emerging situations so Americans have up-to-date information about products on the market.

To enhance the utility of information provided to the public, FDA needs to improve its science-based approach to effective communication, including developing messages, testing how the public understands information, assuring optimal delivery to relevant populations, and assessing the impact of the information on public understanding, attitudes, and behaviors. A major challenge is adapting FDA's communications to rapidly evolving technologies that are driving major shifts in how

[10] FDA's regulations concerning the approval of new drugs or biological products when human efficacy studies are not ethical or feasible are codified in 21 CFR 314.600 for drugs and 21 CFR 601.90 for biological products. This regulatory pathway is commonly referred to as the Animal Rule.

consumers choose to receive and share information on the benefits and risks of FDA-regulated products.

To facilitate the translation of science-based regulatory decisions and information into public health gains, FDA must strengthen social and behavioral sciences in the areas of understanding and reaching diverse audiences, ensuring audience comprehension, and evaluating the effectiveness of communications in changing behaviors related to the use of regulated products.

III. Advancing Regulatory Science: Addressing Priorities and Gaps

FDA uses a variety of approaches to advance its regulatory science priorities and address critical regulatory and scientific gaps associated with the review of medical products. Although not specifically requested in section 1124, a description of these activities provides a context for understanding the metrics we will use in developing the progress reports required as part of the user fee performance reports for fiscal years 2014 and 2016. FDA's approaches to advancing priorities and addressing gaps can be grouped broadly into two categories: our internal regulatory science activities, which include intramural research and scientific working groups and funding programs, and our external regulatory science activities, which encompass a broad range of scientific exchanges and collaborations with partners in government, academia, industry, and non-profit entities.

A. Internal Regulatory Science Activities

FDA scientists are uniquely positioned to see across multiple medical product development programs, regulatory submissions, and postmarket actions. This broad view provides insight into recurrent scientific hurdles to efficient and predictable development, regulatory review, and postmarket monitoring of medical products. Some of those hurdles are best addressed through our laboratory-based and data-driven regulatory science research. Our use of competitive intramural funding programs offers reviewers and laboratory scientists focused opportunities to address defined priorities and scientific gaps.

1. Laboratory-Based Research

In our laboratory-based research programs, there is a critical need to keep current with technological developments, develop solutions to sector-wide science gaps, and maintain state-of-the-art readiness to react rapidly to public health emergencies involving regulated products. The following three examples demonstrate how FDA scientists are addressing some critical gaps in regulatory science.

> **Portable screening technologies for drug ingredients.** Although an increasing number of drug ingredients, drug products, and dietary supplements from other countries enter the U.S., until recently, only a limited number of them could be examined, because all samples had to be sent to FDA district laboratories for time-consuming analyses. FDA is developing and testing advanced portable technologies, including handheld spectrometers, to rapidly screen a larger number of drug products in the field, while sending only those samples suspected to be tainted to the district laboratory for further

investigation. The new technology is being deployed in FDA field offices in the United States, China, and India.[11]

The safety of vaccines. Adjuvants provide a means to increase the immune response to vaccines. However, some adjuvants may induce unwanted immune responses leading to serious adverse events. CBER scientists have developed an assay based upon the use of a monocytic cell line to monitor for release of pro-inflammatory cytokines, which have been shown to be closely correlated with clinical immune response. This method may provide a rapid, inexpensive way to screen novel adjuvants for unwanted immunogenic properties, thus facilitating faster development of safe and effective vaccination programs.[12]

Making devices compatible with magnetic resonance imaging. Magnetic resonance imaging (MRI) machines can heat or move implantable devices and disrupt their function, and implanted devices may distort the MRI images. Thus, patients with certain implanted devices (e.g., defibrillators) have not been able to receive important MRI testing. To develop MRI-compatible implanted devices, FDA scientists have performed electromagnetic testing of novel device designs, developed physical and computer models to evaluate them, and established new standards for new MRI-compatible devices. This research has led to approval of the first MRI-compatible implantable devices.[13]

2. Research Based on Analysis of Regulatory Data

FDA reviewers also analyze regulatory data to inform policy and regulatory decision-making with regard to preclinical testing, clinical trial designs, endpoints and analyses, postmarket safety, and product manufacturing and quality. In addition to the development of new knowledge, tools, methods, and standards, analyses of these data, and additional data from external partners, have been used to develop new regulatory pathways for therapies with high public health impact.

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[11] Kauffman J, et al., 2013, Securing the Supply Chain through Rapid Screening of Pharmaceutical Materials. Biopharma Asia, available at http://www.biopharma-asia.com/magazine-articles/securing-the-supply-chain-through-rapid-screening-of-pharmaceutical-materials/.

[12] Zaitseva M, et al., 2012, Use of human MonoMac6 cells for development of in vitro assay predictive of adjuvant safety in vivo. Vaccine, 30:4859-65, available at http://www.sciencedirect.com/science/article/pii/S0264410X12006755.

[13] Liu Y, et al., 2013, Computational and experimental studies of an orthopedic implant: MRI-related heating at 1.5-T/64-MHz and 3-T/128-MHz. J Magn Reson Imaging, 37:491-7, available at http://onlinelibrary.wiley.com/doi/10.1002/jmri.23764/pdf.

Accelerating evaluation of treatments for hepatitis C. Although the primary endpoint in trials of treatments for hepatitis C had been based on detection of the virus in patient serum at week 24 of follow-up, FDA scientists analyzed data from 18 trials and found that measurements at 12 and 24 weeks of follow-up were concordant across a large population database representing many viral genotypes and treatment regimens. Based on this work, the extent to which the virus is eliminated from serum at 12 weeks can now be used to predict patient response to treatment. The ability to assess patient response earlier in the course of treatment promises to accelerate evaluation of new therapies for hepatitis C and improve the management of patients refractory to a given course of treatment.[14]

Facilitating development of an artificial pancreas. Diabetes affects more than 23 million people in the United States and contributes to approximately 170 billion dollars in health care costs every year. An artificial implanted pancreas, if it could be developed, has the potential to significantly improve the lives of insulin-dependent diabetic patients. FDA has engaged scientists at other Federal agencies and outside groups on ways to overcome the scientific and regulatory obstacles in developing an artificial pancreas and to establish reasonable clinical expectations for these systems. To better share information available to FDA on the existing medical devices that are components of the artificial pancreas, we worked with sponsors and manufacturers of these devices to obtain authorization for certain researchers to access information about the devices from regulatory files that may help their research. These efforts are providing a transparent and predictable regulatory path forward in developing an artificial pancreas.[15] In fact, the Agency has approved three clinical studies for various artificial pancreas devices that will take place at a diabetes camps this summer. This is a major milestone for the artificial pancreas project as it will be the first camp study in the U.S. and will allow for the study of artificial pancreas devices in camp settings where children will participate in camp activities and wear the artificial pancreas during the day and overnight.

Assessing the safety of vaccines for children. Responding to concerns among many members of the public that aluminum in vaccines might pose a risk to infants, our scientists performed an updated analysis of the safety of aluminum adjuvants, taking into account the most current information on how the body accumulates aluminum, how the infant kidney filters out potentially toxic substances, how quickly aluminum spreads

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[14] Chen J., 2013, Earlier Sustained Virologic Response Endpoints for Regulatory Approval and Dose Selection of Hepatitis C Therapies. Gastroenterology, 144:1450-55.e2, available at http://www.sciencedirect.com/science/article/pii/S0016508513002886.

[15] See FDA's Role: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/ucm259561.htm.

away from the site of vaccine injections, and safe levels for aluminum in the body. Calculations of infant aluminum exposure based on computational toxicology modeling showed extremely low risk to infants. The results of this study support the safety of aluminum-containing vaccines and were used to aid decisions by the World Health Organization on vaccine safety.[16]

A pathway for approval of generic liposomal products. FDA review staff evaluated all available data on liposomal product performance and characterization and developed advice on demonstrating bioequivalence for generic liposomal products. This pathway was first described in 2010 draft guidance for establishing bioequivalence.[17] As a result of this science and research investment, FDA was able to respond to a critical shortage of Doxil (doxorubicin liposomal injection), an important drug used to treat cancer, by approving an abbreviated new drug application for a generic version of the product— the first generic liposome product— in 2013.

3. Competitive Intramural Funding Programs

To maximize its investment in intramural regulatory science programs, FDA and its medical product centers use a number of competitive intramural funding programs that offer reviewers and laboratory scientists competitive opportunities to address defined priorities. These programs include the Office of Women's Health Research and Development Program, Critical Path funding programs managed by the Centers, and the Medical Countermeasures initiative funding programs.

a. Office of Women's Health Research initiatives[18]

FDA's Office of Women's Health (OWH) established its Research and Development Program in 1994 to address gaps in current scientific knowledge, encourage new directions in research, and set new standards of excellence in women's health. To date, OWH has funded women's health research initiatives in a wide variety of areas, including cancer, HIV, osteoporosis, dietary supplements, dioxins, and statistical approaches to

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[16] Mitkusa, RJ, et al., 2011, Updated aluminum pharmacokinetics following infant exposures through diet and vaccination. Vaccine, 51:9538-43, available at http://www.sciencedirect.com/science/article/pii/S0264410X11015799.

[17] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf.

[18] For information on the OWH Research Program, visit: http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm171860.htm.

gender analysis. The results of this research have been published in over 170 articles in peer-reviewed journals.

Improving the assessment of a drug's effect on cardiac repolarization. Women have a higher risk for drug-induced serious irregular heart rhythms (QTc prolongation and torsades de pointes (TdP)) than men and investigation of the potential for one of these adverse drug effects (QTc-prolongation) is now a regulatory requirement for approval of pharmaceutical products. Research conducted at FDA contributed significantly to the development of the two international guidance documents for industry used for these investigations.

Improving representation of women in device clinical trials. Funding support and technical assistance was provided by OWH in the development of the draft guidance for industry and FDA staff *Evaluation of Sex Differences in Medical Device Clinical Studies*. OWH funding enabled FDA to conduct two key meetings with diverse groups of Agency, industry and academic experts to gain insight into strategies to improve the quality and consistency of available sex-specific data, which resulted in the draft guidance issued in December 2011. The guidance outlines FDA expectations regarding sex-specific patient enrollment, data analysis, and reporting of study information for medical devices and will strongly contribute to future health benefits for women, particularly in areas like heart disease, implantation, and prosthesis development.

Improving the efficacy and safety of implantable defibrillators. Defibrillators are essential tools in treating abnormal heart rhythms that cause sudden cardiac death, but these devices come with significant risks for some patients. The OWH is supporting research into methods to analyze electrocardiograms to predict which patients are most likely to benefit from implantable defibrillators, and identifying those that might be at increased risk. FDA researchers are investigating methods to optimize this approach so that it becomes an effective, non-invasive tool practical in routine clinical practice. Additional research efforts supported by the OWH have studied differences in myocardial scarring between men and women and the implications of these differences for prognosis of patients treated with defibrillators.

b. Critical Path Initiative

The Critical Path Initiative[19] is FDA's strategy for driving innovation in the way medical products are developed, evaluated, and manufactured. Launched in March 2004 to tackle the pipeline problem, the Initiative strives to narrow the gap between the number of

[19] For more information, please see: http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm.

discoveries occurring in biomedical science and technology and the declining number of new medical treatments submitted for FDA approval. The 2007 FDA Amendments Act authorized funding to support efforts to advance the development of tools needed to stimulate medical product development. The medical product centers have awarded funds to promising project proposals that have provided tangible benefits for medical product development and public health.

Better evaluation of treatments for lung cancer. Computed tomography (CT) imaging is increasingly used to evaluate the effect of lung cancer treatments, especially in terms of tumor size. FDA has produced a publicly available database of CT images of tumor nodules that investigators are using to assess how the settings on the CT machine affect tumor volume measurement. Ultimately, this effort promises to help device manufacturers create software will allow for more accurate estimates of tumor size and thus help physicians to better assess whether lung cancer therapies are working as they attempt to develop more effective treatments.[20]

Database for assessing potential drug interactions mediated by transporters. In the past decade, there has been an explosion in our understanding of membrane transporters, which are a class of proteins that transport a variety of molecules into or out of the cell, or in or out of the cell's internal compartments. These proteins play an important role in drug disposition and response. Having access to a single source containing the most current information on membrane transporters is critical for drug developers and drug reviewers. Working with scientists at the University of California at San Francisco, FDA reviewers created a single public database that reviewers can access to facilitate their reviews to identify possible influences of membrane transporters on the safety or efficacy of a drug.[21]

Improving the nation's blood supply. Increased complications, including high blood pressure and damage to blood vessels and kidneys, are associated with transfusion of whole blood that has been stored for an extended period of time. FDA scientists developed an animal model that showed that these complications are caused in part by release of hemoglobin (the protein in red blood cells that carries oxygen) when damaged transfused red blood cells break open in the circulation. They found that administering haptoglobin, a protein that binds strongly to released hemoglobin, during transfusion of

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[20] Gavrielides MA, et al., 2013, Benefit of Overlapping Reconstruction for Improving the Quantitative Assessment of CT Lung Nodule Volume. Acad Radiol, 20:173-80, available at http://www.sciencedirect.com/science/article/pii/S1076633212004709.

[21] Morrissey, KM, et al., 2012, The UCSF-FDA TransPortal: A Public Drug Transporter Database. Clin Pharmacol Ther, 92:545-6, available at http://www.nature.com/clpt/journal/v92/n5/full/clpt201244a.html.

old blood reduced these complications. This finding may be of great benefit to severely ill patients who must receive large amounts of blood.[22]

c. The Medical Countermeasures Initiative

FDA launched its Medical Countermeasures initiative (MCMi) in August 2010 to build on the its substantive ongoing work to foster MCM development. The goal of this initiative is to (1) promote the development of MCMs by establishing clear regulatory pathways; (2) establish effective regulatory policies and mechanisms to facilitate timely access to available MCMs; and (3) advance MCM regulatory science to create the data necessary to support regulatory decision-making. Under the MCMi, FDA has established a robust regulatory science program to address the unique and complex scientific challenges associated with MCM development and regulatory review.

Working Toward improved vaccines for influenza. An adjuvant is a component added to a vaccine that potentiates or enhances immune response. FDA researchers analyzed immune response in clinical samples derived from influenza vaccine trials using a novel, inexpensive oil-in-water adjuvant that increased the magnitude, duration, and diversity of antibody response, and the strength of antibody binding. An important implication of this research for public health is that inclusion of adjuvants allows for the use of lower concentrations of antigen (the vaccine component that triggers immune response) in vaccine formulations, or fewer vaccinations in an immunization schedule. This effectively increases vaccine supply allowing FDA to be better prepared for a pandemic threat.

Developing New technology to submit adverse events. FDA scientists collaborated to develop and release a "smartphone" software application or "app" for submitting adverse events for FDA-regulated products. The app makes it easier and faster for health care professionals, patients, and caregivers to send voluntary reports of medical device problems to FDA, compared with the traditional reporting methods (e.g., by mail, phone or online). FDA relies on reports of serious problems with medical devices and other products as one important way to help identify and better understand the risks associated with these products. Receiving higher quality reports more quickly helps FDA identify and respond to safety signals and public health emergencies more efficiently and effectively.

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[22] Baek, J.H., et al, 2012, Hemoglobin-driven pathophysiology is an in vivo consequence of the red blood cell storage lesion that can be attenuated in guinea pigs by haptoglobin therapy. The Journal of Clinical Investigation, 122: 1444-58, , summary: http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm326227.htm.

Ensuring the nation's supply of antiviral drugs. Oseltamivir is a common antiviral drug used to treat flu that is often stockpiled by public health authorities. FDA scientists tested oseltamivir tablets for their ability to withstand increased heat and humidity. The researchers found that the capsules packaged in blister packs lasted twice as long as those stored in bottles. These findings offer a means of improving the ability to store and transport the drug to ensure its availability in the event of a pandemic.

B. Scientific Exchange and Collaboration

We recognize that the scientific priorities and gaps identified previously cannot be addressed by FDA alone, or indeed by any single organization. The magnitude of the challenges often requires creative approaches to pooling and sharing data, expertise, and resources in a way that preserves interests and investments of the partners while developing the new publicly available knowledge to fuel innovation. The engagement of multiple stakeholders, from patient organizations to industry and academic scientists, is critical to ensure that the scope of the effort matches the scope of the problem and that all perspectives are brought to bear on defining the goals of the project.

Our scientists actively engage in scientific exchange and collaboration with outside entities and experts using a number of mechanisms: Public-Private Partnerships complement FDA efforts by bringing together multiple stakeholders from industry, academia, patient groups and government to address scientific hurdles in medical product development that require a broad, collective effort. . FDA medical product centers also have available to them a number of technology transfer agreement vehicles, including cooperative research and development awards (CRADAs), material transfer agreements (MTAs), and research collaborative agreements (RCAs). When the medical product centers have very specific regulatory science needs that cannot be addressed internally or through collaboration, they may issue contracts or grants that can leverage the appropriate expertise and facilities. Through these mechanisms for partnering, our research collaborations allow us to leverage the expertise of hundreds of scientists from around the world in academia, industry, patient organizations,and government.

1. Public-Private Partnerships

As authorized by Congress in the FDA Amendments Act of 2007, public-private partnerships (PPPs) enable collaborative efforts between the FDA, industry, and academia that are managed by non-profit neutral third parties to develop "innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product innovation, enabling the acceleration of medical product development,

manufacturing, and translational therapeutics, and enhancing medical product safety."[23] We engage with over a dozen PPPs that are addressing product development challenges ranging from identifying prognostic and safety biomarkers, to refining clinical trial designs, to developing and testing new patient reported outcomes. A few examples follow:

The Patient Reported Outcome (PRO) Consortium. The PRO Consortium is designed to develop, evaluate, and qualify PRO instruments for use in clinical trials. The consortium currently has working groups on advanced breast cancer, asthma, mild cognitive impairment, depression, functional dyspepsia, irritable bowel syndrome, non-small cell lung cancer, and rheumatoid arthritis.[24]

Critical Path to TB Drug Regimens (CPTR) Consortium. The Critical Path to TB Drug Regimens (CPTR) Consortium is a broad collaboration involving industry; government, regulator, and multilateral agencies; academia; civil society; advocates; and non-government organizations that is designed to accelerate the development of safe and highly effective tuberculosis treatment regimens.[25]

Medical Device Innovation Consortium. The Medical Device Innovation Consortium (MDIC) is a public-private partnership for medical device regulatory science to leverage the expertise and resources of industry, government, and non-profits to develop tools to drive innovation in medical device development.[26]

The Reagan-Udall Foundation. The Reagan-Udall Foundation was created by Congress to advance the mission of FDA by advancing regulatory science and research. Current efforts include the development of models that may lead to a better understanding of how drugs called tyrosine kinase inhibitors (a class of drugs shown to be effective treatments for various forms of cancer) lead to toxic effects on the heart and the advancement of the science and tools necessary to support postmarket evidence generation on regulated products.[27]

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[23] Section 566 of the Food, Drug, and Cosmetic Act, 21 U.S.C. 360bbb-5.

[24] Please see: http://c-path.org/PRO.cfm.

[25] Please see: http://c-path.org/CPTR.cfm.

[26] Please see: http://www.deviceconsortium.org/.

[27] Please see: http://www.reaganudall.org/.

2. *Direct Funding Mechanisms*

To meet specific regulatory science challenges that we do not have the internal expertise or facilities to address and are not of the appropriate scale to require PPPs, we may fund contracts or grants that target specific needs. Projects funded through one of the intramural programs listed above may include an extramural component funded by a contract or grant. Following are a few examples:

Developing New Bioequivalence Methods. Generic drugs must be shown to be bioequivalent to the brand- name or innovator drug. This typically involves studies to show that blood levels of the drug over time are the same for the generic and brand-name version. However, for drugs that have a local site of action – patches, creams or inhaled asthma medications for example – the efficacy of the drug may not be related to blood levels. We are funding clinical studies needed to establish new methods for assessing bioequivalence for locally acting drugs.

Fostering Innovative Approaches to Toxicology and Biomarker Development. As part of the Critical Path Initiative, FDA issued requests for proposals and then awarded several cooperative agreements to investigate biomarkers, explore alternative methods of preclinical assessment, and address key needs for drug development for tuberculosis. Currently funded projects are developing blood-based detection methods for biomarkers in patients with metastatic melanoma, devising an in vitro testing strategy to prioritize substances for potential developmental neurotoxicity, evaluating a proteomics-based biomarker to help in the management of neonatal disease, and developing improved in vitro models for male reproductive toxicity.

Centers of Excellence in Regulatory Science and Innovation. In 2011, FDA awarded cooperative agreements to the University of Maryland and Georgetown University to establish Centers of Excellence in Regulatory Science and Innovation.[28] Each institution has developed master's programs in regulatory science and offers professional development opportunities to university investigators and FDA staff. Research topics include drug-drug interactions, emerging medical device evaluations, safe drug use, modeling and bioinformatics, and issues around voluntary sharing of clinical data.

3. *Communicating our Results*

FDA review and laboratory scientists are actively engaged in addressing barriers to advancing regulatory science for medical products. We engage a wide variety of partners

[28] Please see: http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm301667.htm.

using a toolbox of collaborative mechanisms. Results of FDA regulatory science efforts are communicated to the scientific community through scientific publications, abstracts, and presentations. In 2012, scientists in FDA's medical product Centers contributed to well over 1500 peer-reviewed scientific publications, reviews, commentaries, regulatory summaries, abstracts, and presentations.[29]

[29] A searchable database of FDA publications and presentations is available at: http://www.accessdata.fda.gov/scripts/publications/.

IV. Adopting Advances in Regulatory Science for Medical Products

Adoption of new regulatory science occurs through a number of processes and programs that involve individual reviewers and scientists, Agency organizational units, and external stakeholders. The following is a compilation of the many ways FDA adopts regulatory science, grouped into three broad categories. This is not intended to be an exhaustive list, but exemplary.

A. Training and Professional Development

The scientific evaluation of regulatory applications starts with reviewers, who must evaluate the data and provide an expert interpretation of its meaning. Clearly, the quality of scientific review depends, in part, on reviewers' expertise and scientific knowledge. As new science becomes the basis of regulatory submissions, the knowledge and expertise of the review staff must also evolve. In addition, in their role of developing guidance for industry and in other kinds of regulatory decision-making, FDA staff must continually incorporate new scientific information. We provide training and professional development opportunities to ensure regulatory policy and decision-making is informed by the latest science.

FDA's medical product centers and the FDA Office of Scientific Professional Development all sponsor a number of training and professional development opportunities including:

- Courses in scientific disciplines needed for effective review that are offered in-house or through external partnerships with universities
- Seminars, rounds, and visiting lectureships that invite top scientific experts to lecture on recent developments, while providing them with opportunities to interact with staff in small groups[30]
- Experiential learning through a set of center-sponsored programs that incorporate site visits to industry R&D and manufacturing facilities, giving reviewers first-hand knowledge of emerging technologies and scientific approaches to product development (e.g., CBER has a Regulatory Site Visit Program in which its staff visit biologics facilities to learn about and observe biologics industry operations such as

[30] FDA staff who participate in these activities are eligible for continuing education or continuing medical education credits.

manufacturing, packaging, pathology/toxicology laboratory testing, or regulatory affairs operations[31])

- Attendance at professional and scientific meetings to learn about recent developments, and interact with top scientists from around the world

As time permits, reviewers may also be involved in professional development, for example by participating in laboratory research at FDA, clinical care, or clinical research at another institution. These activities keep scientific and clinical skills and knowledge up to date, which is important for interpretation of data. In addition to advancing regulatory science, participation in these projects sharpens reviewers' detailed knowledge of emerging science.

B. Integrating New Science into the Regulatory Process

The first stage of integrating new science into the regulatory process consists of evaluating the new knowledge and adapting it to regulatory purposes. For this stage we have mechanisms to receive and evaluate new types of data generated by emerging technologies and to determine its regulatory implications. We also engage in formal processes to solicit advice from external experts.

The second stage of the process consists of applying new science to the regulatory process. This stage begins as the level of scientific certainty surrounding a particular issue rises to a level that warrants application in a regulatory setting. Applying new science to the regulation of medical products may involve official guidance to industry, rulemaking, or other official communications to prescribers and patients. When new facts about regulated products that may affect medical use or safety become available, this new scientific understanding can be implemented through labeling changes, withdrawals, or other regulatory actions.

1. Evaluating and Adapting New Science for Regulatory Purposes

a. Advisory Committee general matter meetings

FDA has a number of formal Advisory Committees composed of scientific experts, consumer representatives, and industry representatives. For example, at the most general level within the Agency, the FDA Science Board, consisting of 21 authorities in areas

[31] This program is described at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079479.htm.

critical to the Agency's mission, provides advice to the Commissioner and other appropriate officials on specific complex scientific and technical issues and emerging issues within the scientific community. Although the public usually associates advisory committees with meetings to review and discuss the data supporting a specific product under review by the Agency, it is important to recognize that we also use these expert committees to seek input and advice on scientific questions that may have a bearing on general requirements for clinical trials, product manufacturing, product standards, or methods of analysis. When scientific findings developed by FDA, or in collaboration with external partners, are appropriate for integration into the regulatory framework, the scientific data and rationale for these changes are often discussed at a public advisory committee meeting, which provides us with critical independent scientific input from subject matter experts. A few topics of recent advisory committees are described below:

Clinical studies in children. In silico modeling and simulation that incorporates existing data with evolving knowledge about differences in the absorption, distribution, metabolism, excretion, and action of drugs between adults and children may offer insights to improve the design of clinical studies in children. FDA discussed the role of modeling and simulations, [32] including physiologically based pharmacokinetic modeling in pediatric drug development, with external experts at a 2012 meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.[33]

Restoring joint function in patients with chronic hip pain. Hip arthroplasty devices, including metal-on-metal (MoM) hip systems, are frequently used to relieve pain and restore joint function in patients with chronic hip pain or disease that is not responsive to more conservative therapy. . In addition to imposing postmarket surveillance orders for MOM hips, in 2012, FDA convened the Orthopaedic and Rehabilitation Devices Panel to discuss the current knowledge about the safety and effectiveness of Metal-on-Metal (MoM) hip arthroplasty systems. [34] FDA has since issued additional safety communications regarding MoM systems, and on January 17, 2013, issued a proposed order requiring PMA applications to market MoM systems.

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[32] Huang SM, et al.,The utility of modeling and simulation in drug development and regulatory review. J Pharm Sci, published online on May 24, 2013, available at http://onlinelibrary.wiley.com/doi/10.1002/jps.23570/full.

[33] Meeting agenda for March 14, 2012, meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM298460.pdf.

[34] FDA Executive Summary Memorandum: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM309302.pdf.

The use of cell lines from human tumors for vaccine manufacture. Historically, FDA has recommended that cell substrates used to manufacture vaccines should not be tumorigenic in animals. However, recent developments in cell biology and specific requirements pertaining to cells used to propagate certain candidate vaccines, for example, for HIV, dictated that FDA evaluate whether this position was supported by the most recent scientific evidence. FDA convened the Vaccines and Related Biological Products Advisory Committee to discuss and make recommendations regarding the appropriateness of cell lines derived from human tumors for vaccine manufacture.[35]

b. Formal processes that target the evaluation of new science

FDA scientists are uniquely positioned to identify emerging developments that pose regulatory challenges, and we have created formal programs to address these developments. For example, medical product marketing and licensing applications rely increasingly on a set of validated instruments to support claims of clinical benefit and safety (e.g., tests of cognitive function to assess whether a psychoactive drug is truly an improvement over a previous treatment, genetically defined animal models to predict a drug's toxicity, or predictive biomarkers and their associated diagnostic tests). Many of these biomarkers, endpoints, and diagnostic tests are made possible by recent advances in genomics, proteomics, and metabolomics. FDA responded to this trend by inaugurating the Voluntary eXploratory Data Submission Program.

The Voluntary eXploratory Data Submission (VXDS) Program is a Critical Path Initiative first created to facilitate scientific progress in genomics. We encourage developers of biomarkers to voluntarily submit data to FDA through this "safe harbor" mechanism to enable scientific discussions about emerging issues and technologies without a regulatory outcome for the therapeutic or device development program(s). When data are submitted, an interdisciplinary team of FDA scientists with expertise in evaluating biomarkers meet with submitters to analyze the information and provide insights into how the biomarker can be validated and integrated into a medical product development and made available to the wider scientific community. FDA has reviewed more than 50 submissions through the VXDS Program. The content of these submissions has ranged from the technical aspects of biomarker development, to logistical challenges related to data storage and transport.[36]

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[35] Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM326800.pdf.

[36] Goodsaid FM, et al., 2010, Voluntary exploratory data submissions to the US FDA and the EMA: experience and impact. Nat Rev Drug Discov, 9:435-45, available at http://www.nature.com/nrd/journal/v9/n6/full/nrd3116.html.

c. Workshops

Each year FDA convenes scores of workshops in which we invite scientific experts in the academic community, industry, other governmental agencies, and the general public to explore scientific developments that pose challenges for regulatory science. We list four recent workshops below as examples.

Identification and standardization of suitable biomarkers for drugs to treat acute myeloid leukemia. This is the third public workshop organized by the Office of Oncology and Hematology Products to discuss the use of flow cytometry and molecular methods to detect and measure minimal disease (MRD) and its potential as a biomarker of treatment response in leukemia patients (the other workshops addressed the use of MRD in chronic lymphocytic leukemia and acute lymphoblastic leukemia).

Application of Advances in Nucleic Acid and Protein Based Detection Methods to Multiplex Detection of Transfusion-Transmissible Agents and Blood Cell Antigens in Blood Donations. This workshop focused on research and development of multiplex assays and the use of these tests in blood donor screening and blood cell antigen typing.

Post-Approval Studies 2012 Workshop: Design, Methodology, and Role in Evidence Appraisal Throughout the Total Product Life Cycle. FDA organized this workshop, addressed to industry, clinical researchers and others, to address the design and use of postapproval studies for devices regulated under premarket approval regulations and discuss opportunities for innovative use of data generated in these studies.

Assuring the Safety and Effectiveness of Seizure, Cognitive Function, and TBI/Sports Concussion Diagnostic Devices. Neurodiagnostic devices have advanced rapidly to include many software algorithms, including some designed to diagnose neurologic and psychiatric disorders such as sports concussions, traumatic brain injury, Alzheimer's disease, Attention-Deficit/Hyperactivity Disorder, depression and seizures. FDA hosted this workshop to address ways to verify that these devices work as described for the intended patient population. The workshop also addressed the information the device should provide to users so they can understand the output from these devices and incorporate them effectively into clinical practice.

d. Working groups

Cross-Agency working groups and task forces are important means for adopting new advances in regulatory science and initiating innovative collaborative projects in research, education, and outreach for the purpose of fostering the development of safe and effective medical products. We describe three examples below.:

The Genomics Working Group. FDA is responding to the challenge to evaluate unprecedented amounts of genetic information generated by rapid advances in sequencing technologies. For example, scientists expect to review applications in which high-throughput sequencing is used to examine the full range of resistant variants of a viral pathogen after patients are treated with antiviral drugs. FDA will be evaluating the

sequencing devices used to generate whole genome sequence data that might be used for diagnosing human disease. In addition FDA anticipates that advanced sequencing technologies will be used to evaluate the safety of blood, vaccines, tissues, and cell and gene therapies, as well as raw materials and intermediates used to manufacture biologics. Convened in January of 2013, FDA's Genomics Working Group consists of FDA scientists working across the Agency, and with industry and other government agencies, including the NIH and the National Institute of Standards and Technology (NIST), to develop the information technology resources that will enable the Agency to receive, store, and analyze massive amounts of genetic sequence information as it evaluates new drugs and biologics. The group's initial goals are to inventory all existing activities that support acquisition and use of high-throughput sequencing data, identify gaps not currently addressed, and develop a strategic plan to coordinate use of resources and identify the new resources that are required. Additional groups within the Centers are working to develop policy to address this rapidly evolving area as it relates to the products they regulate.

The MicroArray Quality Control Project. Microarray-based technologies that allow simultaneous measurement of the expression of thousands of genes in biological samples are increasingly important for predicting clinical benefit and toxicity. An ongoing challenge has been to ensure reproducibility and comparability of data across the many different microarray platforms in use. The MicroArray Quality Control Project was initiated by FDA's National Center for Toxicological Research as a collaboration of six FDA centers, major providers of microarray platforms, the Environmental Protection Agency, NIST, academic laboratories, and other stakeholders. The initial efforts of the project focused on developing standards and quality controls for the microarray community, in part by making reference data sets and reference RNA samples available and establishing metrics for quality control. A second phase of the project has addressed factors influencing the reliability of genomic signatures to predict drug toxicity and clinical benefit. The project's accomplishments are documented in many recent publications by participating scientists.[37]

The Nanotechnology Task Force. A critical role of the Nanotechnology Task Force, which coordinates its activities with the National Nanotechnology Initiative, has been to ensure that FDA regulatory scientists—review staff, research staff, field staff, and regulatory policy staff—are equipped to deal with the introduction of nanoscale materials in drugs, biologics, ,food, cosmetics, devices and other products. FDA has sponsored several hands-on laboratory courses, some in collaboration with the National Cancer Institute's (NCI's) Nanotechnology Characterization Laboratory, to acquaint these key personnel with the latest developments in nanotechnology manufacturing processes and general principles of the interaction of these materials with biological systems. Through

[37] Please see:
http://www.fda.gov/ScienceResearch/BioinformaticsTools/MicroarrayQualityControlProject/default.htm

the Collaborative Opportunities for Research Excellence in Science (CORES) Program, the scientific research priorities identified by the task force, such as defining physicochemical characteristics of nanomaterials that affect potency and safety, the pharmacokinetics of products containing nanomaterials, and methods to assay their toxicity, are being addressed in the laboratory by FDA scientists and their collaborators in academia and other government agencies.

2. Applying New Science to the Regulatory Process

a. Development and updating of guidances and regulations

One mechanism for the adoption of new scientific information is its incorporation into new or revised guidance documents. These documents, which address every aspect of the development, evaluation, and approval of medical products, are typically issued in draft form and often revised based on comments from the public and industry before issuance as final guidances. They may be revised subsequently in response to new scientific developments or legislation. We provide examples below of how guidances issued by FDA can play a critical role in medical product decision-making.

Creating a pathway for accelerated approval of new cancer therapies. A fundamental problem in developing more effective therapies for cancer is the length of time needed to measure the clinical benefit of a new drug or biologic, and thus it can be of great value to identify endpoints that can be assessed relatively soon after treatment and reliably predict real improvement, e.g., increased survival. As clinical oncologists turned to new preoperative or neoadjuvant chemotherapies for women diagnosed with breast cancer, randomized clinical trials showed that those who had a favorable response to the therapy as evidenced by the post-surgical pathology findings had better outcomes than those who did not. Thus, this favorable response, generally known as "pathologic complete response" (pCR), had the potential to serve as a predictive biomarker. However, the lack of a standard definition for pCR interfered with its use in support of new drugs to treat breast cancer. Recently, based on evidence as to which features of response in the breast and lymphatics were important and taking into account recent developments in surgical practice, FDA issued a guidance for industry[38] that provides a standard definition of pCR that can be readily adopted by the drug development community as a reasonable surrogate endpoint that reviewers can evaluate in the context of an accelerated approval process.

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[38] FDA guidance for industry *Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf. In this guidance, we also specified the design of the trial that should be used to address the drug's efficacy in the preoperative setting, taking into account the fact that beneficial neoadjuvant treatments are already available, i.e., an add-on design in which the new preoperative treatment would be combined with the standard treatment followed by surgery and standard postoperative treatment.

Validation of diagnostic devices to detect biothreat agents. In 2012, FDA issued draft guidance[39] on highly multiplexed assays to detect and identify multiple pathogen nucleic acids in a single human specimen. With the advent of microarrays, multi-well, real-time PCR instruments, and robotics, it has become possible to run multiple assays on a given sample simultaneously. Although the new diagnostic devices may offer several advantages, validating performance with the confidence needed to inform clinical and public health decisions can pose significant scientific challenges. The draft guidance outlines recommendations for studies to establish analytical and performance characteristics relevant to obtaining clearance for highly multiplexed, nucleic acid-based diagnostic assays that are used in the diagnosis of infection, including infection by biothreat agents.

Bioequivalence recommendations for specific products. FDA's Office of Generic Drugs (OGD) maintains a guidance[40] that provides recommendations for demonstrating equivalence for individual products. This guidance currently contains recommendations for over 1,000 products and is updated quarterly. It allows OGD to rapidly communicate scientific advances in equivalence science to the industry. For example, in December 2012 a new bioequivalence study design for warfarin that accounts for its narrow therapeutic index was posted.[41]

The process of rulemaking can also play an important role in adopting advances in regulatory science as described in the following example.

Faster sterility testing of biologics. FDA previously required all parenteral biological products to undergo sterility testing using the compendial sterility method to ensure that products such as vaccines are safe when they reach the market. This method for testing was based on the observation of turbidity in liquid culture media due to the growth of microorganisms. However, the method takes 14 days, a duration that can be a significant limiting factor in the timely release of biological products, particularly for pandemic vaccines and products with short shelf lives. In recognition of new approaches to obtain proof of sterility FDA has conducted in-house studies comparing novel, rapid methods with existing compendial methods. These new approaches prompted the FDA to issue a final rule to revise parts 600, 610, and 680 of Title 21 of the Code of Federal Regulations, "Amendments to Sterility Test Requirements for Biological Products."[42] Among other

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[39] Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm327293.htm

[40] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[41] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf.

[42] 77 FR 26162, May 3, 2012.

things, the final rule encourages use of the most appropriate and state-of-the-art test methods for assuring the safety of biological products.

b. Actions prompted by new science: labeling changes, withdrawals and recalls

New developments in science that will have a direct impact on the safety or use of regulated products may lead to immediate and direct actions such as labeling changes, withdrawals, or recalls.

Labeling changes for statins. In 2012 FDA approved and mandated important labeling changes for the cholesterol-lowering drugs known as statins. Labels for these drugs were revised to remove the need for routine periodic monitoring of liver enzymes in patients taking this class of drugs. These changes were based on FDA's comprehensive review of its Adverse Event Reporting System (AERS) database. FDA concluded that serious liver injury with statin use is extremely rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes, rather than being effective in detecting or preventing serious liver injury, could motivate physicians to alter or discontinue statin therapy, thereby placing patients at increased risk for cardiovascular events.

Recall of defective needles. Adverse events associated with Huber needles were detected by FDA's Medical Product Safety Network (MedSun), a reporting program that works with the clinical community to identify and solve problems with the use of medical devices. These needles are used to access silicone ports implanted under the skin of chronically ill patients for repeated access to veins to withdraw blood and deliver medications. FDA developed reliable test methods to evaluate these products, and the field inspection reports revealed that the needles may cut and dislodge silicone slivers from the ports into which they are inserted, resulting in potential leakage and hazards to the patient. Based on this important safety finding, FDA issued a device safety communication and a Class I recall of more than 2 million Huber needles. The FDA-generated test methods are now being used by manufacturers during needle design and production. [43]

Voluntary Recall of immune globulin (IG). When increased adverse events associated with specific lots of immune globulin were detected, FDA researchers undertook an analysis of a large database of health data for instances of thrombotic events. The results showed varying degrees of risk associated with both IG products and methods of application. This analysis represents one of the first uses of a large administrative health database in a follow-up to adverse event reports.

c. Product-specific advisory committee meetings

Safety and effectiveness of an in-home HIV test. The Blood Products Advisory Committee (BPAC) reviewed the safety and effectiveness of the proposed OraQuick In-

[43] Information about FDA's regulation of Huber Needles is available at http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm198719.htm.

Home HIV Test of OraSure Technologies in May of 2012. This is the first over-the-counter (OTC) home-use HIV test kit and the only OTC home-use test kit available for an infectious agent. BPAC made recommendations on the performance expectations for OTC home-use HIV tests and provided input to the Agency on the safety and effectiveness of the OraQuick Kit based on its performance in Phase III clinical trials.

d. Formal processes for regulatory acceptance of emerging scientific developments

The Drug Development Tool (DDT) Qualification Program was created to provide a framework for development and regulatory acceptance of scientific tools, including biomarkers, clinical outcome assessments, and animal models, for use in drug and biologic development programs.[44] Many of the public-private partnerships in which FDA engages under the authority of the FD&C Act (see 21 U.S.C. 360bbb–5) are focused on the development of biomarkers and other drug development tools for qualification by FDA under this program. FDA scientists work with stakeholders to guide them as they develop or refine a drug development tool for a specific context of use and then rigorously evaluate the submission for approval for use in the regulatory process. FDA also actively encourages the formation of collaborative groups to undertake DDT qualification to increase efficiency of the development process and lessen the individual resource burdens. The validation and approval of drug development tools through the DDT Qualification Program streamlines the evaluation process for drugs, because new tools and measures do not need to go through repeated extensive approval processes in the context of each new drug application.

e. Consultations and collaborations with international bodies

The development, manufacture, testing, clinical evaluation, and regulatory review of medical products is a global enterprise. FDA continually engages with our international regulatory counterparts to work towards harmonizing our scientific standards and approaches for developing medical products, evaluating their safety and effectiveness, and overseeing their manufacture and quality, as illustrated by the following examples.

Establishing International Standards for Biologics. FDA has been a Pan American Health Organization (PAHO)/World Health Organization (WHO) Collaborating Center for Biological Standardization since 1998. It is currently in its fourth four-year term, which will run until February 2016. The current purpose, scope, and areas of activity in this collaboration include establishing physical (reference) standards for biologicals; developing written standards for biologicals; supporting implementation of biological standards by contributing to PAHO and WHO efforts to strengthen the regulatory

[44] Please see: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm.

capacity of National Regulatory Authorities; and contributing research activities that advance standardization for biologicals.

Centers of Excellence in Multi Regional Clinical Trials. The multi-regional clinical trial (MRCT) is the simultaneous conduct of a clinical trial in multiple geographical regions. MRCTs play a major role in providing patients with access to innovative new medicines and are an important driver of investment. FDA is proposing to cosponsor, with the Asia-Pacific Economic Cooperation (APEC), the establishment of a Regulatory Science Center of Excellence (COE) related to MRCTs. Located within an academic institution, the COE would partner with regulatory agencies, academia, industry, and other key stakeholders to develop and deliver an evolving curriculum that enhances regulators' scientific capacity and promotes convergence in the conduct and regulation of clinical trials.

C. Building Infrastructure to Enhance the Evaluation of Regulatory Submissions and Support Adoption of Emerging Science and Technology

Integration of new science and technology into regulatory processes requires continual enhancement of a scientific and technical infrastructure to enable effective and efficient analysis and interpretation. Better tools are needed to manage the growing amounts of data and information, both as a part of the review process and as part of the advancement of science. The current information infrastructure should keep pace with reviewer and researcher needs. For example, postmarket surveillance epidemiologists need to have ready access to the premarket clinical trial data. Therefore, one aspect of integrating new science into our regulatory process is to provide agency reviewers and research scientists with enhancements to equipment, software, and IT infrastructure to handle novel products and data.

1. Developing and/or integrating new data standards, and computer hardware and software tools for data receipt, analysis, evaluation, and visualization, to facilitate efficient, effective, and consistent review of complex data

The Janus Clinical Trials Repository (CTR) is a data warehouse application that supports automated extraction, transformation, loading, management, and reviewer access to standard clinical trials data. Serving as an integration hub for study data, the Janus CTR has been designed to accommodate evolving standards for clinical trials submissions. The CTR provides the infrastructure and functionality to develop and deliver a variety of useful "views" or visualizations of study data to support the regulatory review process and strengthen FDA's ability to analyze and respond to emerging safety issues. Development of the CTR involves (1) developing advanced software, hardware, and business processes for validating and loading data from a variety of sources; (2) creating a centralized database supported by software and hardware for storing standardized data in a way that supports data loading and retrieval; and (3) creating software, hardware, and business processes for analyzing the data in a way that supports review and further scientific research.

The DataFit program. Through multiple current ongoing data standards activities, FDA is developing the ability to effectively leverage standard data to advance the review process. This begins with the DataFit program, which enables FDA to rapidly assess, before filing, whether submitted standard data is fit for use. DataFit performs a detailed assessment of submitted data very early in the review process based on data requirements for identified review activities. Specifications from DataFit will be published to aid sponsors in understanding how to successfully prepare standard data for submission. In addition, other review tools are being implemented that will then take DataFit-cleared data and generate a large number of automated analyses. Finally, FDA is pilot testing the JumpStart program, which is designed to take high-quality standard data and deliver a large number of analyses, including data quality assessments, demographics, and safety signal detection.

The Nonclinical Information Management System (NIMS) is a software tool that incorporates a repository for nonclinical study data that the Agency receives for regulatory review and analytic, data visualization, search, and discovery capabilities in a single platform. NIMS, along with the advances in nonclinical data standards, is part of a transformation in nonclinical review that gives reviewers standard yet dynamic data views and capabilities. In addition to creating positive efficiency and effectiveness outcomes for individual reviews, the repository will allow for cross-study and cross-species analyses that will make possible research on, and improvement of, review science and safety prediction. NIMS and advances in standard data format are being supported with process changes and training.

The High-performance Integrated Virtual Environment (HIVE) is a cloud-based environment for storage and analysis of sequencing data generated using high-throughput technologies. The ability to transfer, analyze, and efficiently store these data will require development of data standards. FDA will hold a public workshop to engage other government agencies and stakeholders in developing these new data standards so that the Agency can advise sponsors on how to submit these data in regulatory submissions.

Medwatch Plus System. MedWatch is an online adverse event and reporting system that allows users to report to the Agency adverse events caused by medical products. Submitting a report is streamlined for members of the public and can be done by simply connecting to the Internet. MedWatch also provides comprehensive, up-to-date information on alerts, recalls, and labeling changes for drugs and devices. The data from the MedWatch system, along with adverse drug reaction reports from manufacturers, are part of a searchable public database.

The Sentinel Initiative, launched in 2008, is a proactive system that will complement systems FDA already has in place to track reports of adverse events linked to the use of its regulated products. The Sentinel System enables FDA to actively query diverse automated health care data holders—for example, electronic health record systems,

administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.[45]

2. Science and Research Infrastructure – Investments in Key Technologies to Prepare for Regulatory Evaluation of Innovative Medical Products and Enhance Evaluation of Existing Licensed Products

As complex new medical products that use emerging technologies like nanotechnology and complex delivery systems are developed, FDA's capabilities to evaluate and analyze them must also evolve. It is critical that we gain hands-on familiarity with the technologies needed to assess these products. Standards for products must be set, acceptable regulatory methods for assessing quality must be developed, and capabilities for analyzing product failures must be in place.

Critical core technologies. We are investing in such core scientific technologies as high-throughput sequencing, high-resolution nuclear magnetic resonance and mass spectrometry, multi-color flow cytometry, and ultra-high resolution confocal microscopy to support regulation of medical products. Access to these critical technologies allows our scientists to perform cutting-edge research using novel technologies that are or will be used by sponsors. Hands-on experience using novel technologies to assess innovative medical products is critical to science-based regulatory decisions and development of policy and guidance based on the best available science and technology.

Nanotechnology Core Facilities. FDA has two core nanotechnology facilities, one in Jefferson, Arkansas managed by the National Center for Toxicological Research and the Office of Regulatory Affairs, and the other in the CDRH Office of Science and Engineering Laboratories on the White Oak Campus in Silver Spring, Maryland. The NCTR-ORA Nanotechnology Core facility has been designed to meet two critical needs: (1) support toxicology studies on nanomaterials and (2) detect nanomaterials in FDA-regulated products. The White Oak facility has been designed to address: (1) physical and chemical characterization of nanomaterials that may be contained in FDA-regulated products; (2) detection and study of migration of nanomaterials in biological matrices; and (3) training of regulatory science staff in the use of characterization equipment.

Computational Modeling. Engineering analysis methods are needed to predict whether a proposed medical device design will function properly and safely. Computational modeling methods can help provide this information by integrating data from a variety of sources (animal, preclinical, and clinical). To facilitate the development of computational modeling, FDA engineers have established a high-performance computer facility to develop models for emerging device technologies. Other applications for use have already included high intensity focused ultrasound designs, deep brain stimulators,

[45] Please see: http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm.

optical diagnostic techniques, and bone densitometry methods. High-performance computing systems are critical in the development of public health simulation systems that can inform advisory committees and regulatory decision-makers of the potential range of effects in terms of benefits and risks of specific public health decisions.

V. Measuring Progress in Advancing and Adopting Regulatory Science

Identifying existing gaps in knowledge and molding those into FDA priorities provides a solid foundation for advancing regulatory science. However, implementation of effective efforts to address these knowledge gaps, then applying what was learned to improve regulatory standards, methods, tools, and capabilities is essential if we are to have the desired impact on public health and medical product development.

This section of our report, on metrics, describes the kind of information we will be providing in four progress reports on advancing regulatory science (each specific to a user fee agreement as requested under section 1124 of FDASIA). Each report will be incorporated into the corresponding user fee performance report.[46] Our goal for these progress reports is to document the progress in addressing priorities and gaps and adopting new science, and describe the link between advances in regulatory science and tangible improvements in regulatory processes and decisions. We will accomplish this by (1) reporting on advances in regulatory science related to the priorities and gaps delineated in section II, (2) explaining how these advances have been integrated into the regulatory process, and (3) describing the impact these advances have on the medical product development and review processes.

Scientific progress involves constant uncertainties and follows an unpredictable path; promising approaches may yield unexpected results that do not always provide the desired advances. As noted previously, significant hurdles in regulatory science remain, despite longstanding efforts to overcome them. Improvements tend to be incremental and ongoing, despite the fact that all our regulatory science and research objectives are tied to addressing identified knowledge gaps. As such, progress related to scientific advancement is best measured by its impact on advancing priorities and filling identified gaps, rather than by individual program measures of productivity. Ultimately, meaningful measures of progress are related to the integration of new science into the regulatory process and the impact this has on medical product development, regulatory review, postmarket safety, and public health.

In the four progress reports, progress will be assessed using two types of metrics.

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[46] The user fee performance reports, containing their respective progress reports, are to be submitted to Congress for fiscal years 2014 and 2016.

- Summary quantitative metrics

These metrics can provide an informative high-level overview that illustrates the extent of FDA engagement and productivity in advancing regulatory science. These include measuring accomplishments such as scientific publications, training opportunities, and workshops. Quantitative metrics alone, however, are not fully informative regarding the nature or degree of progress in addressing the priorities and gaps identifies in section II.

- A more detailed, descriptive enumeration of significant regulatory science activities and outcomes that specifically address priorities and gaps

This provides a more tangible picture of what the activities entail, as well as an understanding of both progress and impact. The descriptions will include a delineation of the regulatory science or public health need, a description of how the project or action addressed the problem, and a clear explanation of projected or actual outcome and impact on regulatory decision-making.

The metrics below follow the organization of the activities directed at advancing priorities, addressing gaps, and adopting new science found in sections III (activities that advance priorities and address gaps) and IV (activities to adopt new regulatory science) and indicate the information that will be included in each progress report. Note that the progress reports that will accompany each of the four user fee performance reports will address a different product area (drugs and biologics – PDUFA; generic drugs – GDUFA; biosimilars – BsUFA; and devices – MDUFA). As such, there may be metrics that have more relevance to particular product areas, so that information included in each report may vary, but will be drawn from the metrics included here.

A. Metrics for Advancing Regulatory Science

Activities that FDA undertakes to advance regulatory science priorities and fill key knowledge gaps are grouped into the two broad categories described in section III: the FDA's internal regulatory science activities and FDA's scientific exchange and collaborations.

1. Internal Regulatory Science Activities

FDA's medical product Centers engage in a wide range of internal regulatory science activities to address priorities and gaps. These efforts include laboratory-based and data-driven regulatory science research projects, a portion of which are funded through competitive programs targeted to priority areas. In addition, consensus around specific scientific questions is developed through the collaborative efforts of internal working

groups. Results of efforts to advance regulatory science are communicated through publications and presentations to the wider scientific community.

- Regulatory Science Programs and Projects (research, both laboratory and non-laboratory) that address the priorities and gaps identified in section II.

  Metrics:
  - We will illustrate the extent of FDA's scientific efforts to address the priorities and gaps described in this plan, and provide a quantitative summary of ongoing regulatory science programs or projects linked to the identified regulatory science gaps.
  - We will illustrate the extent of FDA's scientific productivity in addressing the priorities and gaps described in this plan and provide a quantitative summary of scientific publications that address the priorities and gaps.
  - We will provide a description of the most important regulatory science accomplishments as they relate to identified gaps. We will include explanations of (1) their significance for advancing regulatory science, (2) their impact on regulatory decision-making, and (3) their impact on the scientific community as evidenced by relevant peer-reviewed publications and other publicly available disseminations of the findings.

- Competitive awards made under intramural funding programs (e.g. Critical Path funding) that target priorities and gaps identified in section II.

  Metrics: To illustrate the progress and impact of Agency competitive intramural funding programs with respect to advancing regulatory science, we will provide a short description of each program's goals as they relate to the priorities and gaps described in this plan, and describe the impact of these programs and the projects that they fund.

2. Scientific Exchange and Collaborations to Advance Regulatory Science

Many of the challenges inherent in making significant progress in advancing regulatory science require resources, expertise, technical capabilities, and information beyond what is available to any single organization. Furthermore, because addressing specific gaps is a national priority that affects multiple stakeholders, getting diverse input on priorities and approaches is critical.

There are a variety of mechanisms FDA uses to engage our diverse stakeholders in collaborative projects aimed at addressing regulatory science knowledge gaps, and progress related to all of these will be included in our reports.

Metrics: We will enumerate and describe scientific activities that advance regulatory science priorities and address identified gaps that involve collaborative efforts with external organizations. These will include efforts involving public-private partnerships, foundations, academic and other non-profit institutions, government agencies, NGOs, or industry. For each activity, we will include information on the participating

organizations, purpose, and outcomes for that activity as they relate to the priorities and goals identified in section II.

B. Metrics for Adopting Regulatory Science

The promise of new scientific knowledge is its integration into the regulatory process to reduce uncertainty and improve consistency in regulatory decision-making. The goal is to improve public health outcomes and enhance the predictability of medical product development. Adoption of new regulatory science occurs through a number of processes and programs that involve individual reviewers and scientists, agency organizational units, and external stakeholders.

1. Scientific Training and Professional Development

For effective regulation, reviewers and other decision makers must consider the most current scientific information as part of the decision-making process. The numerous training and professional development opportunities described earlier in this plan are critical for ensuring that our front-line scientific staff keep pace with new developments.

> **Metric** – To illustrate the extent of FDA training opportunities as they relate to priorities and gaps identified in this report, we will enumerate and describe scientific training and professional development opportunities made available to FDA staff.

2. Integrating New Science into the Regulatory Process

FDA has developed a number of systematic processes for translating new knowledge into more effective regulation, some focused on evaluating new science with a view to adapting it for regulatory purposes, and others that are formal processes for regulatory adoption of new science. The goals of these efforts include enhanced scientific clarity and increased predictability for the medical product development process.

- **Processes that target the evaluation of new science**. FDA has a number of mechanisms, such as the Voluntary eXploratory Data Submissions (VXDS) process, that specifically target the evaluation of data with the goal of better understanding its utility in regulatory decision-making.

  Metric: We will enumerate and describe FDA processes and activities undertaken for the purpose of evaluating new science and data in consideration of how to apply it to regulatory decision-making. These should include processes for evaluating novel data, e.g., the VXDS process, workshops and working groups, and relevant advisory committee meetings focused on general matters. For each activity, we will include a description of the process and groups involved, the purpose, and the outcomes for that activity as they relate to integrating new science into regulatory decision-making.

- **Applying new science to the regulatory process**. Once scientific consensus around a particular regulatory gap has been developed and evaluated, FDA incorporates this new science into regulatory decision-making. There are a number of mechanisms to accomplish this as described in the following metric:

  Metric: We will enumerate and describe formal processes and resulting actions that demonstrate FDA adoption of scientific advances into regulatory processes. These should include guidance development, drug development tool qualification, product-specific advisory committee meetings, consultations with international regulators, regulatory actions such as labeling changes and withdrawals, and communications with health care professions and patients. For each type of activity, we will describe the major outcomes and include appropriate measures indicative of stakeholder impact.

3. Building Infrastructure to Evaluate Emerging Science and Technology

Integration of new science and technology into the regulatory processes requires that the infrastructure needed to enable effective and efficient analysis and interpretation of novel products and data be continually enhanced to provide agency reviewers and research scientists with needed enhancements to equipment, software, and IT infrastructure to evaluate novel products and data.

- **Data Standards and Software.** Developing and/or integrating new data standards and software tools for data receipt, analysis, evaluation, and visualization to facilitate efficient, effective and consistent review of complex data

  Metric: We will list and briefly describe significant new programs that include the development of data standards or reviewer software tools. Data that indicate progress in adoption of these tools and standards by reviewers and regulated industry will be included.

- **IT Hardware**. Investments in IT hardware for data receipt management and storage (e.g., next-generation sequencing data storage, transfer, and analysis)

  Metric: We will briefly describe significant new IT investments that enable improved receipt and storage of data while enhancing the effectiveness of data standards and software. We will include measures of impact on efficiency.

- **Research Infrastructure.** Investments in key novel technologies to support intramural regulatory science programs to prepare for regulatory evaluation of innovative medical products and to enhance evaluation tools available for existing licensed products

  Metric: We will list and briefly describe significant enhancements to the scientific infrastructure, including addition of emerging analytical technologies and how they strengthen the ability of the Agency to evaluate emerging technologies while improving its ability to respond rapidly to public health emergencies involving regulated products.