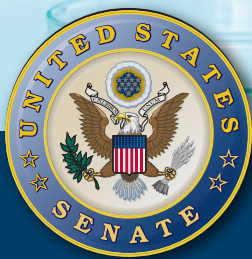


# Innovation for Healthier Americans

## *Identifying Opportunities for Meaningful Reform to Our Nation's Medical Product Discovery and Development*



A Report by Sen. Lamar Alexander (R-Tenn.)  
and Sen. Richard Burr (R-N.C.)

January 29, 2015

**A note to patients, doctors, researchers,  
innovators, and advocates:**

*Together, we can take important steps to ensure that America remains the world's leading global innovator in medicine, and in the process also ensure that our nation's patients have access to the most cutting-edge medical products in as timely a manner as possible.*

*- Senators Alexander and Burr*

# I

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## **II**

### **Foreword**

*Written by Dr. Andrew von Eschenbach*

History is marked largely by important scientific discoveries that radically change our understanding of the world around us, unlocking some of the most vexing mysteries that have faced humanity while irreversibly changing how we live. Gravity, electricity, X-rays, antibiotics, DNA and computers are just a very few examples of those earth-shattering revelations. In no sector of knowledge is that dynamic more dramatic than healthcare, as we are developing medical therapies and technologies to fight disease, save lives, and improve our quality of life in ways our ancestors could never have imagined.

Today, scientific advancements are rapidly expanding our knowledge of the living cell and the biology of human life. We are enhancing our knowledge about genetic and molecular origins and mechanisms that determine the progression of many important diseases. From the discovery of DNA to the mapping of the human genome, the quest to understand how and why individuals are susceptible to, experience, and resist disease is well underway. The future of “precision medicine”—in which we can successfully tailor therapies to specific patients to prevent, delay, manage, or cure certain diseases—is within reach. Today we stand on the precipice of what may prove to be the most impactful and groundbreaking discoveries in the history of healthcare. Before us lies an unprecedented opportunity and also a sobering responsibility.

Over time, our nation became the unquestioned global leader in medical innovation. Here in America, some of the brightest minds in the world have conducted research on, and advanced the development of, medical products that have delivered dramatic improvements in patient care and become a cornerstone of our nation’s economic stability and growth.

Unquestionably, government policy has played an important role in supporting public and private sector efforts that established America’s preeminence in research and development - providing resources, creating infrastructure, and removing barriers to unleash the singular power of our nation’s innovative spirit and indomitable work ethic. However, all too often, when our public policies are poorly aligned or fail to keep pace with progress in discovery and development, they can impede, instead of facilitate, the creation of urgently needed innovative therapies and technologies. As a consequence, progress slows in the delivery of medical interventions that can save or improve patients’ lives, the economic burden of acute and chronic disease increases, and our capacity to effectively protect our citizens from the full range of biological threats is diminished. Beyond the impact on our physical welfare, stifling domestic medical innovation undermines the economic viability of medical product development, deterring investment and destroying jobs.

Government policy can either inhibit or accelerate the next revolution in science and technology. The time has come to examine whether our nation has the right public policies in place to realize the full promise of the discovery, development and delivery of 21<sup>st</sup> century medicine. The opportunity and responsibility of this moment require strong, visionary and principled



leadership, and as this report demonstrates, Senator Alexander and Senator Burr have risen to the challenge. I salute their commitment to asking the hard questions and leading a thoughtful exploration of needed policy changes to refocus our nation in support of medical innovation. Fortunately they are not alone in this effort. I also commend Chairman Upton and Congresswoman DeGette for their work in the House of Representatives to enhance biomedical research and innovation through the Cures for the 21<sup>st</sup> Century Initiative.

“Innovation for Healthier Americans” is an important call to action, soliciting input and participation from the full universe of stakeholders interested and/or involved in medical innovation in America. It directs attention to the National Institutes of Health and the Food and Drug Administration, two prestigious federal institutions that remain vital to our health care ecosystem. Senator Alexander and Senator Burr pose an elegantly simple question: “How could they be even better?” It is the start of a dialogue to determine what policy changes Congress and the Executive Branch must make to reaffirm our undisputed global leadership in discovery, development, and delivery of new medical products.

I believe our objective here is clear: identifying and advancing specific steps to better align public policy to support medical innovation and patient access to new medicines and technologies. While not an exhaustive list, such concepts for Congressional consideration include:

- New strategies to attract the best and brightest minds to, and support them in careers researching and developing innovative medicines and technologies here in America;
- Creative new approaches to optimizing public and private financing of medical research;
- Effective public policies to facilitate the translation of basic research into the successful development of innovative products, including enhanced collaboration between public-sector, academic, and industry efforts;
- Modernized clinical trials and a more efficient and effective regulatory framework for medical products;
- A digital infrastructure that appropriately acquires, aggregates and analyzes the broad spectrum of data emerging from patient-focused modern medicines and technologies.

In order to accelerate and enhance the efficiency of our nation’s healthcare ecosystem – discovery, development, and delivery – all three of these core components must be well-coordinated, consistently evaluated, and effectively nurtured. Not everyone will agree on each specific detail of how we achieve these lofty goals. But it is critically important that diverse stakeholders respond to this report, engage in the HELP Committee’s process, and inform and achieve impactful policy solutions.

The task before us is difficult, but clear. The stakes have never been higher. The opportunities have never been greater. I encourage you to join Sen. Alexander and Sen. Burr, and all of their colleagues on the HELP Committee, on this important journey.

*During the course of his distinguished career, Dr. von Eschenbach has served as FDA Commissioner and the Director of the National Cancer Institute at NIH. Specializing in urologic oncology, he previously held a number of senior medical positions at the University of Texas M.D. Anderson Cancer Center. Dr. von Eschenbach is a three-time cancer survivor.*

### III

#### **Executive Summary**

*“We stand on the cusp of a revolution in health care. Advances in molecular medicine will allow us to develop powerful new treatments that can cure or even prevent diseases like Alzheimer's and cancer. Tomorrow's high-tech cures can also slash healthcare costs and eliminate ineffective treatments. **What will it take to realize the potential of the new medicine?**”*

*Andrew von Eschenbach, former FDA Commissioner, 2012<sup>1</sup>*

The federal government has been an enthusiastic investor in biomedical research for five decades. That investment has helped drive rapid innovation and bring us to a crossroads: Will we use what we have learned to transform the discovery and development of new drugs and medical devices, or will we maintain the status quo, depriving patients of cutting-edge products?

With the release of this report, the Senate Health, Education, Labor and Pensions (HELP) Committee is beginning an inclusive and transparent process to:

- Candidly assess the status quo: What works? What's not working? What can we do better?
- Identify how Congress can improve public policies to promote the efficiency and effectiveness of medical product development to cut down on the total time it takes for these products to get to American patients.
- Pass transformational legislation that the President can sign this year.

Every American is personally affected by the U.S. Food and Drug Administration (FDA) and National Institutes of Health (NIH). Anytime we take medicine, have a routine check-up, or undergo a serious procedure for a health problem, like surgery or cancer treatment, we are using medical products regulated by the FDA. In many cases, the research leading to the discovery and development of these products has been advanced, funded, or enabled in some way by the NIH.

These two agencies have an enormous influence on our economy. FDA-regulated products account for about 25 cents of every dollar spent by American consumers each year<sup>2</sup>.

For generations, America has led the world in medical innovation. The dedicated professionals at the NIH and FDA have helped to instill confidence in FDA-approved products. Scientists from across the globe take seriously the findings and caliber of research that NIH funds, as well as the safety and efficacy of products FDA approves.

But our global edge is slipping.

Medical discoveries and advancements to treat and cure diseases, including new targeted drugs, could, and should, be reaching American patients more quickly and with less cost to developers, without lessening the standards of safety and efficacy. Too many patients with no treatment options wait while potential treatments languish in laboratories awaiting further development, testing, and/or approval. At the same time, each additional \$1 billion spent on pharmaceutical

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<sup>1</sup> Von Eschenbach, D. (2012, February 14). Medical Innovation: How the U.S. Can Retain Its Lead. *Wall Street Journal*. Retrieved December 9, 2014, from <http://www.wsj.com/news/articles/SB10001424052970203646004577215403399350874?mg=reno64-wsj&url=http://online.wsj.com/article/SB10001424052970203646004577215403399350874.html>

<sup>2</sup> Executive Summary: Strategic Plan for Regulatory Science. (2013, January 16). Retrieved December 9, 2014, from <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268095.htm>

research and development results in fewer drugs than in years past.<sup>3</sup> The time and cost of developing medical products is increasing without a discussion of whether there is enough incremental assurance of safety and effectiveness for the additional delays and costs.

“But when the risks are higher, the costs and time required to develop and validate new products is higher too. Regulators are often more skeptical as well, and ask for more evidence to prove that medicines with novel mechanisms of action are safe and effective. As a result, on average it can take well over \$1 billion and about a decade to develop a single new medicine.

That trend is simply unsustainable given the rising disease burden of our aging society and the reality that we don’t have enough money – through program cuts or higher taxes – to pay for existing health care programs like Medicare without wrecking the rest of the economy.

Innovation is not optional. It is a national imperative.”

– Paul Howard, Ph.D., the Manhattan Institute’s Center for Medical Progress

Over the past several decades, FDA’s mission and regulatory reach has expanded dramatically. This has resulted in an increasingly complex bureaucracy while the science of discovery and development has evolved more rapidly than ever in academia and private industry. FDA has struggled to regulate the most cutting-edge medical products. The disparity between the pace of scientific discovery and development outside of the FDA and the pace of growth in FDA’s scientific knowledge threatens America’s position as a global leader in medical innovation.

FDA Commissioner, Dr. Margaret Hamburg, has acknowledged that “... we are left relying on the 20<sup>th</sup> century approaches for the review, approval and oversight of the treatments and cures of the 21<sup>st</sup> century.”<sup>4</sup> While the FDA has reviewed drugs in as little as three months, and meets the timelines set for medical device reviews the majority of the time, the inability of medical product developers to predict what questions will be asked during the review forces a multi-year

process simply to get an application ready for FDA consideration. This lack of predictability is driven by fast-changing and complex science, inefficient and inconsistent processes, and difficulty in hiring and retaining review staff and managers. This challenge will grow as new medical products and the clinical methods used to test them continue to evolve at an exciting pace.

This report aims to examine the current process of drug and device development and identify the inefficiencies that stand in the way of a modern development and review process. We take a close and honest look at what is, and is not, working well at the NIH and FDA. We want to know what successes we can replicate, and what failures must be learned from and fixed.

This report is organized to follow the process it examines—in other words it takes us from discovery to approval. We outline key problems, partnerships, initiatives, dollars, and data involved in helping to bring promising medical products through the research, development, and regulatory review process. We identify the challenges at the NIH and FDA—inefficiencies, unnecessary regulatory burden, a lack of predictability, and ever-increasing regulatory costs—that must be addressed. We identify ways to facilitate stakeholder engagement in these processes, and we intend to continue regular and responsible congressional oversight.

<sup>3</sup> CBO Federal Policies and Innovation, November 2014,

<sup>4</sup> Hamburg, M. (Director) (2010, October 6). Remarks as Delivered of Margaret A. Hamburg, M.D. *National Press Club Speaker Luncheon*. <http://www.fda.gov/NewsEvents/Speeches/ucm229195.htm>

Our goal is simple and ambitious – to work in a bipartisan way with members of the HELP Committee to align public policies to support accelerating medical innovation and patient access to important medicines and medical technologies.

Science has never held greater potential to improve the quality of life and outcomes for America's patients. In order to fully realize this exciting potential, we must identify, candidly assess, and confront existing factors that may be stifling efforts to innovate. We have identified five themes for this effort:

- 1) It costs too much to bring medical products through the pipeline to patients.**
- 2) As science and technology advance, the discovery and development process takes too long for medical products to make their way to patients.**
- 3) FDA's responsibilities have grown to include many activities unrelated to the core function of regulating medical products to advance the public health.**
- 4) The disparity in scientific knowledge at FDA and the fast pace of biomedical innovation are slowing, and in some cases, stifling, innovation in American medicine.**
- 5) A working FDA is essential to continuing biomedical innovation in the United States and maintaining America's global leadership in medical innovation.**

For us to succeed, we need your help. The full spectrum of stakeholders here is incredibly large and diverse, so it may be challenging to identify specific challenges and/or best practices that would have wide-ranging impact. We wish to solicit ideas on how to address these challenges in order to inform action in the 114<sup>th</sup> Congress. This report and the feedback we receive in response to it will inform what we expect will become a bipartisan legislative package to address the challenges we identify through this process. Please send your ideas to us at [Innovation@help.senate.gov](mailto:Innovation@help.senate.gov) not later than February 23, 2015. These comments will be shared with Ranking Member Patty Murray and all of our colleagues on the HELP Committee as we work to achieve this important goal.

## IV

### **Introduction: It Takes Too Long and Costs Too Much to Develop Medical Products for American Patients**

*“Today’s revolution in biomedical science has raised new hope for the prevention, treatment, and cure of severe illnesses. However, there is a growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients. **This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly.**” – FDA Critical Path Report, 2004*

A decade ago, in the wake of the mapping of the human genome, the FDA issued a strong warning that increasing challenges to medical product development, if left unaddressed, would jeopardize our nation’s ability to realize the full potential presented by modern-day medical advances for American patients.

But today, more than a decade after this urgent wake-up call, medical products take more time and money to discover, develop, and reach American patients than ever before. It has never been more difficult to bring a therapy through the development pipeline. The average cost to get a drug approved by the FDA is much disputed—some say \$1 billion or as much as \$2 billion, some say even more—but there is no disputing that the costs have grown over time.<sup>5</sup> Figure 1 below shows the number of drugs that get FDA approval for every \$1 billion of research and development spending. That approval trend continues to go down, and has since 1950. A similar story emerges in the medical device development, where it takes \$31 million to bring to market a low-to-moderate risk device and \$75 million for a higher-risk device.<sup>6</sup>

But these costs only tell part of the story. The amount of time it takes to receive approval also has a cost. A lengthy approval process not only slows down the product under review; it keeps resources, researchers, doctors, providers—from moving onto the next treatment or investigational therapy. Patients in the U.S. wait longer than those outside the U.S. for cutting-edge medical devices. In 2011, the report, *Competitiveness and Regulation: The FDA and the Future of America’s Biomedical Industry*, found that complex medical devices approved in the U.S. were available to patients in Europe on average four years earlier than in the U.S.<sup>7</sup> While the U.S. is spending more and more to develop new drugs and devices, this increased investment is not translating to quicker development of medical products for U.S. patients. The U.S. is spending more and more to do less.

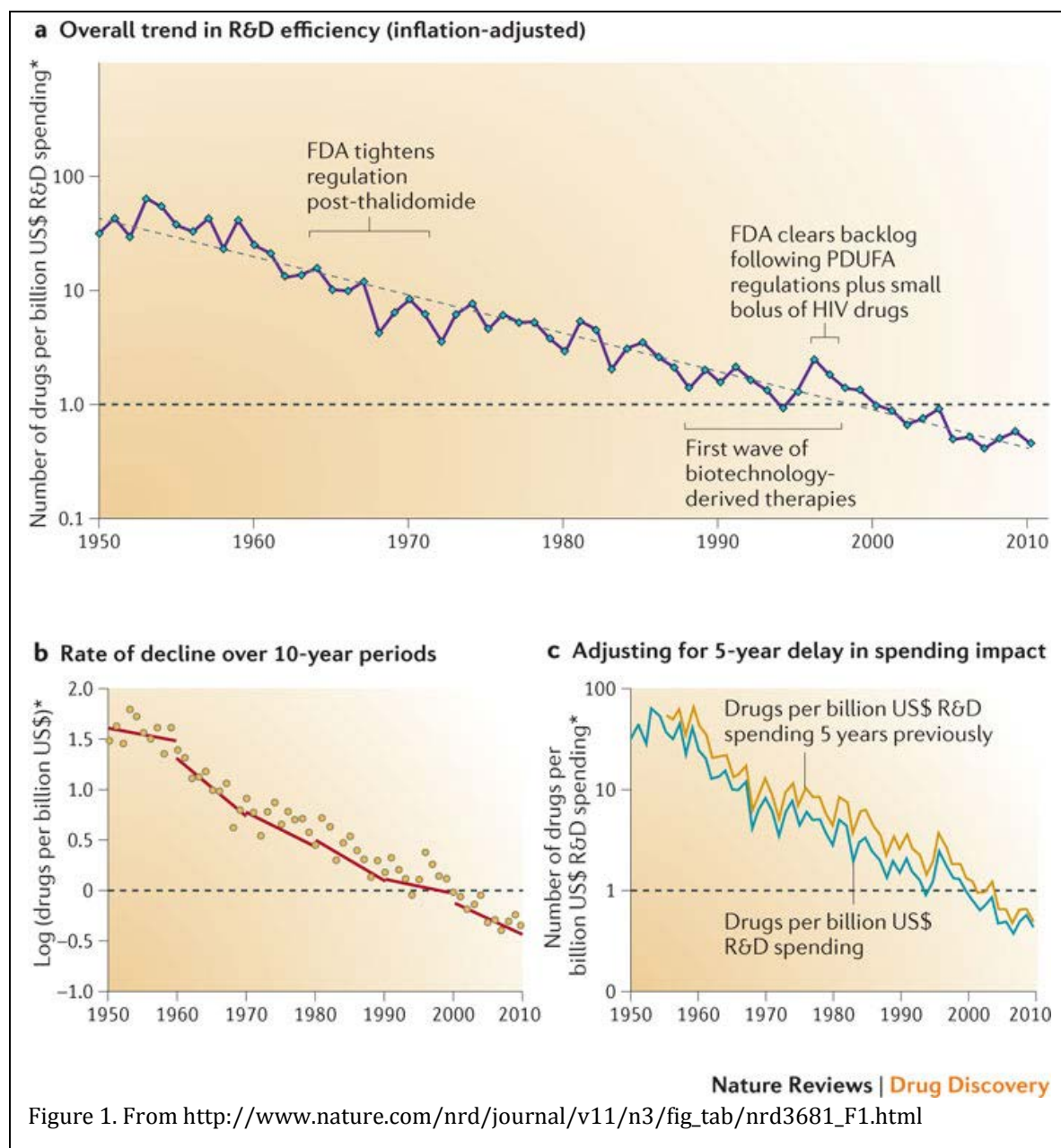
Additionally, we have seen how the venture capital community shifts investments away from drugs and devices as a result of increasing regulatory burden and uncertainty. In 2011, the National Venture Capital Association issued a report confirming that U.S. venture capitalists are reducing their investment in biotechnology and medical device companies and shifting focus overseas to

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<sup>5</sup> Cost to Develop and Win Marketing Approval for a New Drug Is \$2.6 Billion. (2014, November 18). Retrieved December 9, 2014, from [http://csdd.tufts.edu/news/complete\\_story/pr\\_tufts\\_csdd\\_2014\\_cost\\_study](http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study)

<sup>6</sup> Makower, J., Meer, A., & Denend, L. (2010, November 1). FDA Impact on U.S. Medical Technology Innovation: A Survey of Over 200 Medical Device Companies. Retrieved December 9, 2014, from <http://advamed.org/res.download/30>

<sup>7</sup> [http://www.chi.org/uploadedFiles/Industry\\_at\\_a\\_glance/Competitiveness\\_and\\_Regulation\\_The\\_Future\\_of\\_America's\\_Biomedical\\_Industry.pdf](http://www.chi.org/uploadedFiles/Industry_at_a_glance/Competitiveness_and_Regulation_The_Future_of_America's_Biomedical_Industry.pdf)



Europe and Asia, primarily due to regulatory obstacles at the FDA.<sup>8</sup> This report warned of significant adverse effects for U.S. patients and our economy if these concerns are left unaddressed. The implications of these trends are both clear and severe: promising medical therapies and technologies will not be funded, and therefore will not reach patients that need them, and will place the U. S. leadership position in medical innovation in further danger and hamper economic growth.

<sup>8</sup> National Venture Capital Association, & Medical Innovation and Competitiveness Coalition. (2011, October 1). NVCA MedIC Releases Vital Signs Report. Retrieved December 9, 2014, from <http://nvcaccess.nvca.org/index.php/topics/public-policy/245-nvca-medic-releases-vital-signs-report.html>

This is not a new problem. In 1997, Congress passed the FDA Modernization Act (FDAMA), the first significant reform of the agency in a generation. FDAMA aimed at making sure the FDA had the tools it needed to keep pace with modern scientific advances. FDAMA set forth clear pathways for innovative products to reach patients in the most timely and least burdensome manner possible, while meeting the FDA's standards. Congress again tried to address this issue with the FDA Safety and Innovation Act (FDASIA) in 2012.

Unfortunately, many of the challenges FDAMA and FDASIA were intended to mitigate remain today. Just as before FDAMA, Congress, patients, researchers, innovators, and health professionals struggle to ensure that the FDA is equipped with, and is consistently and appropriately applying, the most up-to-date tools necessary to regulate medical products, today and in the future. These challenges have only increased as our understanding of diseases has improved and we have learned how to better target and customize individualized treatments.

**These trends raise important questions about how we got to this point and where we go from here:**

- **How do we ensure that America's patients benefit from and that we preserve our global leadership in medical innovation?**
- **How are the federal government's actions, including legislation and regulation, and inaction contributing to the challenges that impede timely access to cutting-edge products for too many Americans?**
- **What resources have been spent, and where? How can limited resources be utilized in the most efficient manner, what are the most opportune strategic initiatives and how do they get decided?**
- **What are the appropriate metrics to evaluate the numerous initiatives, including countless public-private partnerships, aimed at helping to get medical products to patients in as timely a manner as possible? Have these programs achieved their intended results? What should the policies be moving forward? What should we be measuring for success and accountability?**
- **How do we ensure that appropriate congressional oversight of NIH and FDA produce better metrics on the federal government's efforts to advance new medical products, including oversight of the medical product development pathways for drugs, devices, and diagnostics?**



## V

### **From Bench to Bedside: The Role of Basic Research in New Medical Products**

*“The need for enhanced collaboration between NIH and FDA has never been more pressing, given new scientific opportunities in translational research, new public health challenges, far-reaching economic changes at the national and global level, and the prospect of fundamental changes to the U.S.*

*healthcare system. The [NIH] and the [FDA] share a common goal of advancing public health by promoting the translation of basic and clinical research findings into medical products and therapies. The agencies are complementary in their roles and functions—NIH supports and conducts biomedical and behavioral research and FDA ensures the safety and effectiveness of medical and other products.” -*

*-FDA-NIH Joint Leadership Council Charter<sup>9</sup>*

Early-stage research is high-risk--prone to high failure rates--making it less attractive to industry investment or undertaking, but these basic research findings form the foundation of the biomedical research continuum.<sup>10</sup> NIH plays a vital role in its support of basic research, and the agency represents about half of federal spending for non-Department of Defense research and development, and approximately one-fifth of total federal research and development spending.<sup>11</sup> NIH has grown dramatically over the years from its beginnings as a one-room laboratory established in 1887 for research on cholera and other infectious diseases to the leading source of funding for biomedical and behavioral research in the world today and a major driver of economic growth and innovation.<sup>12</sup> NIH has supported ground-breaking research, from fighting infectious diseases such as Ebola to the mapping of the human genome, and continues to fund a range of basic, clinical, and translational research with the \$30.311 billion appropriated in FY2015.<sup>13</sup>

The vast majority, over 80 percent, of NIH dollars are invested in extramural research, awarded through the peer review process to more than 300,000 scientists at more than 2,500 research institutions (predominantly academic research universities) in every state and around the world. Approximately 11 percent of NIH funding is allotted for intramural research, awarded to approximately 6,000 scientists at most of the 27 different institutes and centers (ICs) at NIH.<sup>14,15</sup> Academic researchers, funded by grants from the federal government--as well as state and local governments, industry and the research institution itself-- conduct basic research, much of which provides the basis for drug and vaccine candidates that are then transferred to industry for development.

Currently, academic research institutions rely predominantly upon grants from the federal government (60 percent) and institutional funds (20 percent) with modest support from industry (6 percent)<sup>16</sup>. This current funding framework leaves an enormous capacity for growth in support

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<sup>9</sup> <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm201654.htm>

<sup>10</sup> [http://smrb.od.nih.gov/documents/reports/VOBR%20SMRB\\_Report\\_2014.pdf](http://smrb.od.nih.gov/documents/reports/VOBR%20SMRB_Report_2014.pdf)

<sup>11</sup> <http://www.crs.gov/pages/Reports.aspx?PRODCODE=R41705&Source=search>

<sup>12</sup> <http://www.nih.gov/about/history.htm>

<sup>13</sup> <http://www.crs.gov/pages/Reports.aspx?PRODCODE=R43341&source=MyCrs>

<sup>14</sup> CRS Report R43304, [Public Health Service Agencies: Overview and Funding](#), coordinated by Amalia K. Corby-Edwards and C. Stephen Redhead.

<sup>15</sup> <http://irp.nih.gov/about-us/organization-and-leadership>

<sup>16</sup> <http://fas.org/sgp/crs/misc/R41895.pdf>



from non-government entities and opportunities for far greater partnership and collaboration between academic research institutions, industry, patient groups, and other stakeholders. NIH funding accounts for approximately two-thirds of all university research funding,<sup>17</sup> and over half of basic research is performed by research universities.<sup>18</sup> After years of decline, private sector investment in basic research has risen recently, but the federal government remains the largest supporter of this area of research.<sup>19</sup> Industry remains the largest supporter of development and applied research.<sup>20</sup> Identifying ways to encourage and facilitate enhanced collaboration between government and non-government entities to support important research will be critical to advancing novel therapies and ensuring America's continued global leadership in medical innovation.

It is difficult to quantify the value of NIH-supported research and track it through the entirety of the research continuum, as research findings could result in anything from generating broadly applicable new scientific knowledge, informing application of this knowledge in a clinical setting, or eventually resulting in an actual product used in patient care. While in some cases there is a clear connection between the research NIH supports and an identified outcome, such as the Human Genome Project, often the basic and clinical discoveries supported by NIH emerge through a variety of pathways.

### **What tools has Congress given NIH to support research to improve health?**

Over the course of 120 years and through various statutory changes, the National Institutes of Health as we know it has taken shape. The last reauthorization, the National Institutes of Health Reform Act of 2006 (PL 109-482) included several key changes to provide the NIH with increased flexibility to execute and support innovative research and provided the Director of NIH with greater oversight authority in order to improve coordination at NIH's 27 ICs. The agency's authorization expired in FY2009.<sup>21</sup>

Even prior to the NIH Reform Act, leaders at NIH recognized the need to be flexible enough in the agency's support of research to recognize larger scientific challenges or obstacles that transcend disciplines and ICs. NIH's response, the "NIH Roadmap," provided an opportunity for the director and institutes' directors to meet with each other as well as outside researchers, the private sector, and others to identify priority areas for research. The NIH Reform Act established the Common Fund, shown in Figure 2, in the Office of the Director to support this

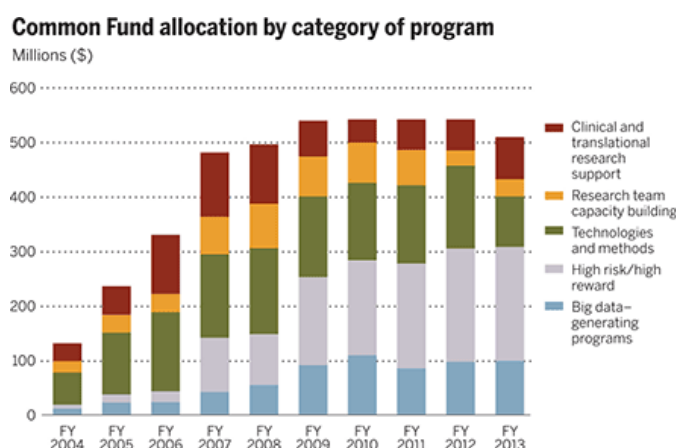


Figure 2: Common Fund Allocations

<http://www.sciencemag.org/content/345/6194/27>

<sup>17</sup> <http://nih.gov/about/budget.htm#note>

<sup>18</sup> <http://fas.org/sgp/crs/misc/R41895.pdf>

<sup>19</sup> <http://www.nsf.gov/statistics/seind14/content/digest/nsb1402.pdf>

<sup>20</sup> [www.nsf.gov/statistics/seind14/content/digest/nsb1402.pdf](http://www.nsf.gov/statistics/seind14/content/digest/nsb1402.pdf)

<sup>21</sup> "NIH and FDA one pager 7.7"

effort and to identify and provide a means of supporting these coordinated, transdisciplinary efforts in areas of emerging scientific opportunity and public health challenges.<sup>22,23</sup>

Roadmap/Common Fund programs have created innovative tools and technologies, such as light-controlled neural activity or “optogenetics,” a product of Common Fund Pioneer and New Innovator Awards; developed publically available large data sets, such as those for the human epigenome; and encouraged risk-taking through the high-risk, high-reward program also known as the “Pioneer Awards,” which funds proven innovators to conduct research in entirely new directions and high-impact areas.

The Clinical and Translational Science Awards (CTSA) program, established in 2006, is administered by the National Center for Advancing Translational Sciences (NCATS), and supports a national consortium of 62 research institutions that work together to accelerate scientific discovery along the entire research spectrum, from basic science to clinical practice.<sup>24,25</sup>

The NIH Office of the Director coordinates priorities across all of the NIH, but each of NIH’s 27 institutes and centers have their own research missions. There may be opportunities missed to coordinate among these centers.

### **What are some of the challenges faced by the NIH and researchers in sustaining early stage research?**

As shown in Figure 3, even with a budget of more than \$30 billion, the purchasing power for the NIH has declined. Between 1998 and 2003, the base budget of the NIH was doubled from \$13.7 billion to \$27.1 billion<sup>26</sup>. Since then funding has hovered around \$30 billion, with the NIH receiving modest decreases or increases. At the same time, other countries around the globe are increasing their respective investments in biomedical research.<sup>27,28,29</sup>

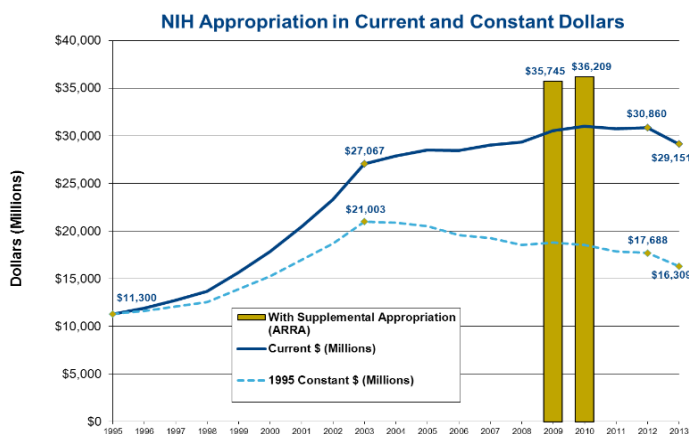


Figure 3: NIH Appropriations  
[https://www.ssr.org/sites/ssr.org/files/uploads/attachments/node/216/2.\\_nih\\_grant\\_data\\_1\\_13\\_14\\_faseb\\_board2.pdf](https://www.ssr.org/sites/ssr.org/files/uploads/attachments/node/216/2._nih_grant_data_1_13_14_faseb_board2.pdf)

This is not a new phenomenon. In “A Short History of the National Institutes of Health,” NIH

<sup>22</sup> Collins, Zerhouni, Wilder “NIH Roadmap/Common Fund at 10 years”. [www.sciencemag.org](http://www.sciencemag.org)

<sup>23</sup> [http://officeofbudget.od.nih.gov/pdfs/FY15/FY2015\\_Overview.pdf](http://officeofbudget.od.nih.gov/pdfs/FY15/FY2015_Overview.pdf)

<sup>24</sup> <http://www.ncats.nih.gov/research/cts/cts.html>

<sup>25</sup> NCATS, 2012-2013 Report

<sup>26</sup> <http://www.crs.gov/pages/Reports.aspx?PRODCODE=R43341&Source=search>

<sup>27</sup> [NIH Global Investment fact sheet](http://www2.itif.org/2012-leadership-in-decline.pdf)

<sup>28</sup> <http://www2.itif.org/2012-leadership-in-decline.pdf>

<sup>29</sup> <http://www.sciencemag.org/content/345/6194/274/F1.expansion.html>

historian Victoria A. Harden, Ph.D., reflects: “Toward the end of the 1960s, the growth of NIH budgets slowed considerably, in part because of inflation in the U.S. economy and the advent of new programs such as Medicare and Medicaid that competed for congressional ‘health’ funding.”<sup>30</sup> This problem persists today, with increasing entitlement spending critically impeding our ability to appropriately prioritize funding for critical research that saves and improves lives.

Many researchers have cited concerns about the increased competition for grants and its impact on the riskiness of the research proposed. The success rate for research project grants was approximately 18 percent in FY2014, whereas the success rates hovered around 30 percent from FYs1998-2003.<sup>31,32</sup> It has hovered around 20 percent or lower since then.<sup>33</sup> Alberts et al, commented that “hypercompetition for the resources and positions that are required to conduct science suppresses the creativity, cooperation, risk-taking, and the original thinking required to make fundamental discoveries.”<sup>34</sup> The NIH has recognized this issue, and through the Common Fund, has been able to fund a high-risk high-reward program to support four types of awards for “exceptionally creative and innovative scientists... who propose highly innovative approaches.”<sup>35</sup>

Additionally, the research community is becoming increasingly concerned that lower success rates for grants and other factors will drive young investigators away from the research field. Some have also said that the doubling of the NIH’s budget has helped build an educational pipeline that produces more scientists than there are positions in academia, government, and the private sector. A couple of ways to examine the state of biomedical research in the U.S. is to look at trends in the percentage of new investigators being awarded NIH Research Project Grants (called an R01) and the average age at which these researchers are awarded their first R01. The average age of an investigator’s initial research project grant has increased since 2001 for MDs and MD/PhDs, while the average age of PhDs has stayed about the same.<sup>36,37</sup> In 2006, approximately 24 percent of all competing R01s went to new investigators. By 2010, the number awarded to new investigators was up to nearly 32 percent.<sup>38</sup>

It is not just securing the first grant award that is a challenge for investigators. The NIH has identified the renewal of that first award as an area in need of increased focus in the context of retaining scientists in research. The agency is addressing this issue by using existing authorities to take into consideration the career stage of the applicant through an Early Stage Investigator Designation and to initiate new award mechanisms, such as the National Cancer Institute’s Outstanding Investigator award.<sup>39</sup> With Early Stage Investigators, the agency identifies new investigators who completed their research degree or medical residency within the last ten years, but have not been awarded a substantial, competing NIH research grant, and designates them as Early Stage Investigators.<sup>40</sup> This is taken into consideration at the time of review and award of the R01 for which the researcher applied. Additionally, through the Common Fund, the NIH Director

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<sup>30</sup> [http://history.nih.gov/exhibits/history/docs/page\\_09.html](http://history.nih.gov/exhibits/history/docs/page_09.html)

<sup>31</sup> [http://report.nih.gov/success\\_rates/](http://report.nih.gov/success_rates/) (#11 under Research Project Grants)

<sup>32</sup> <http://report.nih.gov/NIHDatabook/Charts/Default.aspx?showm=Y&chartId=124&catId=13>

<sup>33</sup> <http://report.nih.gov/NIHDatabook/Charts/Default.aspx?showm=Y&chartId=124&catId=13>

<sup>34</sup> Alberts, B, Kirschner, MW, Tilghman S, Varmus H- “Rescuing US biomedical research from its systemic flaws”, [www.pnas.org](http://www.pnas.org)

<sup>35</sup> [http://officeofbudget.od.nih.gov/pdfs/FY15/FY2015\\_Overview.pdf](http://officeofbudget.od.nih.gov/pdfs/FY15/FY2015_Overview.pdf)

<sup>36</sup> <http://www.grants.nih.gov/grants/funding/r01.htm>

<sup>37</sup> [http://grants.nih.gov/grants/new\\_investigators/index.htm](http://grants.nih.gov/grants/new_investigators/index.htm) (average age link)

<sup>38</sup> Ibid

<sup>39</sup> <http://nexus.od.nih.gov/all/2014/10/28/retention-of-first-time-r01-awardees/>

<sup>40</sup> [http://grants.nih.gov/grants/new\\_investigators/investigator\\_policies\\_faqs.htm#2649](http://grants.nih.gov/grants/new_investigators/investigator_policies_faqs.htm#2649)

established the Early Independence Award to give exceptional scientists early in their careers a way to move into independent research positions by skipping the traditional post-doctoral training period.<sup>41</sup>

### **How do discoveries make it to clinical testing? When they do not – why not?**

Dr. Collins, Director of the NIH, wrote in the 2013 NIH Director's Report that, "Drugs exist for only about 250 of the more than 4,400 conditions with defined molecular causes. And it takes far too long and far too much money to get a new drug into our medicine cabinets. This is an old problem that cries out for new and creative solutions."<sup>42</sup> Since then, the number of conditions with defined molecular causes has increased to 5,389, yet the number of new drugs approved has not kept pace with these discoveries.<sup>43</sup>

There are many other promising candidates that are unable to move beyond animal studies and into the clinic for human testing. These vaccine and drug candidates frequently languish on the shelves of academic research institutions, industry, or elsewhere, with scientific or economic challenges too great to warrant further investment and study until the candidates can be seen as less risky to develop with limited resources.

#### **The Importance of Medical Countermeasures:**

The Ebola outbreak underscores why our nation must be prepared for the full range of chemical, biological, radiological, and nuclear threats we may face, whether naturally occurring, like the Ebola outbreak, or man-made. Medical countermeasures, both vaccines and drug therapeutics, are necessary to protect the American people from the full range of these serious threat agents-- they are a key part of our national security and we must be forward thinking in this area.

Congress created the *Biomedical Advanced Research and Development Authority (BARDA)* to strengthen the public private partnerships that are critical for helping biodefense innovators bridge the advanced research and development "valley of death" for these products because of the unique challenges medical countermeasures face in their development, such as having to rely upon animal models in cases in which human efficacy trials would not be appropriate.

Ensuring FDA is prepared to regulate cutting edge products, including medical countermeasures, is key for making sure that we are prepared with the drugs and vaccines we may need to protect the American people from the most serious threats as well as the most common and costly conditions. BARDA is helping to advance innovations that transcend disease and product spaces. We should fully leverage the innovations NIH, BARDA, and FDA have brought to their medical countermeasure work and apply them more broadly as applicable.

Further narrowing the pipeline, 80 percent of drugs that make it into the clinic for human trials are never approved, and therefore never commercially available to American patients. Over 30 percent of pharmaceuticals fail in human clinical trials because they are determined to be toxic.<sup>44</sup> We have

<sup>41</sup> <http://commonfund.nih.gov/earlyindependence/index>

<sup>42</sup> Collins, Francis, MD, PhD Report of the Director, National Institutes of Health Fiscal Years 2010 & 2011, page 10.

<sup>43</sup> <http://omim.org/statistics/geneMap>

<sup>44</sup> Austin CP, Colvis CA, Innovation in Therapeutics Development at the NCATS, *Neuropsychopharmacology Reviews* (2014) 39, 230-232

known for decades that being able to identify and eliminate unsafe and ineffective candidates earlier in the process could save the research and development system precious money and time. However, many of the preclinical problems remain unsolved because it will not benefit one person or company to invest in solving these problems that would then benefit the entire development enterprise. While many public and private consortia and partnerships are working on solving some of these development challenges, inefficiencies still remain. There are many preclinical challenges that, if solved or even partially solved, would broadly benefit all stakeholders by enabling earlier and more accurate predictions on why some drugs, devices, and diagnostics either will not work or are unsafe before they advance to testing in humans.

To address these issues, the federal government and others have established many programs, consortia, studies, and efforts to try to decrease the rate of failure seen in medical product development work on areas where there are shared challenges.

While not an exhaustive list, some examples of activities to address barriers and challenges facing research and development include the following:

- **Predictive toxicology and efficacy:** We need to improve our ability to predict which new therapeutics will have adverse effects or be ineffective in humans earlier in the process.
  - NCATS Tissue Chip for Drug Screening program, a collaborative effort with other ICs, FDA, and the Defense Advanced Research Projects Agency (DARPA), seeks to develop 3-D human tissue chips that model the structure and functions of human organs.<sup>45,46</sup>
  - Toxicology in the 21<sup>st</sup> Century (Tox21) is a collaborative effort with the National Toxicology Program at the National Institute of Environmental Health Sciences at the NIH, and the Environmental Protection Agency to improve our understanding of the effects of drugs and environmental chemicals on human pathways in order to allow screening- and computation-based predictions of toxicity.<sup>47</sup>
- **Biomarkers:** The NIH and FDA have been working to identify biomarkers to help make drug development more efficient. The identification of biomarkers for certain diseases is critical to accelerating the development of products for the prevention, diagnosis, and treatment of those diseases. The Biomarkers Consortium, a public-private partnership organized by the Foundation for NIH in 2006, seeks to discover, develop, and qualify biological markers to support new drug development and improve diagnosis of disease. The Consortium focuses on biomarkers for cancer, immunity and inflammation, metabolic disorders, and neuroscience. The consortium also launched [L-SPY2 trial](#) in 2010, which hopes to change the way clinical trials are conducted to use the same

*"The main causes of failure in the clinic include safety problems and lack of effectiveness: inability to predict these failures before human testing or early in clinical trials dramatically escalates costs. For example, a 10 percent improvement in predicting failures before clinical trials could save \$100 million in development costs per drug." – FDA Critical Path Report, 2004*

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<sup>45</sup> Austin CP, Colvis CA, Innovation in Therapeutics Development at the NCATS, *Neuropsychopharmacology Reviews* (2014) 39, 230-232

<sup>46</sup> NCATS report 2012-2013

<sup>47</sup> Austin CP, Colvis CA, Innovation in Therapeutics Development at the NCATS, *Neuropsychopharmacology Reviews* (2014) 39, 230-232



infrastructure to test different therapies.

- In early 2014, the NIH announced the **Accelerating Medicines Partnership (AMP)**, a joint \$230 million venture between the NIH, 10 biopharmaceutical companies, and 12 non-profit organizations. AMP launched pilot projects to characterize biomarkers and identify biological targets most likely to respond to new therapeutics for Alzheimer's disease, type 2 diabetes, and autoimmune disorders of rheumatoid arthritis and systemic lupus erythematosus.<sup>48</sup>
- **Patient recruitment:** Enrollment of eligible patients in clinical trials can add time and cost to the research and development process, and many sponsors fail to meet recruitment and retention goals.<sup>49</sup>
  - Disease registries sponsored by governmental agencies, nonprofit organizations, health care facilities, and private companies provide a way for patients with a specific disease to signal their potential willingness to participate in research on that disease.<sup>50</sup>
  - CTSA developed ResearchMate, a secure national registry that connects people who are looking for research studies with researchers at no cost.<sup>51</sup>
  - The Clinical Trials Transformation Initiative (CTTI), hosted by Duke University and with a cooperative agreement from FDA, is working to identify solutions to barriers to recruitment and retention of patients in clinical trials.

#### *National Center for Advancing Translational Sciences (NCATS)*

NCATS, the newest center at the NIH, was established to focus on these problem areas to discover new technologies and other approaches to improve the overall efficiency of biomedical research and development from basic research through FDA approval, called “translational research.” For example, NCATS works with industry, academia, and the FDA to discover new uses of FDA-approved drugs and look at some of the systemic reasons drugs and devices take so long to develop from both a scientific and operational translational perspective. Many programs at NCATS deal with preclinical translational science and seek to tackle the problems that have been identified as obstacles or barriers to improving innovation.

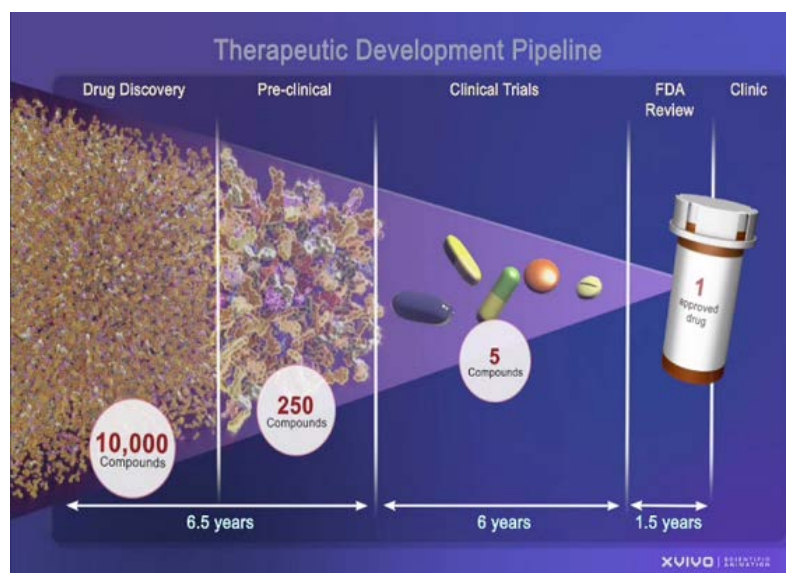


Figure 4: The Drug Development Pipeline

<http://www.ncats.nih.gov/research/reengineering/process.html>

<sup>48</sup> <http://www.nih.gov/science/amp/index.htm>

<sup>49</sup> <http://www.ctti-clinicaltrials.org/what-we-do/study-start/recruitment-retention>

<sup>50</sup> <http://www.nih.gov/health/clinicaltrials/registries.htm>

<sup>51</sup> NCATS Report 2012-2013

NCATS also has a program to assist investigators in conducting key pre-clinical studies needed for regulatory approval of first-in-human trials and to support Investigational New Drug applications to the FDA. This program, Bridging Interventional Development Gaps (BrIDGs), supported 23 projects in 2012 and 2013, when it was just getting underway.<sup>52</sup> Figure 4 illustrates the complications of the drug development pathway and why we must research ways to improve the efficiency of this process.

### *Critical Path Institute*

The Critical Path Institute is an independent, non-profit organization founded in 2005, which brings together scientists from the FDA, industry, and the NIH to improve the drug development and regulatory process. The institute created the Predictive Safety Testing Consortium to identify and test new drug safety testing methods, which then can be submitted for formal qualification by the FDA, European Medicines Agency, and the Japanese Pharmaceutical and Medical Devices Agency.

### **Where do we go from here?**

As these and other initiatives work towards an improved and more efficient biomedical research enterprise, we must ask hard questions about what can be done to keep the U.S. on the forefront of innovation and create an environment that is even more conducive to scientific discovery and medical product development:

- **As we study “whole pathways, organ systems, or even entire organisms rather than limiting the research to a single aspect of cell biology or physiology,” are our research institutions similarly changing to reach across those respective research missions in order to coordinate research agendas, leverage resources, and facilitate scientific discovery?**<sup>53</sup>
- **What do we need to do to ensure that we are fully leveraging the explosion of knowledge of human health and disease across all sectors of discovery and development to continuously improve health and reduce illness?**
- **Are there specific existing regulations, policies, or statutes that are impeding the ability of the NIH to support ground-breaking, research? Are additional authorities necessary to help the NIH achieve this objective?**
- **How can we improve the appropriate sharing of data and information and enhance the impact of our biomedical research dollars?**
- **What can we do to ensure that the scientific advancement and new regulatory tools resulting from our investments in research through the NIH are fully leveraged by the FDA when reviewing medical products?**
- **How can further testing of promising therapeutic and vaccine candidates after preclinical testing be encouraged to ensure patients benefit from these new technologies as soon as possible?**
- **Should scientists with NIH funding (where appropriate) be encouraged to frame their findings in language that meets FDA standards?**

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<sup>52</sup> NCATS report 2012-2013

<sup>53</sup> Report of the Director, National Institutes of Health Fiscal Years 2010 & 2011

## VI

### **Opportunities to Improve Clinical Trials**

*“There is also an urgent need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses. The NIH is addressing very important clinical research infrastructure in its Roadmap initiative, and FDA is collaborating in the Roadmap efforts. In addition, much more attention and creativity need to be applied to disease-specific trial design and endpoints intended to evaluate the effects of medical products.” – FDA Critical Path Report, 2004*

Clinical trials are an increasingly expensive undertaking.<sup>54</sup> Research into the timeline of drug development shows that of the approximately \$48.5 billion spent on pharmaceutical research and development annually by industry, 40 percent is spent on Phase III clinical trials.<sup>55</sup> In terms of medical devices, where device manufacturers historically relied on post-market surveillance, regulators increasingly demand time-consuming clinical data before devices can be approved.<sup>56</sup> To ensure that the best medical products reach patients in a timely and cost-effective way, the clinical trial enterprise should be reassessed, and if necessary, reimagined.

The issues facing clinical trials—spiraling costs, high failure rates, administrative inefficiencies, the rise of precision medicine, and regulatory hurdles—are not new. These challenges have been repeatedly identified, including in the 2004 Critical Path report<sup>57</sup>, the work of the Institute of Medicine’s Forum on Drug Discovery, Development, and Translation<sup>58</sup> dating back to 2008, and the 2012 Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation.<sup>59</sup> There have been some significant efforts made to resolve these challenges over the past decade, but more remains to be done.

*“The enormous cost and risk of Phase III trials create incentives for researchers and investors to avoid work on medications for the chronic conditions and illnesses that pose the greatest threat to Americans, in terms of health spending and in terms of the number of people affected. This avoidance, in turn, harms overall U.S. health outcomes and drives up the cost of health care.” - Avik Roy, Senior Fellow, Manhattan Institute for Policy Research, 2012*

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<sup>54</sup> [http://csdd.tufts.edu/news/complete\\_story/pr\\_tufts\\_csdd\\_2014\\_cost\\_study](http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study).

<sup>55</sup> <http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf> (for the R&D amounts) and Manhattan Institute for the 40% figure.

<sup>56</sup> Makower, J., Meer, A., & Denend, L. (2010, November 1). FDA Impact on U.S. Medical Technology Innovation: A Survey of Over 200 Medical Device Companies. Retrieved December 9, 2014, from <http://advamed.org/res.download/30>

<sup>57</sup> <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf>

<sup>58</sup> <http://www.iom.edu/Reports.aspx?Activity={6C3E4E12-EE9F-4AA6-A99F-74FDB40D9BF7}>

<sup>59</sup> <http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf>



## **Clinical Trial Administration**

The current approach to clinical trials leads to administrative inefficiencies, which in turn increase the time and costs associated with conducting clinical trials.<sup>60</sup> Often each entity involved in the clinical trial process, whether an academic research institution involved in an early Phase I trial or an innovator sponsoring a Phase III clinical trial, tends to conduct much if not all of this clinical trial work in a silo. As each entity involved in clinical trials employs its own approach to clinical trial processes and data collection, it results in an inconsistent and less coordinated approach to the trials and the data that emerge from them. In response, the medical product industry, government agencies, and non-profit disease and patient groups have focused resources on improving the

### **Innovate for Success in ALS: Prize4Life**

In 2006, Prize4Life hosted a conference to identify the obstacles to treating and curing amyotrophic lateral sclerosis (ALS)—a lack of a biomarker, predictive models, and understanding of the disease mechanism. In response, Prize4Life organized targeted challenges with a monetary prize to catalyze research and development of biomarkers, predictive models, and treatments. These challenges harnessed new ideas and disciplines to improve the prognosis and lives of ALS patients and their families.

- In 2011, Dr. Seward Rutkove won the biomarker prize. His approach—which may have applications for diseases beyond ALS—has the potential to reduce Phase II clinical trials by more than 50 percent.
- In 2012, two teams won the prediction prize. Using de-identified clinical trial data, teams designed algorithms that used clinical indicators available in the first three months of data to predict disease progression over the next nine months. Both models outperformed seasoned ALS clinicians in predicting disease progression. With better tools to predict how the disease will progress in a particular patient, physicians are better equipped to care for their patients, and, with predictive tools able to create homogenous clinical trial populations from the start, patient enrollment could be reduced 20-25 percent.

<http://www.prize4life.org/page/4071>; [http://www.prize4life.org/page/prediction\\_faq](http://www.prize4life.org/page/prediction_faq)

administration of clinical trials. Their efforts have looked to address key issues like requirements for multiple Institutional Review Board approvals for multiple trial sites, challenges in patient recruitment for clinical trials, and inefficient data collection and monitoring.

Many initiatives and partnerships have arisen seeking to streamline clinical trials processes and foster innovative approaches to clinical trial design that more closely reflect medicine today and in the future. For example, through Transcelerate BioPharma, drug and device companies come together to streamline the administrative requirements of trials. To date, the group's efforts have focused on setting standards for data collection, site qualification, and investigator training.<sup>61</sup> Transcelerate also has identified new approaches for risk-based monitoring to ensure that patients are monitored for safety and data in the most efficient and effective way. The goal is to monitor trials so that any serious adverse effects of investigational drugs can be seen quickly and possibly prevented.

<sup>60</sup> <http://www.raps.org/regulatoryDetail.aspx?id=7749>

<sup>61</sup> <http://www.transceleratebiopharmainc.com/our-initiatives/>

The Critical Path Institute also has made headway in bringing together stakeholders to define data standards and streamline clinical trials.<sup>62</sup> Through CTTI, the FDA partnered with Duke University to evaluate the way clinical trials are conducted and develop practical tools to improve the process nationally.<sup>63</sup> The Clinical Data Interchange Standards Consortium (CDISC) has developed a standard set of data that should be tracked in clinical development and also a way to track that data. For example, CDISC aims to standardize the way that data like gender or blood pressure are recorded in clinical data. These standards are used in Europe, Japan, and elsewhere, and the FDA plans to require them starting in 2016.<sup>64</sup> Patient-Centered Outcomes Research Institute (PCORI), however, uses alternate standards. Lastly, the NIH has multiple programs through NCATS and its ICs that seek to develop and coordinate national consortia of researchers, so clinical trials can get started sooner.<sup>65</sup>

Additionally, NIH supports a plethora of clinical trial networks to increase patient engagement and involvement with clinical trials. Patient groups have themselves become more savvy and involved in clinical trials, becoming invaluable partners that accelerate patient identification and enrollment in clinical trials. Through these and other examples, we can see the promise of more efficient clinical trials, but the promise has not yet been realized. Currently, efforts are duplicated, best practices are not shared, and transformative innovations are not scaled up.

### **Regulatory Barriers to Efficient and Streamlined Clinical Trials**

FDA requires “adequate and well-controlled” clinical trials to demonstrate that a particular intervention shows “substantial evidence of effectiveness.”<sup>66</sup> Although FDA has considerable latitude to define what constitutes “substantial evidence,” the agency relies on the traditional three phases of clinical trials for proof of safety and efficacy. Over time, these trials have become increasingly time-consuming and complex.<sup>67</sup> Inefficiencies also have developed that increase the time and expense of conducting these clinical trials before making medical products available to

### ***Existing Clinical Trial Networks***

The NIH and many other stakeholders have established, and funded, many clinical trial networks with the goal of finding improved therapies and cures for a range of disease and disorders. Some examples include:

- [Pediatric Trials Network](#)
- [Multiple Myeloma Research Foundation](#)
- [Antibiotic Resistance Leadership Group](#)
- [HIV/AIDS Clinical Trials Network](#)
- [Rare Diseases Clinical Research Network](#)
- [NIH Stroke Trials Networks](#)
- [Undiagnosed Diseases Networks](#)
- [Lysosomal Diseases Network](#)
- [NIDA Clinical Trials Network](#)
- [Clinical and Translational Science Awards Consortium](#)
- [NCI National Clinical Trials Network Program](#)
- [Heart Failure Clinical Research Initiative](#)
- [Autism Clinical Trials Network](#)

<sup>62</sup> <http://c-path.org/programs/cfast/>

<sup>63</sup> <http://www.ctti-clinicaltrials.org/>

<sup>64</sup>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>

<sup>65</sup> <http://www.ncats.nih.gov/research/cts/ctsa/ctsa.html>

<sup>66</sup> Kefauver-Harris Amendments

<sup>67</sup> [http://www.manhattan-institute.org/pdf/fda\\_05.pdf](http://www.manhattan-institute.org/pdf/fda_05.pdf) (From 1999 to 2005, the length of clinical trials increased 70 percent and the number of procedures per trial increased by 67 percent.)

American patients. Some of this inefficiency stems from unpredictable and inconsistent development requirement standards of the FDA review process. When sponsors cannot anticipate with certainty the information that an FDA reviewer will request, they design clinical trials that are unnecessarily expansive. Although described more completely in the following chapter, it bears repeating that efforts to improve regulatory science must be incorporated into all medical product discovery, translation, and development—including clinical trials—in a predictable and consistent manner across the FDA. The chart below in Figure 5, while five years old, shows the trend of increasing complexity and length of clinical trials.

Function	1999	2005	Percent Change
Median procedures per trial protocol (e.g., blood work, routine exams, x-rays, etc.)	96	158	65%
Average clinical trial staff work burden, work-effort units	21	35	67%
Average length of clinical trial, days	460	780	70%
Clinical trial participant enrollment rate (% of volunteers meeting trial criteria)	75%	59%	-21%
Clinical trial participant retention rate (% of participants completing trial)	69%	48%	-30%

Source: Tufts Center for the Study of Drug Development, Impact Report 10, No. 1 (2008)

Figure 5: <http://csdd.tufts.edu/files/uploads/02 - jan 15, 2008 - protocol design - final.pdf>

The typical design of a Phase III clinical trial, with its need for a large sample size, is not necessarily responsive to today's advanced understanding of medicine and the changing needs of the biomedical industry. With improved knowledge of the molecular progression of disease and decreasing costs of genomic sequencing, personalized medicine demands responsive and flexible clinical trial designs.<sup>68</sup> Furthermore, the dramatic rise in computing power allows for advanced statistical modeling with the potential to reshape clinical trials.<sup>69</sup> Such clinical trial designs have the potential to reduce costs and bring treatments and cures to patients faster. There are already examples of complex adaptive clinical trials—Lung-MAP, I-SPY I and II, and CoMMpass—but they remain the exception, not the rule.<sup>70,71,72</sup> In order to fully capitalize on the promise of precision medicine, the regulatory system must not only have the imagination and competencies to navigate and assess new clinical trial designs, but a willingness to incorporate this science into its standards for review.

There is widespread agreement that flexibility in the design of clinical trials has the potential to accelerate medical product development and reduce costs. For example, as part of the most recent drug user fee agreement, FDA and biopharmaceutical industry agreed to greater communication

<sup>68</sup> <http://www.ncbi.nlm.nih.gov/pubmed/24794084>

<sup>69</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3657986/>

<sup>70</sup> <http://www.cancer.gov/newscenter/newsfromnci/2014/LungMAPlaunch>

<sup>71</sup> <http://ispy2.org/about>

<sup>72</sup> <http://www.themmr.org/research-partners/the-commpass-study/>

early in the drug review process to establish the goals of clinical trials.<sup>73</sup> In addition, in establishing regulatory pathways to reduce the time it takes to develop and review promising drugs, Congress built in requirements for increased engagement between FDA reviewers and sponsors to accelerate access to critical treatments.<sup>74</sup> However, the impact of these provisions remains unclear as it has not been long enough to have the data necessary to make an informed analysis. We do not know yet if this enhanced access and communication actually is translating into therapies and cures reaching patients more quickly. The FDA also has undertaken efforts to clarify how to use novel trial designs for regulatory approvals, but these efforts have fallen short. Although published in 2010, FDA's guidance for industry on adaptive design clinical trials remains in draft form and is not being implemented.<sup>75</sup> Additionally, in December 2012, FDA released guidance on enrichment strategies for clinical trials; however, this guidance also remains in draft form.<sup>76</sup> These strategies, when they are embraced, have been adopted inconsistently across FDA review divisions. While industry stakeholders very much welcomed these guidances, their comments reflected a desire for more details and certainty.<sup>77</sup> Unfortunately, it does not appear novel methods are being accepted based on the content of these drafts, but rather FDA is codifying its current 20<sup>th</sup> century methods.

A more flexible and responsive approach to the role and timing of clinical trials in the approval process could reduce the costs in terms of both the time and money it is taking to get treatments and cures to patients. This approach is used under existing accelerated approval pathways for orphan drugs. As a result, Phase III clinical trials for orphan drugs require a median trial size of only 528 patients rather than 2,234 for non-orphan drugs, and cost about half as much.<sup>78</sup>

Beyond pharmaceuticals, increasing demands for clinical data in medical device reviews drives up costs and delays patients' access to these devices. In some instances, the data may be necessary, but there needs to be an understanding of how much certainty is required regarding a drug or device and if the delay in patient access is worth the increased certainty. Historically, FDA has relied on a combination of risk-classification and post-market surveillance, limiting the use of clinical data in device approvals to those devices that pose the highest risk of potential harm to patients in an attempt to balance these potential risks with a market-driven and predictable regulatory environment.<sup>79;80</sup> More recently, however, FDA has demanded more large-scale clinical data during the pre-market approval process.<sup>81</sup> Furthermore, there is regulatory uncertainty in how to shape clinical trials, leaving device developers having to negotiate with regulators about issues like

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<sup>73</sup> <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>

<sup>74</sup> [http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief\\_id=115](http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=115)

<sup>75</sup> <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf>

<sup>76</sup> [www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf)

<sup>77</sup> <http://www.outsourcing-pharma.com/Clinical-Development/Big-Pharma-Seeks-More-Examples-in-FDA-s-Trial-Enrichment-Strategy-Draft-Guidance>; <https://www.bio.org/advocacy/letters/enrichment-strategies-bio-submits-comments-fda-draft-guidance-enrichment-strategies>;

<https://www.bio.org/sites/default/files/20100527a.pdf>

<sup>78</sup> <http://www.healthreformwatch.com/2014/03/06/clinical-trials-of-primary-care-drugs-could-smaller-be-better/>

<sup>79</sup> Makower, J., Meer, A., & Denend, L. (2010, November 1). FDA Impact on U.S. Medical Technology Innovation: A Survey of Over 200 Medical Device Companies. Retrieved December 9, 2014, from <http://advamed.org/res.download/30>)

<sup>80</sup> Ibid.

<sup>81</sup> Ibid.

efficacy and safety endpoints, statistical techniques, and trial size.<sup>82</sup> This has the effect of driving up costs and increasing timelines with scant evidence of improved outcomes for patients.<sup>83</sup>

Today, clinical trials are used to demonstrate safety and effectiveness to the FDA. Given the dynamic changes in the understanding of medicine and disease and in the tools available to evaluate and assess treatments and devices, clinical trials must be allowed to respond and adapt to these changes and keep pace with our more advanced understanding of medicine.

- **What's driving the increased time and cost of clinical trials? What are NIH and FDA currently doing to address these issues? Are these efforts effective?**
- **What could NIH and FDA do to address more effectively the challenges associated with clinical trials, including cutting down the time and expense of such trials?**
- **How can Congress remove barriers and facilitate innovation in the administration and design of clinical trials to reduce the time and resources it currently takes to conduct these trials?**
- **How can we ensure that adaptive and efficient clinical trials designs and modern statistical tools become routinely used across the agency's divisions?**
- **Ultimately, what needs to be done to ensure that the regulatory environment supports and embraces new clinical trial approaches and designs that reflect the most current understanding of medicine and help to get the best treatments and cures to patients?**
- **What policy changes would remove current administrative or bureaucratic barriers to a more efficient and cost effective clinical research process for medical product approval?**

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<sup>82</sup> Ibid.

<sup>83</sup> Ibid.

## VII

### **What does the “Gold Standard” look like in the 21<sup>st</sup> century and beyond?**

*“Although the FDA is just one participant in advancing development science, we have an important role to play. Because FDA’s standards are often used to guide development programs, we need to make sure that our standard-setting process is informed by the best, with the goal of promoting efficient development of safe and effective new medical treatments.” – FDA Critical Path Report, 2004*

The FDA faces challenges in applying cutting-edge science in its review of medical products. The agency must keep up with the fast pace of science as it fulfills its mission to ensure that medical products marketed to American patients are safe and effective. If there are adverse events reported with a product, the FDA will be scrutinized for its decisions and processes. On the other hand, if patients end up waiting longer for therapies that could improve the quality of, or even save, their lives, the FDA will also be scrutinized.

#### **Standards for Approval**

Congress first took action to regulate drugs, food, and cosmetics at the beginning of the 20<sup>th</sup> century, and in many cases the standards that are used today were updated over time. However, many of these standards have not been revisited as our understanding of medicine has advanced.

For the review of drugs, FDA relies on a standard established more than 50 years ago in the 1962 Kefauver-Harris Amendments that required “substantial evidence of effectiveness” for new drugs demonstrated by “adequate and well-controlled investigations, including clinical investigations.”<sup>84</sup> All new drugs must be shown to be safe and effective, either by demonstrating a clinical benefit or having an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit.

The standard for approving generic drugs was established over 30 years ago and is based on showing “sameness.” Most generic drugs do not require any clinical studies to demonstrate that the generic is the same as the brand drug. More recently, Congress established a pathway for follow-on biologics, or biosimilars, but five years later the clinical and marketing requirements for biosimilars are still being developed by the FDA.

The statutory standard for the approval of medical devices is also decades old. Over 35 years ago, in 1976, the Medical Device Amendments required a “reasonable assurance of safety and effectiveness” based on the “valid scientific evidence” for a medical device. However, how the FDA interprets “valid scientific evidence” can vary greatly and has changed over time. Since medical devices are changing constantly and being updated, there is also a pathway that allows a medical device to come to market based on demonstrating that a new device is “substantially equivalent” to a similar device that is already on the market (“predicate device”). This is referred to as the 510(k)

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<sup>84</sup> <http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm>



pathway and is reserved for moderate risk devices. Moderate-risk devices without a predicate device can go through the de novo 510(k) pathway.

In vitro diagnostics are considered devices that health care professionals use to analyze a human specimen to help inform a patient's diagnosis. These in vitro diagnostic devices are subject to the same standard as medical devices that are implanted or otherwise used directly in or on a patient's body. Understandably, the FDA has struggled to apply its standards for regulating devices to information from a diagnostic test. After all, how is the FDA supposed to apply the "safe and effective" standard to information from a diagnostic test? The same medical device definition also applies to mobile medical applications simply used for wellness. The FDA has said it does not plan to regulate the vast majority of these applications, but the line it draws in the current guidance is murky. That uncertainty may freeze this promising industry and keep these products from reaching patients.

The "safe and effective" standard for diagnostic tests has become even more difficult to understand in the context of Laboratory Developed Tests (LDTs). LDTs are created and run by pathologists, geneticists, and other physicians and scientists. The laboratories that run these tests have been regulated by the Centers for Medicare and Medicaid Services under the user-fee program Congress enacted in 1988 with passage of the Clinical Laboratory Improvement Amendments (CLIA). A CLIA-certified lab must pass rigorous controls to ensure lab test results are accurate. In addition, some laboratories voluntarily meet additional requirements in order to obtain accreditation from the College of American Pathologists.

In October 2014, the FDA proposed a draft guidance that would bring LDTs under both FDA and CLIA regulation. Up until this point, LDTs have only been regulated by CLIA, leading some to describe this draft guidance as a "major shift."<sup>85</sup> This guidance has generated significant attention among a range of affected diagnostic stakeholders and been the subject of intense scrutiny.

## Drug Exclusivity

Drug exclusivity refers to the amount of time a drug is on the market before generic competition can be marketed with the same intended use. Exclusivity is seen as an incentive as it assures the manufacturer a certain amount of time they can market their drug without competition. Since the Hatch-Waxman amendments in the early 1980s, a drug that is a new chemical entity receives five years of exclusivity. Congress has used exclusivity periods to encourage innovators to develop treatments in certain patient and disease areas, such as additional exclusivity for rare conditions or conducting studies in pediatric applications. There are additional or longer exclusivities Congress has added include:

- Drugs for Orphan (rare) Diseases: 7 years
- A new use that required clinical studies: 3 years
- Study in pediatrics: 6 months
- Biologics: 12 years
- Novel antibiotic or antifungal: 5 years

In practice, these exclusivity periods may not be this length of time due to litigation between generic drug manufacturers and brand manufacturers. Determining exact exclusivity periods can be quite complicated, but there is widespread agreement that exclusivity has worked to spur development in challenging areas.

<sup>85</sup> <http://www.raps.org/Regulatory-Focus/News/2014/08/01/19934/In-Major-Shift-FDA-to-Regulate-Lab-Developed-Tests-as-Normal-Devices/>

## **Expedited Pathways**

Expediting medical product approval is not a new idea – Congress has provided FDA with many tools to expedite the approval of new drugs, including the breakthrough therapy pathway in 2012. Novel drugs and biologics must go through either a New Drug Application (NDA) or Biologic Licensing Application (BLA) process, for which the fees and timelines for review are re-negotiated every five years as part of the prescription drug user fee agreement. There is a separate process for over-the-counter (OTC) drugs, including ingredients that have been widely available overseas, called the “Time and Extent Application” (TEA) process. Unfortunately, no TEAs have been approved in the more than 10 years since the pathway’s establishment in regulations, even though more than 10 TEAs have been before the agency for years. In practice, this pathway for select OTC ingredients has been anything but “expedited.”

Drugs or biologics can qualify for one of many expedited designations or pathways, including:

- Accelerated Approval: an approval pathway for drugs that treat a serious condition, provide a meaningful advantage over available therapies, and demonstrate an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit. This permits more efficient approval based on an effect on a surrogate endpoint rather than a clinical benefit.
- Fast Track: Fast track designation permits actions to expedite the development and review, and allows for rolling review of the application. Fast track designations are awarded to drugs that treat a serious condition and provide data that demonstrates the potential to address an unmet medical need. Also, qualified infectious disease products receive fast track designation.
- Priority Review: Priority review is for drugs that treat a serious condition and would provide a significant improvement in safety and effectiveness, or can be provided as the result of a voucher. The review clock for priority review is six months, compared with the traditional ten month review time period.
- Breakthrough Therapy Designation: Breakthrough drugs are intended to treat serious conditions and have preliminary clinical evidence that indicates the drug may demonstrate a substantial improvement on a clinically significant endpoint over available therapies.

Most of these pathways are reserved for unmet medical needs or severe and often potentially fatal diseases.<sup>86</sup> While we are in desperate need of cures for chronic conditions, such as diabetes and cardiovascular disease, it is not clear that these pathways are best suited to expedite drugs for large populations with chronic diseases where the risk-benefit assessment may not be quite as dramatic. The Massachusetts Institute of Technology has developed evidence that a type of conditional approval pathway may help in these areas, and the European Medicines Agency is currently piloting a similar idea.<sup>87</sup> Similarly, as our understanding of genomic medicine has advanced, it has challenged the traditional definitions of “unmet need” as well as “clinical benefit.”

In 2014, the FDA released guidance on accelerating medical device approvals and announced a pilot project that would allow devices that treat or diagnose a life-threatening or debilitating disease to

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<sup>86</sup>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>87</sup> <http://cbi.mit.edu/wp-content/uploads/2012/05/clpt2011345a.pdf>



have early and often interaction with the FDA with the goal of shortening the time it takes to get this innovation to patients.<sup>88</sup> The impact of this guidance and pilot program remain to be seen.

### **Systemic FDA Challenges**

In 2010, the Government Accountability Office (GAO) analyzed the FDA and found that opportunities existed to better address management challenges. The GAO found that while the FDA is aware of its challenges and has taken steps to address them, the agency has not fully implemented practices for effective strategic planning and management. The GAO determined that FDA management challenges include recruiting, retaining, and developing its workforce; modernizing its information systems; coordinating internally and externally; communicating with the public; and keeping up with scientific advances. Many of these agency-wide challenges still persist today, including the GAO's specific recommendation that the FDA Commissioner create more results-oriented performance measures for the agency.<sup>89</sup>

#### *FDA Structure*

The FDA's premarket review of medical products is performed by three main centers:

- The Center for Drug Evaluation and Research (CDER), which reviews all small-molecule drugs, generic drugs, biologics, and OTC drugs.
- The Center for Biologics Evaluation and Research (CBER), which regulates vaccines, tissues, and cellular and tissue-based products.
- The Center for Devices and Radiological Health (CDRH), which regulates medical devices, medical imaging, and radiation-emitting products.

As technology has advanced, many novel therapies increasingly do not fit neatly into a single center or one regulatory pathway alone. For example, many biologics are made in syringes (a medical device), many stents (also a medical device) have a drug component, and a tissue scaffold (novel tissue technology that helps rebuild lost human tissue) may have a drug, device, and tissue component. The Office of Combination Products (OCP) can determine which center is lead to review a product that has more than one such drug and device component, but that process can delay the review of the medical product. Under this scenario, the secondary center has no timelines associated with its review of the component for which they are responsible. Further, as personalized medicine increasingly becomes the norm, more drugs are approved with companion diagnostics that help to indicate whether or not the therapy may be appropriate for a specific patient. Data from a recent Booz Allen Hamilton report lists some of the challenges and observations specific just to CDRH. One example of the findings: for combination products (those with drug and device components), the process for consultation between centers needed improvement.<sup>90</sup>

The FDA already has undertaken an effort to align enforcement and inspectors based on product type, moving away from the typical model of having generalist inspectors. This alignment recognizes a dedicated focus in specific product areas, and raises a question of whether it may be

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<sup>88</sup> [Accelerated Draft Guidance](#)

<sup>89</sup> <http://www.gao.gov/assets/590/587000.pdf>

<sup>90</sup> <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MDUFAIII/UCM400676.pdf>

appropriate to do a similar type of alignment among the centers, divisions, and offices that do premarket medical product review.

There are centers, offices, and divisions at the FDA that do not have a clear role in either the premarket or post-market space. A staff guide that contains a comprehensive list of the FDA centers, offices, and divisions shows nearly 430 different offices, centers, divisions, district offices, regional field offices, and laboratories.<sup>91</sup> We need to examine how these centers, offices, and divisions contribute to the FDA's mission regarding medical products, if they are still necessary, and, if so, if they are more appropriate somewhere else in the Executive Branch.

Within CDER, there is performance variability between the divisions that review certain products. As a Manhattan Institute study shows, divisions such as oncology and infectious disease appear to use tools to accelerate therapies the most and approve new drugs roughly twice as fast as the least efficient divisions.<sup>92</sup> The therapies reviewed by these more efficient divisions have a stark risk-benefit profile: they are usually taken for shorter amounts of time, and the potential for a patient to die without intervention is higher. Other divisions, which review products intended to treat chronic conditions such as diabetes, obesity, and cardiovascular disease, have a narrower margin of tolerable risk relative to intended benefit. Some of those therapies are taken for years. Bringing the underperforming divisions up to the standards set by these more efficient divisions would greatly help patients with other diseases and conditions; however, determining the best manner in which to accomplish this a complex challenge that will require the FDA, Congress, sponsors, patients, and researchers to work together.

#### *FDA Staff*

Recruitment, retention, and ongoing education of the FDA staff is critical to consistency and predictability in the review process; however, there have been ongoing issues related to FDA staffing in all of these areas, many of which are systemic issues that cannot be, nor should be, legislated. In reviewing the organizational chart for the FDA, it is clear that the FDA has difficulty filling leadership positions. For example, the position for the Deputy Commissioner for Medical Products and Tobacco, which oversees CDER, CBER, CDRH, and the Center for Tobacco Products, has just recently been filled after being vacant since 2011. The FDA provided information regarding the length of time it takes to train new staff, and the amount of time it takes to hire new employees. For example, the average number of days it takes to hire a Senior Regulatory Health Project Manager is almost 200 days. It takes 18-24 months for a reviewer or inspector to begin working independently on complex applications or inspections.<sup>93</sup> Further, staff turnover at the reviewer level can significantly set back the review of a product. A new reviewer may have new questions on issues already resolved. The FDA was not able to provide data on how long specific employee levels stayed at the agency, but GAO and others have noted the difficulty the FDA has hiring and retaining scientists.

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<sup>91</sup> <http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm136374.htm>

<sup>92</sup> [http://www.manhattan-institute.org/pdf/fda\\_07.pdf](http://www.manhattan-institute.org/pdf/fda_07.pdf)

<sup>93</sup> Appendix C: Correspondence from FDA, January 1/21/15

The FDA has grown significantly in its size and scope over the years (see Fig. 6). Today, there are more than 12,000 employees at the FDA, and this growth has exacerbated management challenges at the agency.<sup>94</sup> While this report focuses on human medical products, these employees also regulate food, tobacco, cosmetics, all radiation-emitting products, and animal drugs and feed.

How does the FDA attract top talent, retain them, and ensure staff is educated on and consistently applying the most up-to-date science, especially when the FDA competes with other agencies and academic research centers, as well as industry?

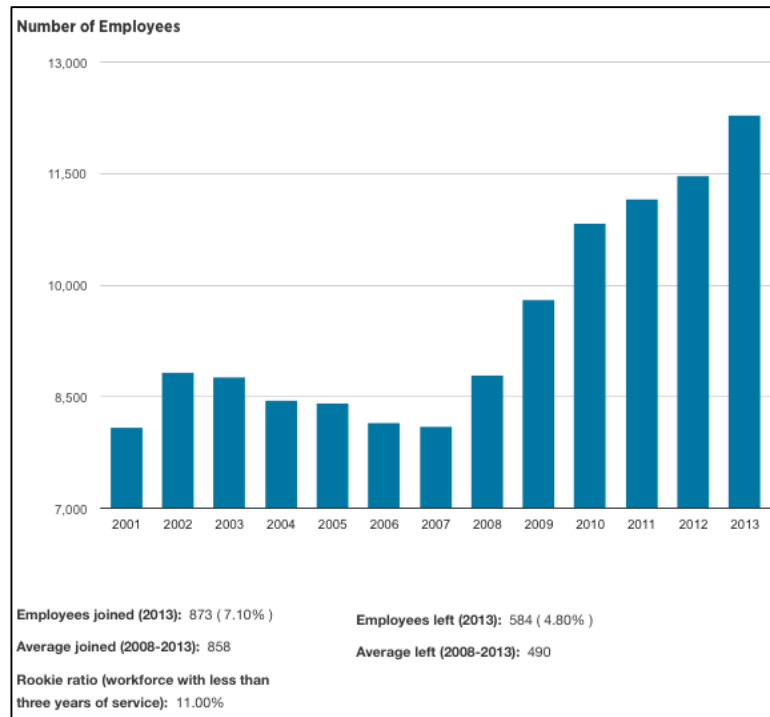


Figure 6: From Partnership for Public Service. *The Best Places to Work in the Federal Government*. 2014. Accessed December 11, 2014 from <http://bestplacetowork.org/BPTW/rankings/detail/HE36>

#### *Information Technology at the FDA*

The FDA has had five different Chief Information Officers (CIOs) since 2008, and has been without a permanent CIO since March of 2013. This turnover makes it difficult for the agency to have a cohesive information technology (IT) plan and keep up with modern century medicine.<sup>95</sup>

The FDA has spent at least \$280 million on one IT system for the whole agency, and CDRH, CBER, and CDER all have different systems.<sup>96</sup> Further, how the centers train on those systems varies, leading to mixed reviews from staff on how helpful those systems are in fulfilling their mission. For example, while CDRH has four different IT systems, there is not one that shows each reviewer's workload, making it more difficult to see who should be working on applications.<sup>97</sup> Most of the drug and device user fee agreements also contained dedicated funds from industry to help the FDA update its IT systems, yet there is widespread agreement that the agency still lacks sufficient modern technology systems that could enable the reviewers to approve medical products and changes to those products as efficiently and quickly as possible.

<sup>94</sup> Partnership for Public Service. *The Best Places to Work in the Federal Governemnt*. 2014. Accessed December 11, 2014 from <http://bestplacetowork.org/BPTW/rankings/detail/HE36>

<sup>95</sup> Article <http://www.fiercebiotechit.com/story/fda-resumes-its-long-search-cio/2014-11-06>

<sup>96</sup> <http://www.gao.gov/assets/590/589351.pdf>

<sup>97</sup> [Booz Allen Report – Page 8, 14, 76-77, 82-84](#)

The increase in computer power and computational tools has dramatically increased the ability to collect and analyze clinical data, but even with dedicated staff working to modernize their systems, unfortunately the FDA has not realized the efficiencies that these technologies could provide.

### **The Role of the FDA in Communication of Evolving Scientific Knowledge**

Part of the FDA's role in communicating scientific knowledge is how it sets standards and expectations for medical products seeking approval, how it interprets standards and regulatory pathways in law, and how it plans to enforce specific requirements. The FDA rarely undertakes rulemaking through the Administrative Procedures Act (APA); rather it communicates changes in policy through less formal guidance documents and "Question and Answer" documents that it posts to its website. Guidance documents are supposed to comply with Good Guidance Practices that require a draft to be published and allow for public comment, as well as finalization of the document before implementation. Guidances, unlike regulations, are not legally binding in most cases and are intended to express and reflect the FDA's most current thinking on specific subjects, standards, or implementation of a new law.

However, it seems that the FDA does not always follow its own practices. In May 2014, a group of Republican Senators on the HELP Committee asked the FDA for a list of all outstanding draft guidances. Unfortunately, these members have still not received a response to this straightforward question. When the agency puts forward policy in these draft guidances it can have unintended consequences. If such guidances are not quickly finalized or withdrawn, those policies become all that sponsors and the public have on which to rely as the FDA's most current understanding of an issue. One analysis in 2013 found that there were 302 draft guidances outstanding related to drug and device regulation, of which 99 were over five years old.<sup>98</sup> FDA guidance also can establish the FDA's policy of regulating through enforcement discretion. In some cases, the FDA states that entire industries are considered subject to enforcement discretion, but then later the FDA can release a guidance that changes that position. Regulating through enforcement discretion may avoid overregulation of certain industries, but also may cause confusion and uncertainty in those industries.

Another key part of the FDA's role in scientific communication is its regulation of medical product labeling. Drug and device companies are restricted in how they can label and talk about FDA approved products. Often, labels are negotiated for weeks during the review process but then may not be revisited for years.<sup>99</sup> These restrictions mean that scientific information that has not been through an FDA review process, even if published in scientific journals or derived from federally funded research, is prohibited from being shared by the drug or device manufacturer with medical professionals, including payers. In today's online world where doctors can look on the internet and find studies, it may be a disadvantage not to be able to discuss this information with the product developers who know the most about the product.

- **What tools does the FDA need to more fully leverage to better fulfill its mission? Are there unnecessary tools or authorities, or others that could be more useful?**
- **Even with the best tools, staffing, IT systems, is it feasible that a single federal agency can evaluate fast moving medical and scientific advances? Should we re-evaluate**

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<sup>98</sup> <http://www.mddionline.com/article/fda-draft-guidances-drag-out>

<sup>99</sup> <http://www.aei.org/publication/todays-ruling-on-commercial-speech-will-rein-in-fdas-regulatory-overreach/>

**FDA's role from both developing and policing the scientific standards to an agency that evaluates whether data meets scientific standards developed by leaders and experts outside the agency?**

- **Does Congress need to re-examine the FDA's current decades-old standards in order to ensure that the agency is prepared to review the most cutting-edge medical products today and in the future? How do we ensure that the FDA is prepared to review the full range of medical products, including those that are the most novel, cutting-edge, and personalized for patients?**
- **Should standards be updated to reflect how they are being applied today for both drugs and devices? How certain do we need to be that a drug is safe and effective, and does that differ for different diseases, populations, or circumstances?**
- **Are there standards that need updating, or regulatory tools that are outdated and no longer appropriately applied to modern medical products?**
- **Are today's regulatory pathways sufficient to ensure a predictable pathway for innovators as they bring forward medical products for review by the agency? Are today's pathways achieving their intended purpose? Are they being fully leveraged on behalf of patients?**
- **Given the advances in medical products, is it time to reassess whether separate centers are the right way to regulate medical products? Are there other ways of organizing the agency and regulatory pathways – based on disease areas, for example – that may be more efficient and effective?**
- **Are there ways to help the agency, through regulatory science or additional tools, be able to determine safety and efficacy for drugs given to large patient populations for chronic conditions other than multi-year studies requiring hundreds of thousands of patients?**
- **How can Congress help ensure the FDA is appropriately organized to enable the agency to more efficiently review medical products and perform post-market surveillance?**
- **How should the FDA rely on outside science when developing policy? How should FDA then communicate timely scientific and regulatory policy changes while still allowing for public comment and debate?**
- **Should there be a larger public debate on the FDA's use of guidances rather than rulemaking to communicate FDA policy? What are the implications of current practices for patients, doctors, industry, and scientists?**
- **Do the current legislative and regulatory policies regarding information sharing, communications, and labeling work?**

## VIII

### **Regulatory Science: The FDA must be prepared to review medical products in the future**

*“What is the problem? In FDA’s view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic science.” - FDA Critical Path Report, 2004*

Finding ways to level the scientific playing field between FDA and the medical industries it regulates will likely go a long way towards making the review process more timely and efficient. Addressing the scientific deficit is an important step towards more meaningfully supporting medical innovation in America. If the FDA does not feel it can adequately assess new technologies, more data may be required to provide greater certainty regarding the safety and effectiveness of these new products. The question we need to examine is how certain do we need to be of a novel technology’s safety and effectiveness, and how much time and resources are we willing to use to get such certainty?

Since the 2004 Critical Path Report, many initiatives have been undertaken at both the FDA and the NIH to provide tools to the FDA and industry to speed the development and review of new medical products. What follows is not an exhaustive list, it highlights some of the major projects at the FDA and the resources dedicated to these efforts.

#### **Public-Private Partnerships**

Public-private partnerships often are discussed as a way to bring academia, government, patients, industry, and others together to solve complex scientific and process questions about medical product development. For example, CDER alone is a part of 22 different public private partnerships.<sup>100</sup> It is not clear, however, who is accountable for ensuring that these partnerships are folded into systemic change.

##### *The Critical Path Public Private Partnership*

While the FDA hasn’t updated the [Critical Path Initiative](#) website since March 2013, there are examples of output from this public private partnership.<sup>101</sup> Critical Path has many projects underway aimed at standardizing data to ease FDA review, finding biomarkers that can be used in drug development, and standardizing the measurement of those biomarkers. Critical Path also has a Patient Reported Outcomes Consortium and the Coalition Against Major Diseases, which focuses on developing the tools and methods to accelerate drug development for Alzheimer’s and Parkinson’s diseases.

##### *The Reagan- Udall Foundation*

Congress created the Reagan-Udall Foundation (RUF) in 2007 in response to the *FDA Science and Mission Risk Report* to advance regulatory science. Congress recognized the need for an independent body to collaborate with patient groups, industry, academia, and FDA and to bring

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<sup>100</sup> <http://blogs.fda.gov/fdavoices/index.php/2014/05/progress-on-the-2012-drug-innovation-report-by-pcast-presidents-council-of-advisors-on-science-and-technology/>

<sup>101</sup> <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>

new resources and perspectives on the most challenging regulatory science projects.<sup>102</sup> While Congress authorized transfers from the FDA to RUF in 2007, no funds were appropriated for that purpose until 2012.<sup>103</sup>

The RUF's activities are wide-ranging. Through the Innovation in Medical Evidence and Surveillance (IMEDS), RUF works to leverage the promise of electronic health data to transform post-market surveillance. Funded by and partnering with the Gates Foundation in its Critical Path to Tuberculosis (TB Drug Regimes), RUF convenes international TB stakeholders to create a global regulatory environment that enables and facilitates TB drug regimen development. RUF also brings the diverse and extensive scientific disciplines necessary to understand systems biology and develop new predictive toxicology tools. Finally, RUF funds a fellowship to bring experienced physicians into the FDA to advance the development of Alzheimer's treatments.

#### *Medical Device Innovation Consortium*

The Medical Device Innovation Consortium (MDIC), a 43 member organization, aims to advance regulatory science in the medical device space by coordinating the development of methods, tools, and resources. These include developing new approaches to computer modeling to develop and design better and more personalized devices, validating new metrics to assess quality in medical devices, improving the design and administration of clinical trials for devices, and discovering how to incorporate the patient perspective into the regulatory approval process. CDRH sends many staff to collaborate in this effort and inform their process.

#### **Inter – Agency Collaboration**

##### *National Center for Toxicological Research*

The FDA has a center dedicated to scientific research, the National Center for Toxicological Research (NCTR), which conducts peer-reviewed research to advance science required to support public health and improve FDA's ability to assess safety of regulated products. NCTR has a budget of \$62.5<sup>104</sup> million for FY2014.

<sup>102</sup> <http://www.reaganudall.org/about-us/>

<sup>103</sup> <http://www.reaganudall.org/about-us/frequently-asked-questions/>

<sup>104</sup>

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM388309.pdf> (page 99)

## A Snapshot of the Regulatory Science Dollars at FDA

Since the Critical Path 2004 report, FDA has spent both user fee and appropriated dollars trying to update the agency tools and science:

- Critical Path:
  - \$8 million, 2008
  - \$16 million, 2009
  - \$18 million, 2010
  - \$10.5 million, 2014
- Centers of Excellence in Regulatory Science and Innovation:
  - \$2 million, 2011
  - \$2.9 million, 2014
- Rare Disease Grant Program:
  - \$19 million, 2014
- Advancing Regulatory Science
  - \$950,000, 2010
- Medical Device Innovation Consortium,
  - \$1.1 million, 2012
- Clinical Trials Transformation Initiative
  - \$1.5 million, 2009
  - \$37.5 million, 2014
- National Center for Toxicological Research
  - Budget of \$62.5 million
- Prescription Drug User Fee Agreement, V
  - around \$30 million over 5 years
- Generic Drug User Fee Agreement I - \$20 million each year for 5 years



NCTR has 34 projects in the area of biomarkers, and is currently conducting 55 projects more broadly supporting personalized medicine including research on biomarkers, technologies, and tool development. One example is scientists examining the FDA Adverse Event Reporting System to identify potential diseases that disproportionately affect men or women.

The FDA has several programs that aim to increase expertise in regulatory research and training, including NCTR's mentoring program. NCTR has trained scientists from over 45 countries and provides opportunities for hands-on lab experience. NCTR has eight formal training programs: (1) Science Training and Exchange Professional Development Program; (2) Faculty Research Program; (3) Foreign National Training Program; (4) Interdisciplinary Toxicology Program; (5) Post-graduate Research Program; (6) Science Internship Program; (7) Summer Student Research Program (21 students in 2014); and (8) Graduate Certificate in Regulatory Science (through Univ. of Arkansas for Medical Sciences with NCTR).

NCTR also works with the FDA's Office of Regulatory Affairs to train reviewers on novel technology such as nanotechnology. This training is meant to provide reviewers and scientists with the ability to evaluate the safety of nanoparticles when incorporated in FDA-regulated products.

According to the FDA, NCTR's work supports the other centers at the agency. One way that is done is through the Science Advisory Board to NCTR. This board meets once annually to provide advice to the FDA Commissioner and advises the Director of NCTR in establishing, implementing, and evaluating research programs to assist FDA in its regulatory responsibilities. One of the goals of this board is to ensure research at NCTR supports the centers that review medical products. Further, 42 research projects at NCTR are done in collaboration with CDER, CBER, or CDRH.<sup>105</sup>

#### *The Advancing Regulatory Science Initiative*

The Advancing Regulatory Science Initiative was launched in February of 2010 to move regulatory science into the 21<sup>st</sup> century. A collaboration between FDA and NIH, the initiative was designed to accelerate the process from scientific breakthrough to the availability of new, innovative medical therapies for patients.<sup>106</sup> FDA released a document outlining the vision for regulatory science in October 2010, a strategic plan for regulatory science in August 2011, and has had multiple public meetings on topics helpful to advancing science in specific areas, such as genomic sequencing and developmental toxicology.<sup>107</sup>

In September 2010, the NIH awarded \$9.4 million over three years in partnership with the FDA, which contributed \$950,000, to projects that would better inform scientists and regulatory reviewers about medical product safety and improve the availability of new medical products.<sup>108</sup> A month later, the FDA announced a \$2.9 million dollar award for six research projects on tuberculosis, headed up by the Critical Path Program. Lastly, in 2011, the FDA invested \$2 million to support Centers of Excellence in Regulatory Science and Innovation to focus on strengthening science and training necessary to improve the way medical products are reviewed and evaluated.

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<sup>105</sup> Correspondence from the Commissioner to Sens. Alexander and Burr, October 2014.

<sup>106</sup> <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm201706.htm>

<sup>107</sup> <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm227842.htm>

<sup>108</sup> <http://www.nih.gov/news/health/sep2010/od-27.htm>



## **Qualification of New Drug Development Tools**

In 2014, CDER finalized<sup>109</sup> a [Drug Development Tools \(DDT\) Qualification Program](#), which was created to provide a framework for the development, regulatory assessment, and acceptance of scientific tools to help drug development.<sup>110</sup> In 2014, the FDA released guidance on how to use the program.<sup>111</sup> CDER has described three types of scientific tools eligible for this process:

### **Biomarkers**

The use of biomarkers in drug development has been heralded as a way to shorten development times, find toxicities earlier in the development process, and enable smaller trials. There is an entire public private partnership at Foundation for the NIH looking at potential biomarkers, as well as other projects such as the Advancing Medicines Project. However, even with the focus and investment in biomarkers, only three have been qualified through the FDA's qualification program. Further, the three qualified already have been used in clinical trials for decades.

### **Clinical Outcome Assessment (COA)**

The second type of tool that the FDA plans to qualify are clinical outcome assessment tools. Only one has been approved thus far, but there are four different types that the FDA will qualify before there is wide acceptance for use in development programs: patient reported outcomes, clinician reported outcomes, observer reported outcomes, and performance outcomes.

### **Animal Models**

Animal models are widely used in preclinical development to try to assess earlier toxicity, safety, and efficacy. As of the date of this report, the FDA had not qualified any animal models.

It is unclear how novel methods, such as the "organ on a chip" project at NCATS, will be qualified to then replace the inefficient, expensive animal models or other methods for assessing toxicity.

## **Qualification of New Medical Device Development Tools**

CDRH released draft guidance for how to qualify development tools for medical device development in 2013 and announced a pilot program to help aid development of devices. The pilot program announced in August 2014 is limited to 15 candidates that can be either clinical outcome assessment tools, biomarker tests, or nonclinical assessment models.<sup>112</sup>

- **How have the resources dedicated to the regulatory science initiatives translated into policy, biomarkers, trial designs, standards, or other outputs that have been used to reduce development and/or review times? How do we assess the success of these programs and partnerships? Have they been successful at achieving their stated purposes and goals?**

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<sup>109</sup> <http://www.nature.com/nrd/journal/v13/n11/full/nrd4435.html>

<sup>110</sup> <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm>

<sup>111</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

<sup>112</sup> <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm374427.htm>; <http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/>

- Can public private partnerships be effective without clear metrics for implementation by the FDA?
- After 10 years of funding many projects from clinical trial standards, to biomarkers, to increased scientific education and regulatory science training, are these projects translating into products reaching patients more quickly? If so, how? If not, what can be done to better use these projects moving forward?
- How could we better leverage the regulatory science initiatives to ensure that novel medical products are reaching American patients in as timely a manner as possible?
- Should a singular partnership be responsible for driving the regulatory science transformation, rather than the multitude of diverse, but important, partnerships with no real accountability mechanism?
- Can regulatory science adequately de-risk novel technology and platforms so the FDA feels comfortable assessing the safety and efficacy of these novel technologies, or are other tools necessary to help de-risk, and therefore encourage investment and development of, such novel platforms and technologies?
- Do we need a structure to review and validate new tools in medical product development? If so, should that be a responsibility of the NIH, FDA, or a different group?
- What specific policy or practice changes would facilitate the timely adoption of new tools, such as biomarkers or informatics?

## IX

### **Rising Global Competition to U.S. Medical Product Development**

*“For at least the past half century, the United States has stood at the forefront of the global life sciences revolution. But amidst intensifying global competition, continued U.S. life sciences leadership is not assured, and is under clear threat from several directions” - Leadership In Decline: Assessing U.S. International Competitiveness in Biomedical Research, 2012<sup>113</sup>*

*“The medical technology innovation ecosystem, long centered in the United States, is moving offshore. Innovators are going outside the United States to seek clinical data, new-product registration, and first revenue.” - Medical Technology Innovation Scorecard, 2011*

The U.S. has long been the predominant global player in the development of innovative drugs and devices, but the competition is growing. Legislators and regulators have a critical role in ensuring that the U.S. maintains superiority in medical product development and that American patients get the best treatment possible. The U.S. is competing globally for both investment and regulatory efficiency. Additionally, the globalization of production means that more drugs and devices are being manufactured, in whole or in part, beyond U.S. borders. This creates additional challenges for regulators because fulfilling their responsibility to protect the public’s health is no longer limited to the borders of the U.S.

#### **Where is Innovation Going?**

Since World War II, the U.S. has dominated the biomedical industry space. Even 20 years ago, studies suggested that the U.S. share of global biomedical research funding was as high as 70-80 percent.<sup>114</sup> However, from 2007 to 2012, the U.S. share of research and development declined from about 51 percent to 45 percent (see Fig. 7).<sup>115</sup> While the U.S. continued to lead the world in public sector investment during this time, private sector investment shrank by almost \$13 billion and largely reallocated to Asia.<sup>116</sup>

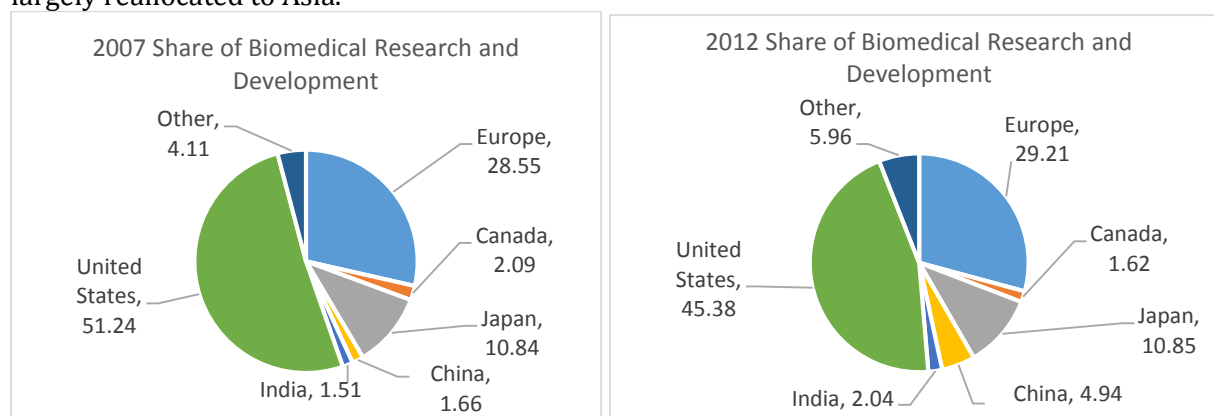


Figure 7: Chart made from: [http://rwjcsp.unc.edu/downloads/news/2014/20140102\\_NEJM.pdf](http://rwjcsp.unc.edu/downloads/news/2014/20140102_NEJM.pdf)

<sup>113</sup> [Report was produced by the Information Technology and Innovation Foundation and United For Medical Research.](http://rwjcsp.unc.edu/downloads/news/2014/20140102_NEJM.pdf)

<sup>114</sup> <http://jama.jamanetwork.com/article.aspx?articleid=185198#ref-joc90144-25>

<sup>115</sup> [http://rwjcsp.unc.edu/downloads/news/2014/20140102\\_NEJM.pdf](http://rwjcsp.unc.edu/downloads/news/2014/20140102_NEJM.pdf) (pg 5)

<sup>116</sup> [http://rwjcsp.unc.edu/downloads/news/2014/20140102\\_NEJM.pdf](http://rwjcsp.unc.edu/downloads/news/2014/20140102_NEJM.pdf) (pg 5)

Venture capital is not only moving away from investments aimed at new company formation in early stage, medical technology, and life science ventures, but it is also moving to other areas of the world. In 2011, The National Venture Capital Association found over 60 percent of their members cite FDA regulatory challenges as the reason for shifting away from biotech and medical device investment, and over 35 percent cite coverage and payment concerns (Figure 8).

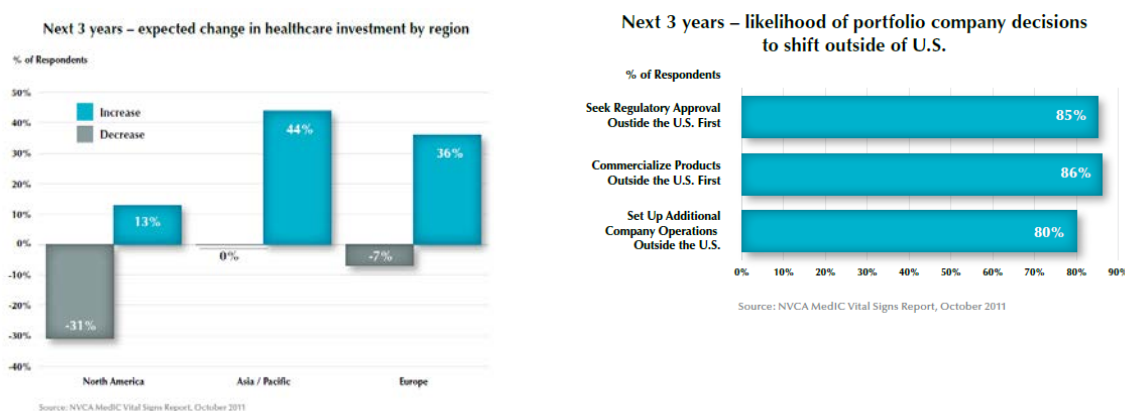


Figure 8: Change in healthcare and outside U.S. investment<sup>117</sup>

In addition to global competition for industry, there is also competition in the regulatory space. Given the significant expense in developing drugs and devices and time-limited patent protections, companies are pressured to get medical products to market quickly. This engenders a form of regulatory competition, as drug and device developers will seek approval from regulatory agencies that are most efficient. While the U.S. remains an attractive market for the launch of new drugs and devices, the regulatory realities of the FDA may encourage companies to seek approval from other regulators first. This both delays access to new therapies and treatments for U.S. patients and drives expertise overseas. Furthermore, innovative regulatory pathways and developments in other countries actively promote innovation and development in those countries.

Countries across the globe have sought to capitalize on America's shrinking competitive advantage in the biomedical space. The European Union (EU) formed the Innovative Medicines Initiative (IMI), creating the world's largest public-private partnership in the life sciences with a 3.3 billion euro budget for 2014-2024.<sup>118</sup> The IMI's core mission is to accelerate development of and access to innovative medicines, and it has engaged regulators, researchers, and industry to advance a coordinated research agenda to achieve its mission.<sup>119</sup> While many similar projects are underway in the U.S., these projects can be uncoordinated, duplicative, and unaccountable. The Chinese government also has sought to create a favorable economic climate for investment and innovation in the biomedical industry. Between 2007 and 2012, funding for biomedical research increased 33 percent, which has translated into rapid growth for its businesses.<sup>120</sup> For example, armed with a \$1.58 billion line of credit from China Development Bank, Beijing Genomics Institute went from performing one percent of the Human Genome Project to analyzing 10-20 percent of all DNA

<sup>117</sup> National Venture Capital Association Vital Signs Report, October 2011.

<sup>118</sup> <http://www.imi.europa.eu/content/mission>

<sup>119</sup> Ibid.

<sup>120</sup> [http://rwjccsp.unc.edu/downloads/news/2014/20140102\\_NEJM.pdf](http://rwjccsp.unc.edu/downloads/news/2014/20140102_NEJM.pdf)

sequenced around the world.<sup>121</sup> Through partnerships like these, China is poised to leverage its resources and skills to be on the cutting edge of biomedical innovation.

This trend is concerning as a robust biomedical research enterprise plays a pivotal role both in the economy—supporting more than seven million jobs and contributing \$69 billion to the U.S. GDP<sup>122</sup>—and in ensuring that the best treatments and cures are available to Americans. For a variety of reasons, medical product manufacturers seek to bring their products to market quickly and will often seek approval from the regulatory agencies that are least burdensome and most consistent and timely. Overall, we need to ensure that U.S. policies align with the goal of advancing and rewarding biomedical innovations that help patients.

### **Regulatory Harmonization**

Regulatory harmonization initiatives present an opportunity to reduce the costs of drug development internationally by streamlining and limiting the requirements that an individual company must fulfill to market a drug or device globally. Some suggest that it is difficult for the FDA to accept foreign clinical trial data, and that many innovators have to conduct additional, redundant trials. In some cases, it has been said that manufacturers must re-do entire clinical programs to market in the U.S., regardless of the safety and efficacy data seen pre and post- market overseas, counter to FDAMA and FDASIA. Efforts are already underway to find ways for regulators to collaborate, including efforts by Congress and consortia like the Critical Path Institute.

- The International Medical Device Regulators Forum (IMDRF) was created in 1992 as the Global Harmonization Task Force and reconceived as the IMDRF in 2011. It seeks to achieve greater uniformity between national medical device regulatory systems, including creating a single audit program, and exchange of post-market surveillance information globally.
- The International Conference on Harmonization was created in 1990 to standardize drug applications, medical terminology, and electronic standards across regulatory agencies, thereby reducing duplicative requirements on drug developers.

Unfortunately, there have been examples where the FDA participates and supports an international standard, only to then raise the bar in its draft guidance, so the policy is not in line with the international standard supported by the agency. For example, a recent guidance on diabetes test strips required more stringency than an international standard that the FDA agreed to for test strip accuracy and testing.<sup>123,124</sup>

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<sup>121</sup> <http://www.technologyreview.com/featuredstorey/511051/inside-chinas-genome-factory/>

<sup>122</sup> <http://www2.itif.org/2012-leadership-in-decline.pdf> (pg. 2)

<sup>123</sup> <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM380325.pdf>

<sup>124</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3692210/>

### **Regulatory Competition: Case Studies**

Medical Devices: EU's system of Notifying Bodies provides a decentralized and more responsive approval process for medical devices. Furthermore, in the EU, devices must only be shown to be safe, whereas in the US a device must be efficacious, as well.

These differences mean that European patients have access to devices that improve and save lives well before American ones, in some cases years before.

A heart valve that can be installed through a catheter was available in Europe beginning in 2007, but not until 2011 in the US.

Genetic Testing: In 2010, FDA stated that genetic tests are medical devices that must have pre-market approval. Currently, it seems that genetic tests must be approved for each marker, unless a doctor orders the same test from CLIA lab.

Canada has a similar overlapping regulatory environment to the U.S., but when a company began selling genetic kits to consumers in Canada in 2013, Canadian regulators said they regulate only the safety of the kits not how the information is used.

### **Regulating in a Globalized World**

Currently FDA regulates a complex array of products including drugs, medical devices, and food that come from 150 countries.<sup>125</sup> For context, 40 percent of finished drugs and 80 percent of the active pharmaceutical ingredients are manufactured outside the U.S.<sup>126</sup> More than 35 percent of the medical equipment market comes from overseas.<sup>127</sup> Imports of FDA-regulated food products almost doubled between 2002 and 2013.<sup>128</sup> The growth and complexity of FDA's oversight responsibility requires an adaptive, collaborative, and engaged approach.

In response to food safety issues in 2007, the FDA began establishing international offices and outposts, which has allowed FDA to respond more quickly and effectively.<sup>129</sup> Additionally, in 2012, Congress addressed the dangers of the global supply chain for medical products and provided FDA with new resources to fulfill its mission of protecting the public's health.<sup>130</sup> FDASIA strengthened the FDA's authority and ability to inspect foreign manufacturers, to develop risk-based approaches to determining when and what facilities to investigate, and to penalize facilities that refuse inspections.<sup>131</sup>

- **How can Congress and the FDA work to align public policy and regulation to support biomedical research as a vibrant and healthy component of the U.S. economy? What**

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<sup>125</sup> <http://blogs.fda.gov/fdavoices/index.php/2014/05/ensuring-pharmaceutical-quality-through-international-engagement/>

<sup>126</sup> Ibid.

<sup>127</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM298578.pdf> (6)

<sup>128</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM298578.pdf> (5)

<sup>129</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM298578.pdf> (10)

<sup>130</sup> <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDASIA/ucm366058.htm>

<sup>131</sup> <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDASIA/ucm366058.htm>

**can be learned and leveraged from successful international programs and initiatives to improve our domestic discovery and development programs?**

- **Are there international regulators that are advanced enough that their approvals could be recognized by the U.S.?**
- **What are the opportunities to streamline and harmonize regulation and review of medical products to ensure that the U.S. regulatory system remains competitive and attractive to drug and device innovators in a global economy?**
- **How do we ensure that the FDA policies are appropriately harmonized with international standards? If the FDA participates in and endorses such efforts, under what circumstances should the FDA not adopt and apply the resulting standard? How do differing international standards affect discovery, development, and ultimately, patients?**
- **What tools are needed for the FDA to build a regulatory system that is efficient, predictable, streamlined, and aligned to the needs of a globalized medical product industry? Are additional authorities or pathways needed for the FDA to collaborate with its international regulatory partners to expedite approvals for medical products that have already been reviewed and approved by countries with whom we partner?**
- **Given the increasingly global context of FDA regulation, is the agency effectively using the tools provided by Congress to ensure equal inspection of foreign manufacturers and that medical products made overseas meet FDA standards?**



# **X**

## **Conclusion**

As Dr. Elias A. Zerhouni, former director of NIH reflected, “The ability of any institution to adapt to its changing environment will remain a key to its success.”<sup>132</sup> The NIH and FDA must keep pace with today’s cutting-edge scientific advances, manage and stay focused on their primary missions, and consistently and fully leverage the tools that Congress provides. Otherwise any legislative efforts to address these challenges and reverse these worrying trends will almost certainly fall short. No one would be more disappointed by this outcome than America’s patients.

After 10 years and countless resources, programs, policies, and hard work, we still are not where we want to be to best serve American patients. Getting new medical products to patients is not a novel idea. Legislation, such as FDAMA in 1997 and FDASIA in 2012, emphasized the need for flexibility and provided the FDA with tools to use that flexibility. Work by the NIH, FDA, various consortia, and public private partnerships have been ongoing to address problems that affect all of medical innovation: clinical trials, medical product development tool research, biomarker development, and consistency and transparency in the review and data necessary to be safe and effective. However, it still takes too long and costs too much for novel therapies that can be a patient’s only hope to become available.

The FDA and NIH should redouble their commitments to fully leveraging public-private partnerships to expand the medical treatment and cures for America’s patients. Through the NIH’s continued focus on basic research and translating new science into health, and focusing the FDA on its core mission of both protecting and promoting public health, these agencies should continue their commitments to making sure that new medical discoveries reach American patients as quickly as possible. This will help to preserve Americans’ trust in our country’s ability to be exceptional in an increasingly global medical products environment. Finding cures will not only help American patients, but will provide a tool to help with the challenge that rising health care entitlement spending poses for our economy. Delaying, curing, or preventing costly diseases such as Alzheimer’s, diabetes, and heart disease will improve the quality of life for these patients and free up resources that could be invested in domestic priorities, such as further biomedical research.

This Congress, the HELP Committee hopes to address five major themes to change the worrying trends and to get more medical products to the patients who need them:

- 1) It costs too much to bring medical products through the pipeline to patients.**
- 2) As science and technology advance, the discovery and development process takes too long for medical products to make their way to patients.**
- 3) FDA’s responsibilities have grown to include many activities unrelated to the core function of regulating medical products to advance the public health.**

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<sup>132</sup> Elias A. Zerhouni Interview, Our Nation’s Health, Celebrating 125 Years of the National Institutes of Health, page 13.

- 4) The disparity in scientific knowledge at FDA and the fast pace of biomedical innovation are slowing, and in some cases, stifling innovation in American medicine.**
- 5) A working FDA is essential to continuing biomedical innovation in the United States and maintaining America's global leadership in medical innovation.**

It will not be an easy task to solve even one of these, much less all five. How can Congress:

- Enable the FDA to consistently and transparently apply the best science to reviews and policymaking that guides development protocols?
- Eliminate barriers and inefficiencies that increase cost, increase time, and distract FDA from its core mission?
- Ensure the cost of development is not a barrier to new medical products?

For each of these, we hope that you can help provide us some ideas at [Innovation@help.senate.gov](mailto:Innovation@help.senate.gov). Simply creating a new partnership has not worked over the last ten years. Merely putting out guidance may not help if it is applied inconsistently and is never revised to account for the best science that exists outside the FDA. We need to leverage the brilliant innovators, scientists, and entrepreneurs outside of government to reform the process, ensuring American patients have access to the best care possible. Together, we can confront these challenges head on and ensure that America innovates for patients—now and in the future.

## **Appendix A: Definitions**

**Biomarker:** refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly. Medical signs stand in contrast to medical symptoms, which are limited to those indications of health or illness perceived by patients themselves. Examples of biomarkers include everything from pulse and blood pressure to more complex laboratory tests of blood and other tissues.

**Biosimilar:** is a biological product (a biologic) that is highly similar to an FDA-approved biological product notwithstanding minor differences in clinically inactive components. A biologic is a large molecule typically derived from living cells and used in the treatment, diagnosis or prevention of disease. Unlike generic medicines where the active ingredients are identical, biosimilars are similar to but not identical copies of the originator biologic. For a biosimilar to be approved, it must be so similar to the original biologic that statistically speaking you can't tell the difference in terms of ability to treat the disease, safety, and quality.

**Companion Diagnostic:** is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks. Companion Diagnostics and Personalized Medicine go Hand-in-Hand.

**Extramural Research:** Research supported by NIH through a grant, contract, or cooperative agreement. ([NIH](#))

**Intramural Research:** Research conducted by, or in support of, employees of the NIH. ([NIH](#))

**Low to Moderate Risk Medical Device:** FDA classifies devices according to the risk they pose to consumers.

Class I devices present a low risk of harm to the user and are subject to general controls that are sufficient to protect the user. Most are exempt from the regulatory process. Examples of Class I: arm slings, examination gloves, elastic bandages.

Class II devices are more complicated and require special controls for labeling, guidance, tracking, design, performance standards, and postmarket monitoring. Most require Premarket Notification 510(k). Examples: contact lens care products, CT Scanners, powered wheel chairs. ([FDA](#))

**High-Risk Medical Device:** High-Risk Medical Devices are considered Class III devices. These devices usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury. They have the toughest regulatory controls. Examples: pacemakers, implanted weight loss devices. ([FDA](#))

**Medical Countermeasure:** A drug or device that is used to diagnose, mitigate, prevent, or treat harm from any biological, chemical, radiological, or nuclear agent or a condition that may result in an adverse health consequence that may be caused by administering such drug or device.

**Phase I:** First stage of the clinical trial process, and the emphasis is on safety. Phase 1 studies are usually conducted in healthy volunteers. The goal here is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted. The number of subjects typically ranges from 20 to 80. ([FDA](#))

**Phase II:** Phase 2 studies begin if Phase 1 studies don't reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300. ([FDA](#))

**Phase III:** Phase 3 studies, usually the last premarket study and largest trial, begin if evidence of effectiveness is shown in Phase 2. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people. ([FDA](#))

**Surrogate Endpoint:** Measures that can replace or supplement other endpoints in evaluations of experimental treatments or other interventions. Surrogate endpoints are useful when they can be measured earlier, more conveniently, or more frequently than the "true" endpoints of primary interest.

**Translational Research:** The “bench-to-bedside” enterprise of using knowledge from basic research to produce new drugs, devices, and diagnostics for patients. ([JAMA](#))

## **Appendix B: Acronyms**

ALS: Amyotrophic Lateral Sclerosis

AMP: Accelerating Medicines Partnership

APA: Administrative Procedures Act

BLA: Biologic Licensing Application

BrIDGs: Bridging Interventional Development Gaps

CDISC: Clinical Data Interchange Standards Consortium

CBER: Center for Biologics Evaluation and Research

CDER: Center for Drug Evaluation and Research

CDRH: Center for Devices and Radiological Research

CLIA: Clinical Laboratory Amendments

CIO: Chief Information Officer

COA: Clinical Outcome Assessment

CoMMpass: A longitudinal study of patients with newly-diagnosed active multiple myeloma. The goal is to map each patient's genomics profile to clinical outcomes to develop a more complete understanding of patient responses to treatment.

CTSA: Clinical and Translational Science Awards

CTTI: Clinical Trial Transformation Initiative

DARPA: Defense Advanced Research Projects Agency

EU: European Union

FDA: Food and Drug Administration

FDAMA: Food and Drug Administration Modernization Act

FDASIA: Food and Drug Administration Safety and Innovation Act

GAO: Government Accountability Office

HELP: Senate Health, Education, Labor, and Pensions Committee

ICs: Institutes and Centers

IMDRF: International Medical Device Regulators Forum

IMEDS: Innovation in Medical Evidence and Surveillance

IMI: Innovative Medicines Initiative

I-SPY I and II: A national study to identify biomarkers predictive of response to therapy throughout the treatment cycle for women with Stage 3 breast cancer.

IT: Information Technology

LDTs: Laboratory Developed Tests

Lung-MAP: Lung Cancer Master Protocol, first-of-its kind clinical trial that uses a multi-drug, targeted screening method to match patients with studies of investigational new treatments

MD: Medical Doctor

MDIC: Medical Device Innovation Consortium

NCATS: National Center for Advancing Translational Sciences

NCI: National Cancer Institute

NCTR: National Center for Toxicological Research

NDA: New Drug Application

NIDA: National Institute of Drug Abuse

NIH: National Institutes of Health

OCP: Office of Combination Products

OTC: Over-The-Counter

PCORI: Patient Centered Outcomes Research Institute

PDUFA: Prescription Drug User Fee Act

RUF: Reagan-Udall Foundation

TB: Tuberculosis

TEA: "Time and Extent Application"

Tox21: Toxicology in the 21<sup>st</sup> Century

## **Appendix C: FDA Correspondence**

- I. Letter to Commissioner Hamburg from Senate HELP Members, May 2014
- II. Letter to Commissioner Hamburg from Sens. Alexander and Burr, August 2014
- III. Response, Commissioner Hamburg to Sens. Alexander and Burr, October 2014
- IV. Response, Commissioner Hamburg to Sens. Alexander and Burr, January 2015



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## United States Senate

COMMITTEE ON HEALTH, EDUCATION,  
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WASHINGTON, DC 20510-6300

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<http://help.senate.gov>

May 6, 2014

The Honorable Margaret Hamburg  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20093

Dear Commissioner Hamburg:

We write today to express significant concern about the U.S. Food and Drug Administration's (FDA) use of draft guidances to make substantive policy changes.

According to the FDA website, "Level 1 guidances set forth the agency's initial interpretations of new significant regulatory requirements; describe substantial changes in FDA's earlier interpretation or policy; and deal with complex scientific or highly controversial issues."

Stakeholders tell us that draft guidances are increasingly becoming default FDA policy and position. Draft guidances state that the "guidance document is being distributed for comment purposes only." However, in the absence of finalized guidance, drafts are the only information that FDA review staff, patients, clinicians, and FDA-regulated entities have on the agency's most current thinking on important issues.

One major concern is that the agency's website does not differentiate between draft and final guidances, making it seem that the documents have equal weight, and undercutting the important purpose of soliciting public comment on draft guidances.

A second concern is that these draft guidances are not being revised, finalized, or withdrawn in a timely manner. We believe that public comment from FDA-regulated entities, health care providers, consumers, and patients not only will help shed light on any unintended consequences of the agency's draft guidance, but better inform and, ultimately, improve that guidance. It is integral that those improvements are reflected in updated guidance documents and the guidance is being appropriately and consistently applied by product reviewers.

Third, we are concerned that, although the agency's draft guidances state that the "guidance document is being distributed for comment purposes only," in the absence of finalized guidance these drafts are the only information that FDA review staff, patients, clinicians, and FDA-regulated entities have on the agency's most current thinking on important issues and feel compelled to follow draft guidances as if they were final.

For example, at the Health, Education, Labor and Pensions Committee Hearing on Thursday, March 13<sup>th</sup>, there was a discussion on the guidance on abuse-deterrent formulations and you said that “the guidance is very important and lays out how we’re thinking about it”, yet that guidance is still in draft form and states “Not for implementation.”

Another example: draft guidance, published in June 2013 on cyclosporine emulsion bioequivalence, is still available in draft form even after doctors and patients, including the American Academy of Ophthalmology and American Glaucoma Society, submitted comments expressing concerns regarding the safety and reasoning behind the guidance. Because that draft is still available, and is FDA’s only public statement, FDA application reviewers, drug manufacturers, doctors, and patients may believe that it is the Agency’s current thinking. If that draft guidance is not FDA’s current thinking, or FDA’s current thinking has changed due to the concerns raised in the comments, it would be best to withdraw, revise, or finalize the draft guidance.

In addition, according the President’s Council of Advisors on Science and Technology in the *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation*, drug manufacturers require greater clarity about how innovative products are regulated. The report states that “the development of rapid, clear, and thorough guidance documents that reflect the consensus of the scientific community on new and emerging areas of scientific innovation could help address this need.”

Our fourth concern is that, despite those findings, FDA issues guidance that seemingly does not take into account, or may even conflict with, the scientific community. For example, FDA recently issued a draft guidance on the use of blood glucose monitoring systems in patient care settings, and chose not to follow the international scientific community’s recommendation on regulatory standards.

To help us better understand the FDA’s use of guidances to effectively communicate with FDA-regulated entities seeking advice on how to bring life-saving medical products to patients, we respectfully request that you provide information and answers to following questions:

1. A list of all Level 1 Draft Guidances, including the date issued, and the timeline with which you plan to withdraw, revise, or finalize each guidance.
2. An update on Agency-wide activities to implement the “best practices” to make the finalization of guidance more efficient and expeditious, as discussed in the 2011 report *Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency*.
3. Have you implemented the President’s Council of Advisors on Science and Technology recommendation to rely more on the biomedical community in help developing and revising guidances, and if so, could you provide examples of specific guidances?

4. For the guidances still in draft form, how do you ensure your staff does not follow the guidance in the absence of any other policy or final guidance?
5. What is the average amount of time in calendar days that the FDA has taken to finalize draft guidances in the last five years? What is the range?

Thank you for your consideration of this request. If you have any questions, please have your staff reach out to Ranking Member Alexander's staff Grace Stuntz at (202)224-6770.

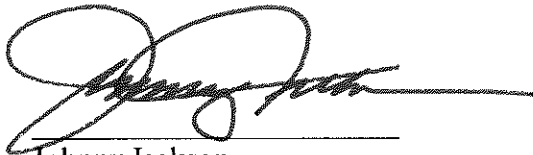
Sincerely,



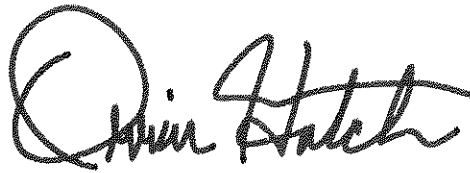
Lamar Alexander  
Ranking Member



Richard Burr  
U.S. Senator



Johnny Isakson  
U.S. Senator



Orrin G. Hatch  
U.S. Senator

BARBARA A. MIKULSKI, MARYLAND  
PATTY MURRAY, WASHINGTON  
BERNARD SANDERS (I), VERMONT  
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TIM SCOTT, SOUTH CAROLINA

## United States Senate

COMMITTEE ON HEALTH, EDUCATION,  
LABOR, AND PENSIONS

WASHINGTON, DC 20510-6300

PAMELA J. SMITH, STAFF DIRECTOR  
DAVID P. CLEARY, REPUBLICAN STAFF DIRECTOR

<http://help.senate.gov>

August 1, 2014

The Honorable Margaret Hamburg  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20093

Dear Commissioner Hamburg:

We write today to request information and details about hiring and training, information technology, regulatory science programs, and human medical product regulation at the U.S. Food and Drug Administration (FDA). We have heard from many patients, innovators, and providers regarding both the opportunities available and challenges faced when ensuring the FDA is well prepared to regulate medical products in the 21<sup>st</sup> century.

The FDA regulates about 25 cents of every dollar of the U.S. economy, and as the agency's responsibilities and authorities have increased in recent years, many of the challenges facing the agency have compounded. Strong management of the agency's workforce, including its approach to hiring and training, the agency's utilization of information technology, and prioritization and incorporation of regulatory science into the review of medical products, are all key aspects of meeting the challenges of regulating products in the 21<sup>st</sup> century.

Therefore, to enable us to better assist the agency in each of these key areas, please provide detailed answers to the following questions:

### *Hiring and Training*

1. How long, on average, does it take for the FDA to hire an individual not currently employed by the federal government? Please sort by Center and the level or type of position (lawyer, scientist/reviewer, etc.).
2. Once a new reviewer is hired, how long is that employee trained before beginning review of applications or submissions? What FDA-wide training programs are available for FDA employees, including training on pre-approval considerations and post-approval evaluation and surveillance matters? Have employees requested any additional specific training in the last three years, and if so, in what areas?
3. Are regional employees, and employees located outside the U.S., able to take advantage of the agency's training opportunities? Please provide information by Center, and if it

varies among divisions please include that information as well. If there are differences in training in district offices and in FDA offices outside the U.S., please describe the differences and the rationale for such different training programs.

4. How long does it take for a new employee to become a full-fledged reviewer of human medical products or, in the case of field staff, a full-fledged inspector or investigator? Are employees subject to minimum annual training or continuing educational requirements? Please include variability by division, center, or office if applicable, and information on training for agency staff sponsored by FDA's National Center for Toxicological Research (NCTR).
5. If there is variability in training and time to be an independent reviewer or inspector, how often do Centers or divisions meet to discuss different methods of training?
6. What is the average duration employees stay at the FDA? Please specify by level and type of position if possible.
7. How many vacancies and acting positions are there currently at the agency? Please separate leadership vacancies and acting positions. What are the biggest hurdles to filling these positions?
8. How many contractors perform work for the agency as compared to the number of FDA employees?
9. Please provide a list of all the contracts awarded or renewed in the last five years, provide a description of the contract goal and funding awarded, and designate for which Center(s) contractors performed work.
10. In 2009, the Government Accountability Office (GAO) reported that your agency faced challenges fulfilling and managing its growing medical product oversight responsibilities. GAO recommended that FDA take steps to establish a comprehensive and reliable basis for substantiating the agency's resource needs. FDA subsequently contracted with Booz Allen Hamilton to develop an evidence-based approach to enable the agency to make accurate and repeatable estimates of the resources needed to fulfill its medical product responsibilities. Please share this report, and any other reports done by contractors regarding management and human resources, and describe how useful this approach has been and how the agency has incorporated it into its resource planning.

#### *Information Technology (IT)*

1. What IT functionalities and equipment does each Center, or division where applicable, currently use to review the increasingly novel technologies coming before the agency for review and consideration?
2. What specific technologies or IT improvements does the FDA need, but currently does not have, to better achieve the agency's mission?
3. How much has the FDA spent, by Center, on IT systems over the last 5 years? Please list all the contracts for IT over the last 5 years, including the name of the contractor, the worth and duration of the contracts, and the renewal terms for the contracts.

4. How are FDA employees trained on new IT systems? Do medical product review employees and others have input on what functionalities would be most helpful to them in meeting their day-to-day responsibilities?
5. In what form are applications and submissions submitted and then tracked through the agency's review process? Please provide information by Center, and also by type of application and submission.
6. Are applications and submissions submitted in standardized data formats? Are FDA employees required to do conversions, or other data manipulations, before analysis can begin? Are there any efforts ongoing at FDA to standardize the submissions?
7. Please provide an update on the status of the Mission Accomplishments and Regulatory Compliance Services (MARCS) program, which we understand to be FDA's largest system modernization effort, with a cost of about \$280 million.
8. Please describe the current status of the PREDICT system including a list of the products subject to screening, the locations where it has been utilized, the staffing levels at each location, the sources of data that informs the screening rules, and the benefits realized to date. Are the same protocols followed at each of the locations where PREDICT is used?
9. Has FDA developed a comprehensive list of its IT systems, as called for in guidance issued by the Office of Management and Budget and GAO in 2012?
10. We understand that FDA had a goal of retiring eight legacy IT systems in 2013 and 2014 and replacing them with modernized systems. Has that taken place? Why or why not?

### *Regulatory Science*

1. Please provide a list of the public-private partnerships that focus on examining novel regulatory science questions, accelerating innovation, and assisting in the development of medical products that the FDA is involved with, including both by providing funding or providing expertise and employee time.
2. For each of the list above, please provide the amount of funding provided by the agency and an estimate of staff resources delegated to each partnership. How many employees are involved in these partnerships? On average, how much time do each of these staff members spend on partnership-related activities each month?
3. In the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health, how are patient risk/benefit documents and discussions from patient group meetings informing the review process and prioritization of the agency's regulatory science work?
4. How are real world data, patient reported information, and foreign clinical trial data being used by employees of the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health both in the premarket and post-market evaluation and surveillance of drugs, biologics, and medical devices?

5. Given the increase in the number of applications and submissions to the Office of Combination Products, how are the various centers coordinating the review of combination product submissions to ensure that these products move through the review process as quickly as possible, without any unnecessary delays, especially in the case of drug and device combination products whereby more than one center will review such product? And given the need to coordinate with multiple Centers, how are the statuses of these submissions tracked?
6. Please describe the costs and accomplishments associated with (a) FDA's Advancing Regulatory Science Initiative, which was launched in February 2010, (b) the implementation of FDA's Strategic Plan for Regulatory Science, which was issued in August 2011, and (c) the creation of FDA's Centers of Excellence in Regulatory Science and Innovation at the University of Maryland and Georgetown University, which were established in October 2011.
7. In 2010, FDA announced it was establishing a new collaborative effort with the National Institutes of Health (NIH) to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. What is the status of this collaboration? What activities have the two agencies engaged in together and what distinguishes the role of each agency? What has been the cost to FDA and NIH?
8. What routine collaboration exists across medical product centers? How do Centers typically communicate and share information with each other? Do senior managers meet with their counterparts in other Centers on a regular basis? Can they access information—at least in a “Read Only” mode—in one another's various IT systems?
9. What role does FDA's National Center for Toxicological Research (NCTR) play in regulatory science, given biomarkers, regulatory science training, and personalized medicine are three of NCTR's five research focus areas? How do the medical product centers interact with NCTR staff and leverage their expertise in the review of medical products?

#### *Medical Product Regulation*

1. The standard for drug approval has remained unchanged since 1962. Since then, however, Congress has repeatedly signaled an interest in allowing flexibility to meet the standards of safety and efficacy. Can you please provide, for 1980-89, 1990-99, 2000-09, and 2010-present a list of the types of pre-clinical and clinical studies that were performed and the questions asked to show safety and efficacy?
2. The standard for medical device approval and substantial equivalence has been unchanged since 1976. Can you please provide for the same time periods as described in question 1, the types of pre-clinical and clinical studies that were required to meet the statutory standard?



3. In both questions above, if the types of studies changed over time, please provide rationale for why the additional types of studies were necessary to meet the standard when they may have not been previously necessary.
4. What do you consider the least risky medical products that you regulate?
5. To what extent has FDA considered alternatives to clinical trials as a means of establishing a product's safety and efficacy? For example, please describe the progress of FDA's collaboration with the Medical Device Innovation Consortium and the potential use of computational modeling and simulations.
6. Please describe the role of staff who review medical product applications in monitoring post-market safety. With much emphasis placed on the preapproval of medical products, how does FDA ensure that staff devote sufficient attention to post-market responsibilities?

*Over-the-Counter Drug Regulation*

1. How many new drug applications have been submitted for over-the-counter (OTC) products? Please provide data for the last five years by year, and categorize by the type of submission, including a switch from a prescription drug to OTC status, a new version of an existing ingredient, etc.
2. How many supplemental new drug applications were submitted for OTC products? How many of these were submitted in response to a request from FDA? Please categorize when possible the type of submission, such as a label change, safety update, or other type of supplement.
3. What is the revenue generated by FDA by OTC products, by type of application?
4. What is the status of each uncompleted monograph? Where in the approval process is each monograph regulation?
5. How many FTEs are working on OTC monographs? Could you please provide the number of FTEs for each of the past five years?
6. Please provide a detailed outline of the approval process for rulemaking related to OTC monographs.

Please respond in writing no later than August 29, 2014. If you have any questions, please have your staff contact Grace Stuntz at (202)224-0623 and Anna Abram at (202) 224-3154.

Sincerely,



Lamar Alexander  
Ranking Member



Richard Burr  
U.S. Senator



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

The Honorable Lamar Alexander  
Ranking Member  
Committee on Health, Education, Labor and Pensions  
United States Senate  
Washington, D.C. 20510-4206

OCT 10 2014

Dear Senator Alexander:

Thank you for your letter of August 1, 2014, cosigned by Senator Richard Burr, regarding hiring and training, information technology, regulatory science programs, and human medical product regulation at the Food and Drug Administration (FDA or the Agency). As we discussed with your staff, we will be providing rolling responses. This is our first partial response and addresses Question 9 under the topic *Regulatory Science* regarding the FDA's National Center for Toxicological Research (NCTR) and complete responses to the *Over-the-Counter (OTC) Drug Regulation* section.

*Regulatory Science*

The 21st century has seen rapid advances in biomedical research. New cutting-edge technologies that have led to thousands of new drug candidates include: the sequencing of the human genome; combinatorial chemistry, a new method of chemical synthesis that makes it possible to prepare thousands of compounds in a single process; biosynthesis, which enables scientists to synthesize complex chemicals in living cells; and high throughput screening, which allows researchers to quickly conduct millions of genetic, chemical, or pharmacological tests. In addition, cutting-edge electronics and materials science have the power to transform medical devices, and research on nanotechnology-based materials will provide a better understanding of the safety of the use of nanomaterials in food, over-the-counter drugs, and cosmetics. FDA's regulatory science research agenda is critical to help translate new technologies and basic science discoveries into safe and effective real-world diagnostics, treatments, and cures and reduce the time, complexity, and cost of product development.

FDA recognizes that advancing regulatory science is necessary to enable FDA to keep abreast of emerging technologies, and indeed, to stay ahead of the curve. In 2011, the Agency released its strategic plan entitled "Advancing Regulatory Science at FDA." Since that time, FDA has been modernizing its scientific infrastructure by enhancing its internal research capacity and access to outside scientific expertise, and by expanding external collaborations. As we discuss below, NCTR has been an important part of FDA's effort in this area.

We have restated in bold below, Question 9 under *Regulatory Science*, followed by our response.



**9. What role does FDA's National Center for Toxicological Research (NCTR) play in regulatory science, given biomarkers, regulatory science training, and personalized medicine are three of NCTR's five research focus areas? How do the medical product centers interact with NCTR staff and leverage their expertise in the review of medical products?**

NCTR is part of FDA's overall efforts to advance regulatory science. As a national scientific resource, NCTR conducts peer-reviewed research to advance scientific approaches and tools required to support public health and to improve FDA's ability to assess the safety of regulated products. Many of these projects are conducted in collaboration with or funded by the other FDA medical product Centers. Some examples of NCTR's contributions to regulatory science for FDA are noted below in the areas of biomarkers, personalized medicine, and regulatory science training.

**Biomarkers:**

NCTR is currently conducting 34 projects in the area of biomarkers. Researchers there identify and evaluate translational biomarkers of toxicity and disease in preclinical and clinical studies. An example of biomarker research includes the identification of a set of 16 predictive genes for non-small cell lung cancer that may have potential as both a prognostic and predictive biomarker with clinical applications, allowing for earlier medical intervention.

**Personalized Medicine:**

NCTR is currently conducting 55 projects in the area of personalized medicine that include the development of biomarkers, technologies, and tools to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Classifications include genetics, sex, age, and lifestyle and environmental factors, such as smoking and obesity. These studies could then lead to changes in clinical studies or practice to maximize benefits while minimizing side effects and unnecessary treatments and tests.

Scientists from NCTR, FDA's Center for Drug Evaluation and Research (CDER), and the Marshfield Clinic Research Foundation demonstrated the potential utility of the FDA Adverse Event Reporting System (FAERS) for identifying disease characteristics in drug-safety monitoring. In this pilot study, data-mining approaches were used to identify potential sex-biased diseases from FAERS. This approach could be further applied to other publicly available disease surveillance databases and used to study other disease risk factors, such as age or ethnicity. Future plans for research in the area of personalized medicine include determining whether some drugs cause a higher incidence of liver toxicity in women than in men and completing research that promotes women's health with personalized approaches to breast cancer.

**Regulatory Science Training:**

The global nature of products coming under FDA scrutiny requires partnerships in regulatory research and training. FDA is addressing this issue via several programs, including NCTR's continued long history of mentoring. NCTR has trained hundreds of scientists from over 45 different countries. NCTR provides opportunities for undergraduate and graduate students,



post-graduate scientists, scientists from other countries, college/university faculty members, and others to obtain hands-on laboratory experience by working with experienced scientific researchers. NCTR formal programs include: Science Training and Exchange Professional Development Program, Faculty Research Program, Foreign National Training Program, Interdisciplinary Toxicology Program, Post-graduate Research Program, Science Internship Program, Summer Student Research Program (21 students in 2014), and the Graduate Certificate in Regulatory Science (through University of Arkansas for Medical Sciences in conjunction with NCTR).

In addition to providing training to the broader research community, NCTR also provides the technical expertise and capability to support regulatory research and surveillance needs of FDA and government agency partners. An example of this is the NCTR/Office of Regulatory Affairs (ORA) Nanotechnology Core (NanoCore) Facility's third annual nanotechnology "Hands-On" training course for FDA employees, held in August 2014. Participants from six FDA Centers and ORA were introduced to the strengths and weaknesses of the most common methods used in characterizing nanoparticle size. The training opportunity is designed to equip reviewers and scientists with the ability to evaluate the safety of nanomaterials incorporated into FDA-regulated products.

Regarding NCTR interaction with FDA's medical product Centers, mechanisms are in place to ensure that NCTR conducts research to support the Center for Biologics Evaluation and Research (CBER), CDER, Center for Devices and Radiological Health (CDRH), Center for Food Safety and Applied Nutrition (CFSAN), Center for Veterinary Medicine (CVM), and the Center for Tobacco Products (CTP). One mechanism is the Science Advisory Board (SAB), with FDA Center representatives and a board of scientists advising NCTR on research directions and projects. NCTR has a 22-year Interagency Agreement with the National Institute of Environmental Health Sciences National Toxicology Program, and research projects conducted under this program are discussed with regulatory scientists and subject-matter experts from the FDA Product Centers to ensure that NCTR conducts innovative scientific research that assists FDA in fulfilling its regulatory responsibilities. As a result of communication between NCTR and FDA Centers, NCTR scientists are currently conducting 42 research projects in collaboration with CDER, CBER, or CDRH.

Regulatory science is an area we continue to develop. NCTR is part of that plan.

### OTC Drug Regulation

By way of background, we are providing information about the two regulatory pathways potentially available for an OTC drug product to reach the market: the New Drug Application (NDA) process and the OTC Monograph process.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires FDA review and approval of all new drugs before they may be marketed in the United States. An NDA<sup>1</sup> involves evaluation

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<sup>1</sup> The FD&C Act also enables premarket review and approval of drug products that are generics of other approved new drugs, under an Abbreviated New Drug Application (ANDA). OTC drug products may be approved under NDAs or ANDAs. For FDA to approve a drug product for OTC use under an ANDA, the reference listed drug must also be approved for OTC use.



and approval of a specific drug product (in a particular formulation). Under the NDA process, some drug products are approved initially for OTC use (i.e., without a prescription), but many are first approved for prescription use only and later approved for OTC use based on data showing that the drug product is safe and effective for use in self-medication. Often the submission includes data from the following types of studies: (1) a label-comprehension study, which assesses the extent to which consumers understand the information on the product's labeling; (2) a self-selection study, which tests whether consumers can apply the product labeling information to their personal medical situations and make correct decisions to use or not use the drug product; and (3) an actual-use study, which assesses how consumers will use the drug product. FDA reviews the new data, along with any information known about the drug from its prescription use. Once approved, an OTC drug subject to an NDA may be marketed only in the particular formulation approved by FDA.

The second regulatory pathway is inclusion in the OTC monograph system, a system which grew out of the OTC drug review program that was established to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972. The OTC Drug Review covered drug products that had been marketed in the United States up to that time and that would not be considered "new drugs" as defined in the FD&C Act. To avoid "new drug" status as defined in the FD&C Act, a drug must be generally recognized as safe and effective (the GRAS/E standard), and also must have been marketed to a material extent and for a material time under the conditions described in its labeling (the material time-and-extent standard), 21 United States Code (U.S.C.) 321(p). Unlike the NDA process, which focuses on the approval of individual specific drug products, the ongoing OTC monograph program is a four-phase public rulemaking process (each phase requiring a *Federal Register* publication), resulting in the establishment of monographs for various OTC therapeutic drug categories. Each monograph is a regulation that establishes conditions under which drug products in a given therapeutic drug category are GRAS/E and not misbranded. Unlike an NDA, the OTC drug monographs do not address every aspect of formulation for the finished drug products that fall within their ambit, but describe general characteristics, such as active ingredients and labeling tied to the use of product. Under an OTC drug monograph, manufacturers market a variety of differently formulated individual drug products so long as the products conform to the terms of the monograph as well as other general requirements for OTC drugs. FDA's determination that all OTC drugs in the therapeutic category covered by the monograph would be GRAS/E for use under the conditions described in that monograph must be supported by publicly available data that satisfy the requirements and evidentiary standards specified in FDA's OTC drug regulations.

In order to ensure that the active ingredients and other conditions included in the OTC monographs satisfy both the GRAS/E and material time-and-extent standards described above, the OTC monograph process was originally open only to active ingredients and other conditions that were marketed for OTC use in the United States before the inception of the OTC Drug Review in 1972.

The Time and Extent Application (TEA) process, established by regulations finalized in 2002 (21 CFR 330.14(g)), expanded the scope of the OTC Drug Review. This regulation provides a



potential pathway to OTC monograph status for newer active ingredients and other conditions<sup>2</sup> (primarily those with no U.S. marketing history) by enabling sponsors to establish that a condition satisfies the threshold eligibility requirement of a “material time and extent” of OTC marketing, based on historic marketing data other than the date of U.S. market entry (TEA eligibility requirements). Active ingredients and other conditions that satisfy the TEA eligibility requirements are subject to the same evidentiary requirements and GRAS/E standard that apply to other active ingredients and conditions under the OTC monograph process. In addition, consistent with the processes described above for the OTC drug monograph process generally, ingredients found eligible under TEA applications are subject to multi-step notice-and-comment rulemaking procedures before they may be included in a final OTC drug monograph. The TEA process is not supported by user fees.

FDA has been assessing the OTC monograph process, including the TEA process, and, in particular, has been considering how effectively the monograph system is functioning in today’s world, 40 years after its inception, from the scientific, policy, and process perspectives. To inform its thinking, FDA held a public Part 15 hearing (21 CFR Part 15) on March 25 and 26, 2014, to solicit opinions about whether and how to modernize the process for the future. Specifically, FDA sought input from the public on the strengths and weaknesses of the current OTC monograph process, and sought to obtain and discuss ideas about modifications or alternatives to this process. The Agency is currently reviewing the input received in conjunction with the hearing.

We have restated Questions 1 through 6 from the *Over-the-Counter Drug Regulation* in your letter, below in bold, followed by FDA’s responses.

- 1. How many new drug applications have been submitted for over-the-counter (OTC) products? Please provide data for the last five years by year, and categorize by the type of submission, including a switch from a prescription drug to OTC status, a new version of an existing ingredient, etc.**

Between October 1, 2009 (the beginning of fiscal year (FY) 2010) and August 13, 2014, 26 NDAs were received by the Office of New Drugs (OND) for OTC drug products.<sup>3</sup> Of these 26 NDAs, nine were resubmitted applications following refusal to file incomplete applications or issuance of complete response or not approvable actions. Below are data for five years by type of submission. Note that these counts do not include ANDAs for OTC drug products submitted to the Office of Generic Drugs (OGD) over this same period.

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<sup>2</sup> In addition to active ingredients, new “conditions” can include for example, new dosage forms, or additional indications for active ingredients already regulated under OTC monographs.

<sup>3</sup> Seventeen new drug applications were submitted for the first time and nine new drug applications were resubmitted following refusal to file incomplete applications or issuance of complete response or not approvable actions.

FY	Rx to OTC Switch <sup>a</sup>	New Molecular Entity	New Active Ingredient	New Dosage Form	New Combination of Active Moieties	New Formulation*	New OTC Indication	Total
2010	4	1	1	1	1			7 <sup>+</sup>
2011	1			1	1	1		4
2012	1		2	1				4
2013	4		1	1	1	2	1	10
2014				1				1
								26

<sup>a</sup> Rx to OTC switch NDAs propose that some of the conditions of use for an approved prescription drug product be available in the OTC setting only. This is often referred to as a partial Rx to OTC switch.

\* A new formulation is a significant change in inactive ingredients of a drug product that requires bioequivalence or clinical studies for approval.

<sup>+</sup> One NDA was classified as a New Molecular Entity and a New Combination of Active Moieties.

**2. How many supplemental new drug applications were submitted for OTC products? How many of these were submitted in response to a request from FDA? Please categorize when possible the type of submission, such as a label change, safety update, or other type of supplement.**

Three hundred fifty-two supplemental new drug applications (SNDAs) were received by OND for OTC drug products between FY2010 and FY2014. These applications propose various changes to drug products already approved under NDAs. We do not keep a list of which were submitted in response to an FDA request, but we believe it would be a minimal number. Below we have categorized SNDAs by type of submission. The SNDAs also include safety-related updates, though we cannot generate a report on the number of safety-related supplements specific to OTC drug products. Most labeling supplements are for changes to the products' packaging (e.g., design, graphics, font changes).

FY	Efficacy Supplements <sup>a</sup>	Labeling Supplements	Chemistry Supplements*
2010	17 <sup>+</sup>	49	49
2011	3	56	11
2012	2	51	10
2013	5	36	10
2014	4 <sup>+</sup>	48	1

<sup>a</sup> Efficacy supplements propose changes to approved NDAs that are related to effectiveness claims in product labeling.

\* Chemistry supplements propose changes to information in the chemistry, manufacturing, and controls section of NDAs for approved drug products (e.g., manufacturing processes, test methods and specifications, product expiration date, stability information).

<sup>+</sup> Includes full Rx to OTC switch SNDAs, where all conditions of use for a prescription drug product are proposed for the OTC setting only. FY2010 included four such SNDAs and FY2014 included one SNDA.



### 3. What is the revenue generated by FDA by OTC products, by type of application?

OTC drug product applications that are reviewed under the NDA process are assessed user fees under the Prescription Drug User Fee Act (PDUFA).<sup>4</sup> Most OTC drugs are regulated under the OTC drug monograph system and are not subject to PDUFA or any other form of fees or funding for FDA. PDUFA fees are proscribed from use for non-PDUFA activities.

OTC User Fee Revenue				
Fiscal Year	New Applications	Resubmitted Applications	Supplemental Applications	Total
FY 2010	\$ 6,324,785	\$ 589,000	\$ 3,259,100	\$ 10,172,885
FY 2011	-	1,071,700	771,000	1,842,700
FY 2012	2,762,250	-	1,841,500	4,603,750
FY 2013	13,711,600	1,247,200	2,938,200	17,897,000
FY 2014	2,169,100	-	1,084,550	3,253,650
	\$ 24,967,735	\$ 2,907,900	\$ 9,894,350	\$ 37,769,985

The changes in revenue from year to year vary because of the number and type of applications submitted, as well as being subject to changes in fee structure on the PDUFA schedule.

### 4. What is the status of each uncompleted monograph? Where in the approval process is each monograph regulation?

The Agency's Internet website includes a webpage entitled "Status of OTC Rulemakings," which provides links to the individual pages that discuss the status and regulatory history of each of the OTC drug monographs, organized by therapeutic category.<sup>5</sup> The therapeutic category pages contain links to the Advance Notices of Proposed Rulemakings, Proposed Rules, and Final Rules associated with the therapeutic category. On these webpages, you can find the status of each uncompleted monograph. In addition, the Unified Agenda of Regulatory and Deregulatory Actions provides information about rulemakings that we plan to issue within approximately one year from publication of that edition of the Unified Agenda.<sup>6</sup> All other rulemakings are undergoing or awaiting division development, or division or office level review, and their progress may be delayed because FDA must allocate its limited resources among competing public health priorities.

Below is information about the status of the OTC drug review program more generally, including an estimate of the numbers of ongoing monograph rulemakings. Note that these estimates change depending on whether more than one issue can be combined into a single

<sup>4</sup> As noted in footnote 1 above, the FD&C Act also enables premarket review and approval of drug products that are generics of other approved new drugs, under an ANDA. OTC drug products may be approved under NDAs or ANDAs. For FDA to approve a drug product for OTC use under an ANDA, the reference listed drug must also be approved for OTC use. GDUFA provides for the assessment of fees for ANDAs and for FY 2013, the first year of assessment of fees, FDA collected \$154,560.

<sup>5</sup> <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/default.htm>

<sup>6</sup> See Unified Agenda published June 13, 2014 at <http://www.gpo.gov/fdsys/pkg/FR-2014-06-13/pdf/2014-13125.pdf>

rulemaking or if multiple rulemakings are necessary to address different components of one monograph.

#### Current Status of the OTC Drug Review Program (including TEAs)

- There are 26 original therapeutic categories (e.g., oral hygiene aids, analgesics)
- 88 current categories. For example, what was originally oral hygiene aids has become several separate monographs for the following categories of products:
  - Oral Anesthetic, Astringent, Antimicrobial, Debriding, Demulcent, Expectorant, Decongestant
  - Antigingivitis/Antiplaque
  - Oral Antiseptic
  - Toothache Relief, Tooth Desensitizer, Oral Mucosal Analgesic, Oral Mucosal Protectant
- Each category or subcategory covers multiple indications and ingredients (e.g., the antiseptic health care products monograph has 29 active ingredients and 5 indications).
- Approximately 20 rulemakings that are currently at the Tentative Final Monograph (TFM) (proposed rule) stage have never been finalized and products may be marketed in compliance with the applicable TFM pending monograph completion, consistent with a general or category-specific enforcement policy.
- Some monographs that have been finalized were later reopened to address a new safety concern, an advance in technology (e.g., new testing methods), or another issue.
- 14 TEAs have been found eligible for inclusion in an OTC monograph based on information regarding time and extent of marketing:
  - 8 are for sunscreen active ingredients, 5 of which have received letters conveying FDA's initial determination that the safety and effectiveness information provided did not provide a sufficient basis for FDA to determine that the ingredients could be added to the sunscreen monograph and identifying data gaps and other issues.
  - 6 others request the addition of new ingredients for dandruff (3), acne, laxative, and oral health care/antigingivitis products.
- Approximately 70 rulemakings are currently in the queue. These include:
  - monographs that have not been finalized and need to have final rules developed and issued
  - other monographs that have not been finalized, but because of new information (usually safety issues identified from use in the United States) will need to be amended and reissued as new TFMs or proposed rules and then finalized
  - monographs that have been finalized but because of new information (again, usually safety issues) must be reopened to obtain new information and for amendment (usually to remove an ingredient or add a new warning or change in directions for use or dose)



**5. How many FTEs are working on OTC monographs? Could you please provide the number of FTEs for each of the past five years?**

Please note that the number of FTEs identified below does not represent the full level of effort for the OTC monograph process, but captures those FTEs readily identifiable as mostly dedicated to the monograph process. There are staff in other divisions and offices that provide substantial input to the OTC monograph process (e.g., project managers, chemists, compliance officers, toxicologists, clinicians and especially policy and legal staff).

CDER's Division of Nonprescription Regulation Development (DNRD) staff is primarily responsible for monograph related work. The number of FTEs allocated to DNRD for the last 5 years (FY 2010 – FY2014) is 27. However, because DNRD staff also perform PDUFA-funded work for OTC NDA products, the number of dedicated FTEs to monograph work is approximately 18 for each of these years.

**6. Please provide a detailed outline of the approval process for rulemaking related to OTC monographs.**

As noted above, the use of rulemaking to address categories of OTC drug products began in 1972, when FDA initiated a scientific review of the active ingredients that were in marketed OTC drug products to evaluate their safety and effectiveness. The establishment of this review, called the OTC Drug Review or OTC Drug Monograph process, has thus far resulted in rulemakings to develop OTC drug monographs for each of 88 therapeutic categories of OTC drug products. The OTC Drug Review was prompted by the need to implement a statutory amendment requiring drugs to be effective, not just safe. Because of the large number of OTC drugs already on the market at that time (over 100,000 products featuring ~800 active ingredients and 1,400 uses), FDA determined that a product-by-product evaluation would not be feasible. Instead, FDA determined that it would be more efficient to focus its review on the active ingredients used in each OTC therapeutic category.

The OTC drug review is a four-phase rulemaking process to establish OTC monographs as prescribed by regulations (found in 21 CFR Part 330). Each phase requires publication in the *Federal Register* and allows for a period of public comment. The process culminates in the promulgation of regulations (sometimes referred to as final monographs) that establish standards under which drugs in each OTC therapeutic drug category are considered to be GRAS/E. In brief, the process includes:

- Publication of a call for data on the safety and effectiveness of active ingredients and other conditions that are eligible to be considered for monograph status;
- Review of data submissions by an advisory panel, followed by publication of the panel's initial evaluations and recommended GRAS/E active ingredients and conditions (Panel Report);
- FDA review of the Panel Report and related public comments, tentative GRAS/E determinations, and publication of a proposed monograph (proposed rule); and



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

The Honorable Lamar Alexander  
Chairman  
Committee on Health, Education, Labor, and Pensions  
United States Senate  
Washington, D.C. 20510-4206

JAN 21 2015

Dear Mr. Chairman:

Thank you for your letter of August 1, 2014, cosigned by Senator Richard Burr, regarding hiring and training, information technology, regulatory science programs, and human medical product regulation at the Food and Drug Administration (FDA or the Agency). As we discussed with your staff, we will be providing rolling responses. On October 10, 2014, we provided our first partial response. This is our second partial response, addressing Questions 1 through 8 under the topics *Hiring and Training* and *Regulatory Science*.

*Hiring and Training*

As noted in the recent release of the FDA's "2014-2018 Strategic Priorities" document,<sup>1</sup> FDA recognizes the importance of being a good steward of resources—both taxpayer dollars and user fees from industry—to achieve our mission. As our responsibilities increase and resources remain limited, we acknowledge that it is even more vital for FDA to enhance organizational excellence and accountability to the American public. As a result, FDA continues its commitment to the development of our workforce, systems, and infrastructure needed to address the emerging, complex challenges brought by the current operating environment.

A key component of FDA's ability to respond to the emerging challenges presented by today's complex, globalized regulatory environment is our ability to attract and retain a talented and diverse workforce. To address the challenge, FDA has developed and currently utilizes a fully integrated, Agency-wide human capital management approach to aggressively recruit, hire, develop, and retain skilled, high-performing employees so that FDA possesses the capabilities and capacities required to meet the breadth and depth of our statutory requirements. This human capital management program includes strategies such as the use of recruitment and retention incentives for hiring and retaining highly qualified scientific, medical, analytical, legal and management talent to fulfill our mission; tracking the development and advancement of science and research expertise in our internal workforce; promoting cross-disciplinary, regulatory-science training and research to address potential gaps and challenges posed by novel products; and improving opportunities for continuous learning, career development, and work-life balance throughout FDA's workforce. This integrated strategy will help ensure that we can develop

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<sup>1</sup> <http://www.fda.gov/aboutfda/reportsmanuals/forms-reports/ucm227527.htm>

high-impact solutions in a timely manner to address critical public health and regulatory challenges.

The responses to *Hiring and Training* questions below will provide a snapshot of FDA's current state and continued efforts. We have restated each question below in bold type, followed by our responses.

**1. How long, on average, does it take for the FDA to hire an individual not currently employed by the federal government? Please sort by Center and the level or type of position (lawyer, scientist/reviewer, etc.).**

From October 1, 2012, to present, on average, FDA is able to hire an individual from a vacancy announcement advertised for non-status Federal service within 132 days. Even though the Department of Health and Human Services (HHS), of which FDA is a part, as a whole is striving for 80 days, 132 days is the average, primarily because of the demand and expertise sought for specialized positions, such as Instructional Systems Specialists, Microbiologists, Consumer Safety Officers, and Consumer Safety Technicians, which can take longer than 80 days to fill. FDA is currently working to implement a corporate recruitment approach to fill key mission critical occupations through the use of open continuous announcements to ensure a ready source of candidates in an attempt to reduce hiring time frames.

The following is a breakdown of the average time to hire for non-status vacancies (i.e., individuals not currently employed by the Federal government) by position title and FDA Center. It should be noted that due to reliance on manual data entry within the human resources data system, possible data entry errors could have a statistical impact on the averages below.

Chart #1: Position Titles and Average Time to Hire:

Position Title	Average # of days to Hire
Accountant	221
Biologist	135
Chemist	125
Consumer Safety Officer	121
Consumer Safety Technician	120
Economist	79
Epidemiologist	121
Health Scientist	115
Information Technology Specialist (INFOSEC)	84
IT Project Manager	192
IT Specialist	117

Management and Operations Specialist	100
Management Assistant	157
Mechanical Engineer	40
Microbiologist	147
Operations Research Analyst	97
Policy Analyst (Tribal Affairs)	549
Policy Counsel	95
Program Support Specialist	101
Public Affairs Specialist (Press Officer)	116
Regulatory Health Project Manager	171
Regulatory Information Specialist	199
Regulatory Scientist	61
Research Microbiologist	61
Sample Custodian, WG-05	153
Senior Advisor	146
Senior Regulatory Health Project Manager	199
Sr. Health Science Project Specialist	135
Student Trainee (Biological Science)	61
Writer-Editor	91
Budget Analyst	108
Mathematical Statistician	198
Quality Assurance Officer	111
Interdisciplinary Scientist	124
Instructional Systems Specialist	208
Administrative Management Specialist	118
Secretary	117
Laboratory Support Tech	113
Consumer Safety Technician	165
<b>Average % of days</b>	<b>132</b>

Chart # 2: Centers Average Time to Hire:

AGENCY	DAYS
FDA Wide	132
CENTERS	DAYS

Office of the Commissioner	123
National Center for Toxicology and Research (NCTR)	153
Center for Veterinary Medicine (CVM) and Center for Food Safety and Applied Nutrition (CFSAN)	89
Center for Devices and Radiological Health (CDRH)	105
Office of Regulatory Affairs (ORA)	135
Office of Operations	137
Center for Biologics Evaluation and Research (CBER)	115
Center for Tobacco Products (CTP)	154
Center for Drug Evaluation and Research (CDER)	189

**2. Once a new reviewer is hired, how long is that employee trained before beginning review of applications or submissions? What FDA-wide training programs are available for FDA employees, including training on pre-approval considerations and post-approval evaluation and surveillance matters? Have employees requested any additional specific training in the last three years, and if so, in what areas?**

In general, new reviewer curricula across FDA is 24 months long, and encompasses both training programs and on-the-job training. For example, a new CBER reviewer must complete the New Reviewer Training, which is comprised of six classroom courses. Under the close supervision of a senior reviewer who has demonstrated the ability to review difficult submissions, the new reviewer begins working on the review of applications/submissions.

Similarly, the CDRH evaluates the knowledge, skills and abilities of newly hired reviewers. New employees are immediately assigned a mentor to help them learn and navigate the regulatory review process. A new reviewer will typically be an observer on a review team to begin to learn the process, followed by being asked to provide a consult on a submission. If timing and resources permit, the new reviewer may then be assigned a submission as co-lead with an experienced reviewer. Regardless of the roles, new reviewers are provided constant oversight by their mentors who have reviewed similar types of products, and by their management. As a reviewer gains more experience, more complex submissions are assigned and the need for support and oversight by the mentors, peers, and management decreases. Additionally new review staff are assigned to participate in the CDRH Reviewer Certification Program (RCP) within their first 90 days of arrival. The RCP is a 10-month program consisting of:

- 20 courses (18 required and 2 elective) available via online and classroom formats and totaling 136 hours of training. The training addresses the basic core competencies required for completing the premarket review process.
- Practical activities



- Submission Review Audit Process to ensure that review staff are prepared to meet the required performance expectations
- Knowledge assessment, which includes pre and post-testing of training content and a comprehensive exam at the conclusion, in order to be certified

CDRH employees have requested training (and have been trained) in the following areas:

<b>Information Technology</b>	<b>Leadership and Professional Development</b>	<b>Scientific and Regulatory</b>
Center-specific Information Technology Systems	Supervisory Leadership Training for Non-supervisors Negotiation Time Management Project Management Conflict Resolution	Guidance Training Clinical Trials Finite Element Modeling Quality Systems Anatomy and Physiology Human Factors Animal Models Biomaterials Risk Management Design Control

For new reviewers, the CDER provides approximately 20 courses in the Core Competency and Drug Review areas. New reviewers work with their team leaders and mentors to learn the review process and actively pursue the scientific/regulatory knowledge necessary to work at the full performance level.

Regarding FDA-wide reviewer training, the “FDA Training Policy Council” (TPC), created in 1993, is designed to facilitate networking and information-sharing among the Agency Senior Training Officials (STO). In 2010, the TPC established the “Learning and Development Council” (LDC), which includes both STO and Center training staffs, thus enabling wider training policy considerations to ensure that Center-specific reviewer training considerations are heard (see Attachment 1).

In association with the TPC and LDC, the FDA Office of Scientific Professional Development (OSPD) provides FDA-wide training through such programs as the Chief Scientist’s Distinguished Lecture Series, the Chief Scientist’s Special Lecture Series, Human Subjects Research Training, Medical Countermeasures Initiative Training, and FDA 101.

Finally, in regard to employee requested training, the following are examples of training needs highlighted by the Centers’ respective review staffs over the last three years:

- Information Technology (Center-specific Information Technology Systems);
- Leadership and Professional Development (Supervisory, Leadership Training for Non-Supervisors, Negotiation, Time Management, Project Management, Conflict Resolution);

- Scientific and Regulatory (Guidance Training, Clinical Trials, Finite Element Modeling, Quality Systems, Anatomy and Physiology, Human Factors, Animal Models, Biomaterials, Risk Management, Design Control).
- 3. Are regional employees, and employees located outside the U.S., able to take advantage of the agency's training opportunities? Please provide information by Center, and if it varies among divisions please include that information as well. If there are differences in training in district offices and in FDA offices outside the U.S., please describe the differences and the rationale for such different training programs.**

The Office of Regulatory Affairs (ORA) invests a significant amount of effort and resources to provide training opportunities to regional employees and investigators stationed outside the United States. ORA's national training courses are attended by all investigators. As investigator staffing is increased for international posts, training needs are developed and met accordingly. The training itself remains the same, but may be offered to FDA employees in a way that best meets the needs of the Agency.

ORA offers face-to-face courses as well as e-learning opportunities to investigators located regionally and outside the United States. The learning delivery format depends upon Agency needs and resources, course availability, and the best fit for the investigator. E-learning courses are developed and delivered by ORA and UL EduNeering (a business line within Underwriters Laboratories Life & Health's business unit, as part of a cooperative research and development agreement (CRADA). Training, whether on-demand e-learning or face to face, helps investigators maintain their inspectional knowledge as well as prepare them to conduct inspections.

In addition, Regional employees and employees located outside the United States, as well as all FDA employees within the United States, are able to take advantage of the Agency's training opportunities through FDA's Learning Management Systems. This system allows employees to register for both on-line or instructor-lead courses. The following are core course topics and training opportunities provided and available to all employees:

- Acquisitions
- Budget
- Equal Employment
- Ethics
- Federal Acquisitions Regulations
- Information Technology
- Manager Training
- Plain Language
- Record Keeping
- Safety
- Self-Development
- SES Candidate Development
- Supervisor & Manager's Classes
- Travel

- Labor & Employee Relations

In contrast to the core or Agency-level courses, each Center identifies and provides a number of operationally centric courses. The following is the total number of courses offered by each Center during FY14:

- CDER – 103 Courses
- CDRH – 40 Courses
- CFSAN – 99 Courses
- CTP – 52 Courses
- CVM – 50 Courses
- NCTR – 16 Courses
- CBER – 96 Courses
- OHR – 6 Courses
- OO – 94 Courses
- ORA – 89 Courses

In addition to the core and specific courses offered by FDA, listed above, there are thousands of other courses offered by FDA on a variety of topics to enhance communication skills, individual development plans, labor relations dealing with stressful situations, and effective writing. In order to support sound scientific review considerations related to novel products, FDA strives to ensure that courses are identified and made available, as needed, to train and reinforce special or unique employee skill sets. To help meet this need, FDA University currently partners with the FDA Learning Centers, which include FDA Training Officers and other Agency Senior Training Officials from the following FDA organizational entities:

- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)
- Office of Information Management (OIM)
- National Center for Toxicological Research (NCTR)
- Office of the Commissioner (OC)
- Office of Regulatory Affairs (ORA)
- Center for Tobacco Products (CTP)

Finally, FDA University also partners with the Office of Personnel Management's (OPM) HR University<sup>2</sup> and the Graduate School USA (previously USDA Graduate School).<sup>3</sup> The University of Maryland also provides discounts for course work for HHS/FDA employees.

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<sup>2</sup> [https://hru.gov/about\\_us.aspx](https://hru.gov/about_us.aspx)

<sup>3</sup> <http://www.graduateschool.edu>

- 4. How long does it take for a new employee to become a full-fledged reviewer of human medical products or, in the case of field staff, a full-fledged inspector or investigator? Are employees subject to minimum annual training or continuing educational requirements? Please include variability by division, center, or office if applicable, and information on training for agency staff sponsored by FDA's National Center for Toxicological Research (NCTR).**

Typically, it takes approximately 18-24 months to become capable of working more independently on complex applications. Each Center is responsible for determining Center-specific reviewer training needs.

CDER provides over 30 "in-house" training courses for reviewers. In-house training courses include training in scientific, regulatory, communications, technology, and soft skills. In addition, the CDER training staff meets regularly with CDER office representatives who conduct reviews to determine if the training courses offered meet the office's needs. Additionally, as funding permits, CDER staff may access continuing education account funds, which can be used to gain additional expertise and training.

During FY14, CDRH conducted 710 learning events to address the training needs of Center staff, including premarket review staff and managers. The focused training areas included Scientific and Regulatory Education, Leadership and Professional Development, and Supervisory and Center-specific IT Training. Specific examples of the CDRH training conducted during FY13 and FY14 (Q1-3) is provided in Attachment 2, "CDRH FY14 Q1-3 Internal Training Data Summary Report" and "CDRH FY13 Training Data Summary Table." In CDRH, new supervisors are required to complete mandatory training based on Title V – 40 hours during their first and second years, 24 hours during their third year, and 16 hours for each year beyond three years. Additionally, new premarket reviewers in CDRH are required to complete up to 20 courses (18 required and two elective), available via online and classroom formats within their first 10 months of coming onboard. This translates to a requirement of 136 hours of training during their first year.

CDER provides over 65 courses for reviewers to provide essential information in the areas of regulatory, advanced science, communications, and soft skills. In addition, individual offices provide specific technical scientific training for the various disciplines. These courses increase the knowledge and skills necessary to perform review work covering areas unique to that office. For example, new drug review, product quality, biostatistics, clinical pharmacology, and pre-market and post-market surveillance.

ORA and OIP employees have a variety of different experiences and academic backgrounds. As such, the time varies for how long it takes a new employee to become a full-fledged investigator, also known as a Consumer Safety Officer. That is, in general it takes about 18-24 months to become a full-fledged investigator; however, the length of time varies depending upon the background and experiences of the individual, which are evaluated by their supervisor. ORA and OIP first-line supervisors evaluate their employees' ability to do their job. As with any determination of competence, the supervisor is expected to monitor, evaluate, and provide for performance and training needs. The role of the supervisor is key to working with the employee and determining what training is needed on an annual basis as part of the Individual

Development Plan (IDP). Therefore, the minimum annual training and continuing educational requirements are set by the supervisor to some degree, rather than the position, depending upon the specific background, experience, and credentials of the FDA investigator. In addition, ORA training courses, combined with on-the-job training, mentoring, and coaching, provide the necessary development for both ORA and OIP investigators. Districts may also offer specific internal training programs, and as employees develop their skills, they may attend industry and trade organization conferences as resources permit. These are the ways that investigators are developed. Varying opportunities for career progression are available to investigators, depending upon the specific needs of the Agency, related vacancy announcements, and the background, skills, and experience of the investigator.

With regard to continuing education requirements, FDA does not set continuing education requirements for reviewers. These are typically set for medical professionals, such as physicians and nurses by states or professional organizations. However, to address relevant scientific issues that arise for review staff and help ensure that licensure requirements are met, reviewers typically have access to, and are encouraged to use, funds for continuing education, allowing individuals to attend classes, symposiums, and conferences.

FDA's Continuing Education (CE) Program provides in-house continuing medical, pharmacy, and nursing education for scientific and regulatory activities offered by the different Centers. Specifically, the FDA CE program provided a total of 310.75 continuing education hours for activities offered by CDER, CBER and CDRH for the time period from September 1, 2013 – August 31, 2014.

To further support reviewer training needs, the FDA's National Center for Toxicological Research (NCTR) provides supplemental regulatory science technical training in areas such as nanotechnology, pathology, and toxicology.

**5. If there is variability in training and time to be an independent reviewer or inspector, how often do Centers or divisions meet to discuss different methods of training?**

As mentioned above, while there is variability of training needs based on the product type, in general it takes approximately 18-24 months to become capable of working more independently on complex applications or inspections. FDA's Learning Development Council (LDC), made up of Agency Senior Traveling Officials (STO's) and Center level training officers, meets bimonthly to address learning and development reviewer needs and opportunities.

To support inspector training, ORA has ready access to subject matter experts (SMEs) in FDA product centers and regularly collaborates with these SMEs to develop and deliver training. ORA also uses a course advisory group (CAG) in its course development and delivery process. The CAG meets annually or in response to new or changing needs, job responsibilities, technologies, policies, regulations, and other emerging requirements. Working in collaboration with its Center counterparts, ORA's inspection cadre and FDA Product Center SMEs produce effective education and training products administered in-person and at a distance via e-learning products.

**6. What is the average duration employees stay at the FDA? Please specify by level and type of position, if possible.**

Based on employee separations in FY 2014, an employee remains with FDA for an average of approximately 13.61 years. It would be difficult to specify by level and type of position, given that there are over 15 grade levels, 50 position types, and eight Centers.

**7. How many vacancies and acting positions are there currently at the agency? Please separate leadership vacancies and acting positions. What are the biggest hurdles to filling these positions?**

Below is a breakout of the number of vacancies by Center, as of September 1, 2014, including the number of leadership and acting positions. For the purpose of consistency, we defined "leadership" positions as all supervisory positions down to the Branch Chief level (first-line manager).

**Number of Vacant and Acting Positions as of 9/1/14:**

	<b>Total Number of Positions - Vacant</b>	<b>Total Number of Leadership Positions – Vacant (Subtotal)</b>	<b>Total Number of Acting Leadership Positions</b>
OIP	31	5	9
ORA	665	83	83
CDER	735	106	92
CDRH	75	25	25
CBER	74	6	6

FDA has encountered the following challenges in filling the vacancies that we identified above:

- Volume of applicants applying to vacancies are trending upwards; in many cases, hundreds of applicants need to be evaluated for a small number of positions. The increased workload evaluating high volumes of applicants, many who are not qualified, slows down the hiring process significantly.
- Delays in bringing selected candidates onboard; because of the time between applicants applying to a vacancy and execution of the hiring certificate. At the point that the applicant is called for an interview with the selecting official, they may have already accepted other positions;

- Outside competition for qualified applicants;
- Frequent and necessary changes in Agency hiring goals and objectives;
- Challenges in offering competitive salary packages that compete with industry to individuals with the necessary technical knowledge;
- Challenges in enticing qualified individuals who are interested in the positions to relocate to the DC metropolitan area due to the high cost of living;
- Challenges in finding candidates with the necessary skills, leadership, experience, and who are willing to routinely travel, which may include travel overseas;
- Limitations on filling legal positions using the Attorney occupational series. As a regulatory agency many of our Centers' need the skill of trained attorneys to complete regulatory policy work.
- Additional time required to request approval to backfill vacant Senior Executive Service (SES) positions. As positions are vacated, additional time is needed to assemble a package requesting approval to advertise and fill the recently vacated position slowing down the process.
- Title 42 (f) Exhaustion Requirements, (Title 42 is a hiring authority that allows non-competitive appointment in the excepted service):
  - Appointments under this authority (42 U.S.C. § 209(f)) may only be used to fill scientific positions when recruitment or retention efforts under other available personnel systems, including Title 5 of the U.S. Code, the Senior Biomedical Research Service (SBRS), and PHS Commissioned Corps, have failed to yield candidates that possess critical scientific expertise.
  - Before 42 U.S.C. §209(f) may be used, the Agency must demonstrate that the following criteria have been met:
    - Efforts to recruit and/or retain under other available personnel systems were attempted, but unsuccessful, and these recruitment efforts must be completed prior to commencing recruitment under Title 42;
    - The recruitment efforts utilized for other available personnel systems were as extensive as those used to recruit under Title 42 (e.g., nationwide search, ads in professional journals, vacancy information shared with professional organizations, etc.); and
    - The applicant's credentials, experience, and stature in the scientific community are commensurate with, and directly related to, the position being filled.

FDA is working with HHS to expand the Agency's ability to designate categories of key scientific leadership positions as Title 42(f) to avoid the need to initially recruit using other hiring authorities, which historically have failed to attract qualified candidates. The current requirement to exhaust adds significant additional work for both hiring programs and human resources and causes significant delays when filling key positions. Additional approvals required for salaries and recruiting incentives above a certain level also delay bringing candidates on board once selected. Autonomy in setting salaries and incentives within established government regulations would speed up the process and help FDA avoid losing interested candidates due to delays in finalizing job offers.

FDA is able to utilize direct-hire authority for physicians, one of many identified STEMM mission-critical positions. Expanded use of direct-hire authority for certain mission critical positions would enable FDA to recruit and fill highly technical positions more quickly than the current 132 day average, and help ensure adequate staffing to meet the requirements of FDA's critical public health mission and support authorized user fee programs. FDA has been granted direct hire authority for mission critical positions previously and successfully managed use of the authority.

**8. How many contractors perform work for the agency as compared to the number of FDA employees?**

As of October 1, 2014, there are approximately 14,587 FDA employees (13,278 civil service/1,309 Commissioned Corps) and 5,103 contractor employees.<sup>4</sup>

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<sup>4</sup> For purposes of this data request, "contract employee" is defined as an individual who is listed in the FDA Outlook e-mail system as a contract employee.



### *Regulatory Science*

Regulatory science is the science of developing novel tools, standards, and approaches to assess the safety, effectiveness, quality, toxicity, public health impact, or performance of FDA—regulated medical products. FDA’s advancement in regulatory science and innovation is fundamental to FDA’s core mission of protecting and promoting the public health. As a science-based Agency, FDA strives to ensure that it has access to the best available scientific data to inform regulatory decision-making and thus improve access to FDA-regulated products that benefit the public health, and enhance oversight of all FDA-regulated medical products.

With the 21st century comes rapid advances in research and new cutting-edge technologies, such as sequencing of the human genome; novel cell and gene therapies; screening to quickly conduct millions of genetic, chemical, or pharmacological tests; rapid detection methods; and state-of-the-art electronics and materials science to transform medical devices. FDA reviewers must keep up with the rapid advances in research and new cutting-edge technologies to be able to better assess data needs for new products and thus better evaluate new products.

FDA has identified, and for several years has been implementing, a strategy to close any critical gaps in scientific knowledge required to support regulatory decision-making. By closing these gaps, FDA’s regulatory science initiative has begun to leverage new technologies and basic science discoveries, transforming them into real-world diagnostics, treatments, and cures, potentially reducing the time, complexity, and cost of developing products and bringing products to market sooner. In short, regulatory science tools are essential to speed new safe and effective therapies to patients who need them.

The responses to the Regulatory Science questions below provide a picture of FDA’s continuing efforts in this area. We have restated each question, below in bold, followed by our responses.

- 1. Please provide a list of the public-private partnerships that focus on examining novel regulatory science questions, accelerating innovation, and assisting in the development of medical products that the FDA is involved with, including both by providing funding or providing expertise and employee time.**
- 2. For each of the list above, please provide the amount of funding provided by the agency and an estimate of staff resources delegated to each partnership. How many employees are involved in these partnerships? On average, how much time do each of these staff members spend on partnership-related activities each month?**

**Response to 1 and 2:** A public-private partnership (PPP) is a collaborative enterprise in which FDA and its stakeholders agree to leverage combined resources and knowledge, collaboratively and under aligned missions, for public benefit. PPPs allow FDA to partner with a wide range of other organizations including, but not limited to, patient advocacy groups, professional societies, charitable foundations, industry members, trade organizations, academic institutions and other government and state entities. PPPs are usually governed by not-for-profit or 501(c)(3) organizations which serve as third-party conveners of these collaborative activities. The “neutral ground” position of such PPP conveners uniquely allows them to bring together multiple not-for-profit and for-profit organizations to support common goals. Attachment A (enclosed) lists the

PPPs in which FDA is involved, organized by the Center that is the primary contact, and includes the amount of funding provided by the Agency for each PPP in FY14.<sup>5</sup>

FDA staff time spent on PPP activities is not centrally tracked. FDA personnel do not participate in PPP activities as a primary work assignment, as each employee has other primary duties, including review of regulatory applications, monitoring of post-market safety, project management, research, or development of guidance and policy. The time that FDA employees spend on PPP activities varies and depends on the type of partnership and may include such activities as participation in working groups, workshops, or meetings, or drafting or reviewing of scientific publications or white papers, in addition to consultation and advice to developers of new clinical outcome assessment tools, to review of tools for regulatory qualification at the appropriate stage of their development.

**3. In the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health, how are patient risk/benefit documents and discussions from patient group meetings informing the review process and prioritization of the agency's regulatory science work?**

Efforts to increase consumer understanding and awareness of benefit and risk, both in FDA and direct to consumer messaging, has led to an expansion of FDA's research efforts in the social sciences. Priority area 8 of the FDA Strategic Plan for Regulatory Science is to "Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products."<sup>6</sup> FDA has been soliciting and funding research proposals related to this strategic priority through its Broad Agency Announcement related to regulatory science, and updated accomplishments related to its Strategic Plan for Risk Communication in 2012.<sup>7</sup>

Patients inherently play a critical role in FDA's assessment of safety and effectiveness. For example, they participate in clinical trials and report adverse events, and this information is essential to our assessment of risks and benefits. In addition, FDA meets with patient groups and works on guidance documents related to patient-reported outcomes in clinical trials.

We are committed to making more opportunities for patients to participate in FDA decision-making. Our Patient Representative Program brings the patient voice to the discussions about new and already-approved drugs and devices and policy questions.<sup>8</sup> FDA has long used the public input part of Advisory Committee meetings to better understand the patient perspective on the products that FDA regulates. Patient representatives also serve on FDA advisory committees and provide patient perspectives on drug, biologic, and medical device therapies that are undergoing FDA review.

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<sup>5</sup> CBER does not independently participate in any PPPs. However, it does participate along with the other medical product centers in the Clinical Trials Transformation Initiative (CTTI) described in Attachment A. CBER and CDRH also participate in the CTTI, which is funded by CDER.

<sup>6</sup> <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm>

<sup>7</sup> <http://www.fda.gov/about/fda/reportsmanuals/forms/reports/ucm183673.htm#update>

<sup>8</sup> <http://www.fda.gov/forpatients/about/ucm412709.htm>

One of the PDUFA V commitments relates to a Patient-Focused Drug Development program that provides for a more systematic approach for obtaining the patient perspective of disease severity and its impact on daily living as well as their perspective on currently available treatments for specific diseases. The benefit of FDA's Patient-Focused Drug Development program is that this conversation can now be conducted with the patient as the focal point of the entire discussion, rather than an individual drug under FDA review, as in an Advisory Committee meeting setting. The input FDA receives in these meetings will be used, as this input has always been used—to help shape FDA's benefit-risk assessment for current and future drugs under review. CDER's Professional Affairs and Stakeholder Engagement (PASE) team has been meeting with patient groups to collect information regarding their experiences. These meetings have frequently included representatives from CDER's Office of New Drugs, with the discussions helping to better inform the regulatory review process. Also, many of the PPPs in which FDA is involved include patient representatives to incorporate the patient perspective into drug development.

As medical devices and biologics grow increasingly complex, many factors impact our benefit-risk determinations, and safety and effectiveness data alone may not provide a complete picture of the benefits and risks. To help provide direction to the industry, in 2012, CDRH published guidance that describes the key factors we consider when making benefit-risk determinations during the premarket review of certain medical devices ("Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" is available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm>).

CDRH has also established the Patient Preference Initiative to develop the tools and methods to reliably characterize patients' benefit preferences and risk tolerances to inform guidance and develop the framework necessary to incorporate patients' preferences into the full spectrum of CDRH regulation and inform medical device innovation by the larger medical community. CDRH is currently developing guidance on patient preferences.

In September 2013, CDRH convened a public workshop entitled "The Patient Preference Initiative: Incorporating Patient Preference Information into the Medical Device Regulatory Processes" that brought together patient groups and other stakeholders to solicit information on ways to capture, collect, and validate patient preferences and how to incorporate them into the regulatory process. The goal of this CDRH initiative was to develop a process to elicit patient views on benefit versus risk and consider these patient preferences in relation to a patient's medical device exposure and severity of illness.

CDRH continues to meet with patient groups and preference methodology experts to obtain feedback on the Patient Preference Initiative. CDRH is also working to create a Patient Engagement Advisory Committee to bring together patient representatives to discuss regulatory science and policy issues to improve patient engagement, clinical trial designs, consideration of benefit-risk, and device access for patients.

CDRH is also working with the Medical Device Innovation Consortium (MDIC)<sup>9</sup> to develop a framework for incorporating patient preferences into the device assessment process. MDIC plans to publish a methods catalogue and framework on how patient preference information can be collected and used to develop, design, and market devices that meet the needs of patients.

**4. How are real world data, patient reported information, and foreign clinical trial data being used by employees of the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) both in the premarket and post-market evaluation and surveillance of drugs, biologics, and medical devices?**

For drugs, biologics, and devices, FDA's premarket and post-market evaluations are based on different types of data and information from a wide variety of sources.

CDER, CBER, and CDRH review all data submitted as part of either an Investigational Drug Application (IND), a New Drug Application (NDA), a Biologic Licensing Application (BLA), an Investigational Device Exemption (IDE) application, a Premarket Approval (PMA) application, or a Premarket Notification [510(k)] submission including, for example, manufacturing data, non-clinical evaluations, *in vitro* studies, simulated modeling, clinical trials data, published literature and adverse event reports. The source of the data may be from clinical investigations, which may include patient-reported outcomes, and may come from U.S. and foreign sites. In making regulatory decisions, FDA looks at the totality of the available evidence as part of benefit/risk determinations, which includes an assessment of safety and efficacy for the life cycle of the medical product.

FDA's responsibilities also include ensuring the safety of medical products after they are approved. The Agency works diligently to leverage a comprehensive range of data sources in its post-market safety activities. FDA has adopted and implemented new initiatives described below over the last several years to accomplish this integrated, comprehensive approach to drug safety evaluation. This approach gives FDA access to real-world data, patient-reported information, and foreign data in its ongoing drug safety evaluations.

**Safety First Initiative:** This CDER initiative enhances the quality, timeliness, and transparency of drug safety decisions throughout a product's life cycle. This includes prioritization of potentially new drug risks of which we become aware; review of those new potential risks by a collaborative team of medical and scientific experts working in a defined timeline; early communications to the public of potential drug safety issues; and documentation, oversight, and accountability to the decision-making and evaluation process. The statutory authorities for post-market drug safety as outlined in the Food and Drug Administration Amendments Act (FDAAA) and subsequently updated as provisions of the Food and Drug Administration Innovations Act (FDASIA) were successfully implemented through the Safety First Initiative.

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<sup>9</sup> The Medical Device Innovation Consortium is an independent non-profit organization that brings together industry, government, and other stakeholders to advance medical device regulatory science through collaboration. See, <http://mdic.org/>

**Safe Use Initiative:** CDER's Safe Use Initiative was launched to reduce the harm caused by inappropriate use of medications. These non-regulatory efforts support the work of FDA to address post-market drug safety and are accomplished through partnership with other Federal agencies, health care professionals, and consumers. One example of the Safe Use Initiative in action is the work to reduce prescribing errors and misuse of opioids through formation of the Opioids Patient Prescriber Pain Treatment Agreement Working Group. This Working Group brings together leaders, patient advocacy organizations, pain-management experts, and health literacy experts, and is part of a multi-faceted, multi-agency effort to address the public health concerns associated with inappropriate use and abuse of opioid analgesics.

**The Sentinel Initiative:** In 2008, responding to the congressional mandate in Section 905 of FDAAA, FDA launched its Sentinel Initiative. This Initiative seeks to leverage existing health care information to enable FDA to conduct active post-market safety surveillance to augment its existing post-market capabilities and to allow for evaluation of potential medical product safety issues quickly and securely. The Sentinel Initiative's pilot, called "Mini-Sentinel," has enabled FDA to assess medical product safety issues utilizing secure access to large health-care databases provided by 17 data partners across the nation. Data generated through the Mini-Sentinel effort to date have been used by FDA's multi-disciplinary teams along with data from other post-market sources to better understand safety issues and have led to communications about important safety updates to health care professionals and patients.

**Pharmacoepidemiology Research:** In addition to the Sentinel efforts, FDA has various programs to conduct epidemiologic studies. Both U.S. and international data are evaluated by FDA researchers and its external partners. Studies are also carefully conducted by collaborative, multi-disciplinary teams to investigate important drug safety questions. FDA also collaborates through the use of contracts and interagency agreements with external experts with extensive experience in pharmacoepidemiology, including drug and device safety and effectiveness, comparative effectiveness, and use of the expanding electronic health records (EHR) and non-EHR electronic data sources for both adults and children. FDA has access to the Clinical Practice Research Datalink (CPRD). The CPRD provides extensive data from the United Kingdom's health system to provide researchers with access to high-quality health care information. Other major advances in FDA's post-market monitoring of medication safety includes improved methods of statistical analysis, continuous advances in the science and methods of pharmacogenomics ("personalized medicine"), improved adverse event surveillance, and leveraging government resources by partnering with other Federal agencies.

**FDA Adverse Event Reporting System (FAERS):** FDA's FAERS is a database that contains information on adverse event and medication error reports submitted to FDA for drugs as well as devices. FDA receives adverse event and medication error reports via MedWatch from health care professionals (voluntary), consumers (voluntary), and manufacturers (mandatory). The reports in FAERS are evaluated by clinical reviewers to monitor the safety of products after they are approved by FDA. If a potential safety concern is identified in FAERS, further evaluation is performed.

At CDRH, premarket pivotal trials are encouraged to include as many aspects of real-world use as possible in the trial design to allow assessment of the performance of the medical devices in as close to the expected clinical setting for use as possible. The shift from controlled clinical trials to real-world use may result in differences in both safety and effectiveness outcomes, depending on medical device learning curves, and the expertise needed to use the devices effectively and safely. Some of these concerns are mitigated through training or pre-use expertise requirements for use.

Patient-reported information, including Patient-Reported Outcomes measures (PROs) and patient preferences, are encouraged to be included in clinical studies on medical devices. These are evaluated carefully together with other clinical data in decision-making regarding devices requesting clearance or approval for marketing. User study data is important to evaluate User-Device interface to allow for safe and effective use of medical devices. When foreign clinical trial data are submitted with medical device applications, the data are reviewed for their outcomes. Important aspects regarding patient demographics, medical training, and availability of other medical products that are used together with the device under consideration are also reviewed. Foreign clinical trial data may not always reflect U.S. demographics of the population that is to be treated with the device if marketed in the United States, which may be important under certain circumstances.<sup>10</sup> Further, FDA has seen differences in outcomes with data from clinical sites that are outside of the United States. Consideration is given to site inspections that may be required for clinical sites outside the United States when included in a pivotal clinical study.

Post-market information from CDRH's MedSun program and adverse event reporting (which includes "patient-reported information") from "real-world" use are evaluated on a regular basis. As noted previously, patient reports of adverse events as captured in FDA's MEDWATCH system are important to post-market evaluation and surveillance of medical devices.

Staff in CDRH's Office of Surveillance and Biometrics are responsible for overseeing post-approval studies (PAS) under 21 CFR 814.82 and post-market surveillance studies required under section 522 of the Federal Food, Drug, and Cosmetic Act ("522 program"). CDRH is also heavily involved in developing methods and infrastructure supporting national and international collection of data on medical device use and associated outcomes through a series of partnerships organized under the auspices of the Medical Device Epidemiology Network (MDEpiNet) and the FDA Epidemiology Regulatory Science Program (ESRP).

Post-approval studies and "522" studies are often designed to collect data using observational methods from consecutive patients receiving a medical device in an "all-comers" design. Traditionally, these types of studies have been established using standalone infrastructure unique

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<sup>10</sup> This is true for drugs too. Regarding clinical trials conducted outside the United States, see <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073117.pdf>, <http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm073120.pdf>. In addition, 21 CFR 312.120 addresses criteria for acceptance for review of data from foreign studies not conducted under an IND.

to each specific manufacturer or device. While there is still need for this type of study in some circumstances, CDRH has been working with professional societies, medical device manufacturers, patients, physicians, hospitals, HHS' Agency for Healthcare Research and Quality HHS' Center for Medicare and Medicaid Services, and other stakeholders to establish and promote registries to collect data from all patients receiving a given device or procedure, recognizing that many post-market questions are similar among devices within a class or type.

Using a registry infrastructure for surveillance has several distinct advantages, including: (1) predictability of post-market commitment and data capture; (2) collection of sufficient "denominator" data to calculate accurate rates of adverse events; (3) near "real-time" update of data to detect and respond to an adverse signal quickly, limiting patient exposure to potentially poorly performing devices; (4) standardized data collection across a product type to make interpretation and comparisons of various factors more reliable; and, (5) significant cost reductions for all stakeholders, considering that operating costs for registries can be less than stand alone studies, and can be more easily distributed among multiple partners, including the Federal government.

In recent years, CDRH has worked with stakeholders to establish the Pelvic Floor Disorders Registry, Transcatheter Valve Therapy (TVT) registry, National Breast Implant Registry, Vascular Quality Initiative Registry, American Joint Replacement Registry, and many others. These registry efforts are a central component of the post-market surveillance infrastructure used by CDRH to ensure the continued safety and effectiveness of medical devices. CDRH has also initiated the process for international harmonization of registry data, multiplying the population of patients receiving devices on which data is being collected. The FDA-led International Consortium of Orthopedic Registries (ICOR) is the first of these efforts, but has spawned several other efforts in cardiovascular and plastic surgery devices.

In addition to registry efforts and other studies designed to collect real-world data from consecutive patients, CDRH has been working with partners to gain access to and analyze administrative claims data. These data can be used on their own or linked to registry or clinical trial data to evaluate health outcomes years after a device has been implanted. The Centers for Medicare and Medicaid Services (CMS) has been an excellent partner, working with the American College of Cardiology (ACC) and FDA to link together registry and claims data for patients receiving TVT.

CDRH is working with our partners to develop new ways to validate administrative claims data for other procedures to evaluate long-term health outcomes for a variety of medical device procedures that would obviate the need for expensive, time-consuming direct follow-up case report forms. Using data collected from routine doctor/patient appointments and hospital charges, many outcomes can be detected and acted upon. CDRH has also invested in the development of analysis methodology to continuously monitor observational data sources (e.g., registries, claims) to detect any change in the rate of adverse events and immediately alert when a value is out of bounds for historical averages. The Data Extraction and Longitudinal Trend Analysis (DELTA) system has been installed with the ACC National Cardiovascular Data Registry, and is being evaluated for use with other data sets as well. Because missing data can create challenges for interpretation of data, FDA has been working with leading methodologists

to develop specialized ways to characterize and account for missing data in observational data sets so that CDRH can draw accurate inferences and conclusions that lead to meaningful public health interventions.

FDA will continue to explore and leverage a comprehensive range of available data sources to maintain a rigorous, scientific approach in the Agency's efforts to ensure the safety of medications available to the American public.

- 5. Given the increase in the number of applications and submissions to the Office of Combination Products, how are the various centers coordinating the review of combination product submissions to ensure that these products move through the review process as quickly as possible, without any unnecessary delays, especially in the case of drug and device combination products whereby more than one center will review such product? And given the need to coordinate with multiple Centers, how are the statuses of these submissions tracked?**

Combination product applications and submissions are generally submitted to the Center that has primary jurisdiction over the product (CBER, CDER, or CDRH). When this is unclear, the Office of Combination Products (OCP) coordinates the determination by the Agency regarding which Center should have primary jurisdiction. The lead Center is responsible for ensuring that the premarket application for the product is reviewed in a timely fashion. When the lead center reviewing a combination product needs scientific expertise from another center, it can request a consult from the other center (e.g., CDRH as lead center can request CDER input on chemistry and toxicology). Such consultations are important to ensure appropriate and consistent review of these submissions, and the efficiency of the consultation process is important to ensuring timely Agency responses to sponsors. The process for requesting a consult from another Center is provided in the 2004 Staff Manual Guide (SMG) 4101 "Combination Product Inter-Center Consultative/Collaborative Review Process."

(<http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm>).

That process includes the use of an electronically accessible inter-center consult form to request review from another Center, and e-mail notification to OCP to log and track the consult.

The status of premarket applications is tracked using the lead Center's database. In addition, an OCP log is used to track the status of the inter-center consults, based on communications from the Centers' project managers. User-fee timelines identify timing expectations for review of the application. For example, if an NDA is submitted to CDER for a combination product, the PDUFA timelines govern the review, including the timing for a CDRH consult review. For a combination product reviewed under PMA, the MDUFA timelines govern the review, including the timing for a CDER consult review. The lead Center tracks the inter-center consults to make sure they are completed in a timely manner. In the event that there is a delay, the lead center contacts OCP for assistance in achieving completion of the consult.

Also, for premarket applications in which OCP is requested to participate, OCP proactively tracks the consults and attends milestone meetings and end-of review meetings. The number of inter-center consults has risen steadily over the last several years, with a particularly significant increase from 2012 to 2013.



OCP and the Centers are currently evaluating the standard operating procedures for inter-center consultations and options for modifying information technology systems to improve efficiency. We are also evaluating resource allocations in light of significantly increasing demands on resources to support this important aspect of combination product review and oversight.

- 6. Please describe the costs and accomplishments associated with (a) FDA's Advancing Regulatory Science Initiative, which was launched in February 2010, (b) the implementation of FDA's Strategic Plan for Regulatory Science, which was issued in August 2011, and (c) the creation of FDA's Centers of Excellence in Regulatory Science and Innovation at the University of Maryland and Georgetown University, which were established in October 2011.**

In February 2010,<sup>11</sup> FDA announced the launch of the Advancing Regulatory Science Initiative, followed by release in October 2010<sup>12</sup> of the white paper, Advancing Regulatory Science for Public Health. This document outlined a broad vision for advancing regulatory science and unleashing its potential to improve public health. It assigned a key role in this process to FDA's Chief Scientist to "coordinate internal and external outreach to identify critical regulatory science and innovation needs and develop a strategic plan for science at FDA" and the FDA Science Board Advisory Committee to "review and inform the scientific strategic plan and regulatory science priorities."

The Strategic Plan for Advancing Regulatory Science at FDA, published in 2011,<sup>13</sup> contained eight scientific priorities that provide guidance for proposals and inform the review of competitive grant applications from FDA scientists and those outside the Agency; a ninth area was added in 2013.

Priority areas are:

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
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to US and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products
9. Strengthen the Global Product Safety Net (added in 2013)

Attachment B describes examples of Agency-wide accomplishments and activities that illustrate FDA's progress in applying regulatory science to support our regulatory mission, organized

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<sup>11</sup> <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm>

<sup>12</sup> <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228131.htm>

<sup>13</sup> <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm>

within the eight priority areas identified in the Strategic Plan for Regulatory Science. Because the ninth priority area was only recently added, illustrative examples in this area are not included.

Identification of costs specifically associated with implementation of the Advancing Regulatory Science strategic plan is difficult because regulatory science activities occur throughout FDA's centers and offices, including activities that have been initiated since publication of the strategic plan. It is not possible to identify whether these regulatory science expenditures, or some portion of them, are attributable to the strategic plan. However, there are several programs within the Office of Chief Scientist that are outgrowths of FDA's Advancing Regulatory Science initiatives and have been developed with the strategic plan's priority areas in mind. These are the Chief Scientist's Challenge Grants (which fund intramural regulatory science projects), the Broad Agency Announcement (see below), which funds extramural regulatory science projects, and the Centers of Excellence in Regulatory Science and Innovation (CERSIs, see below). A table listing the funds for each of these three programs for FY 2012-2014 is included below.

	FY 2012	FY 2013	FY 2014	Total
Intramural Chief Scientist's Challenge Grants	\$0.35M	\$0.27M	\$1.0M	\$1.6M
Broad Agency Announcement	\$4.1M	\$17.8M	\$20.5	\$42.4M
Centers of Excellence in Regulatory Science and Innovation	\$2.0M	\$2.1M	\$2.0M	\$6.1M
Total	\$6.5M	\$20.2M	\$23.5M	\$50.1M

In 2012 a new funding mechanism, called the Broad Agency Announcement (BAA), was launched to spur regulatory science innovation in the scientific community and leverage its knowledge and infrastructure in areas where FDA has limited expertise or capacities. The contract mechanism's flexibility enables FDA to better leverage the breadth of innovative scientific and technical solutions available to the Agency. The BAA follows the priority areas developed under the Strategic Plan for Regulatory Science. Currently FDA is collaborating on 28 BAA projects and in FY 2014 the amount of funding for BAA projects totaled \$20 million.

FDA is modernizing its scientific infrastructure by enhancing its internal research and expanding external collaborations like the Centers of Excellence, which promote cross-disciplinary regulatory science training, scientific exchanges, and research. A strong in-house contingent of scientific and technical experts proficient in cutting-edge science and technologies, together with a network of collaborations, is key to FDA's capacity to evaluate increasingly complex products and promote innovation that addresses unmet public health needs. In October 2011, FDA awarded \$2 million to launch CERSIs (or the Centers) at the University of Maryland and Georgetown University. Two more centers were added in August 2014 at the University of California at San Francisco-Stanford University consortium and at Johns Hopkins University. The investment is part of FDA's effort, outlined in the Agency's strategic plan, to

foster a robust, collaborative, regulatory science culture that enables FDA to address the scientific challenges presented by revolutions in medical product development and to improve food safety and quality.

All CERSIs have three common goals: regulatory science academic programs, professional development, and collaborative research projects. The Centers have developed cross-disciplinary regulatory science training by facilitating development of new educational programs. University of Maryland has developed a Master of Science in Regulatory Science curriculum, and Georgetown University offers a unique concentration in Regulatory Science as a part of the Master of Science in Clinical and Translational Research. Importantly, the CERSI centers have engaged students beyond the degree programs such as participating in regulatory science case studies, small student projects and regulatory science competitions.

Professional development opportunities for FDA staff have been greatly enhanced by the availability of seminars, workshops, and conferences, and through scientific exchange and access to cutting-edge research technologies. Workshops and seminars have addressed diverse topics, such as modeling in pediatric drug development, nanotechnology, leveraging big data, and tissue phantoms for standardization in photonics. Importantly, remote participation in rounds and lectures being held beyond FDA's campus are often available for Continuing Education Credits. These opportunities enable FDA staff to remain engaged with the academic and medical practice communities, both as they develop leading-edge medical advances and as they use the products they regulate.

To advance specific regulatory science goals, a number of targeted research projects were planned and implemented in close collaboration between the CERSIs and FDA scientists. Projects include furthering understanding of the role of transporters in drug-drug interactions, clarifying current practices around the use of patient prescriber agreements for opioid analgesic drugs, applying machine data classification algorithms to flag events reported in the Vaccine Adverse Event Reporting System and possibly related to autoimmune mechanisms, and developing new imaging methods and standards.

- 7. In 2010, FDA announced it was establishing a new collaborative effort with the National Institutes of Health (NIH) to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. What is the status of this collaboration? What activities have the two agencies engaged in together and what distinguishes the role of each agency? What has been the cost to FDA and NIH?**

In 2010, FDA and NIH established the ongoing Joint Leadership Council<sup>14</sup> (the Council) to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. As an early illustration of the Council's efforts, the Council sponsored the issuance of the Request for Application (RFA) entitled "Advancing Regulatory Science through Novel Research and

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<sup>14</sup> For more information, see <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm201654.htm>.

Science-Based Technologies.”<sup>15</sup> The program, providing four awards totaling \$7M, was funded exclusively by NIH. The four awarded studies included:

- Accelerating Drug and Device Evaluation through Innovative Clinical Trial Design
- Replacement Ocular Battery
- Heart-Lung Micromachine for Safety and Efficacy Testing
- Characterization/Bioinformatics-modeling of Nanoparticle: Complement Interactions

In early 2014, FDA and NIH co-hosted close-out meeting(s) for the grants referenced above to gain an understanding of the accomplishments garnished by these scientific studies and to identify follow-on activities.

In April 2014, the Council met and established collaborative work on antimicrobial resistance. One of the deliverables from that meeting was a workshop co-produced by FDA and NIH in late July 2014 on approaches to antimicrobial drug development for resistant pathogens. The workshop was entitled “The Development of New Antibacterial Products: Charting a Course for the Future.”

The two agencies are also working together on a \$20 million prize to develop diagnostic devices to identify antimicrobial resistant bacterial infections. This prize was announced by the White House in September 2014.<sup>16</sup> FDA provides technical input and support for the prize but is not involved in the funding. Agency representatives serve on the Council and support its efforts in a regulatory advisory capacity.

**8. What routine collaboration exists across medical product centers? How do Centers typically communicate and share information with each other? Do senior managers meet with their counterparts in other Centers on a regular basis? Can they access information—at least in a “Read Only” mode—in one another’s various IT systems?**

Center Directors and other senior-level Center staff meet at a weekly meeting for senior FDA staff and at a biweekly meeting for FDA leadership. FDA reviewers consult on reviews for products regulated by other Centers when appropriate. In the premarket setting, the Centers’ review teams and OCP collaborate as appropriate in review of premarket applications and meetings with sponsors. The Centers also meet to resolve scientific or regulatory challenges regarding specific combination products and products that may pose jurisdictional questions. Senior managers meet when an issue requires input from staff at those levels from various Centers. Center staffs communicate and share information via e-mails, phone calls, or face-to-face meetings.

OCP creates and chairs inter-center working groups to address recurring combination product questions and to develop guidance, regulations, and standard operating procedures (SOPs). Examples of such efforts include a final rule regarding current good manufacturing practice requirements for combination products, a proposed rule regarding post-marketing safety reporting requirements for combination products,<sup>17</sup> and guidance documents related to glass

<sup>15</sup> Available at: <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-10-006.html>.

<sup>16</sup> For more information, see [http://www.nih.gov/about/director/09182014\\_statement\\_brain-qmr.htm](http://www.nih.gov/about/director/09182014_statement_brain-qmr.htm).

<sup>17</sup> <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for->

syringes<sup>18</sup> and injector system marketing application review. OCP and the Centers also work together on initiatives for which one Center has the lead that affect combination products (e.g., the final rule regarding unique device identifiers, and guidance on drug-eluting stents and on *in vitro* companion diagnostic devices).

Regarding senior manager meetings, when a particular issue rises to the level of requiring input from senior managers in the Centers (i.e., Division Directors, Office Directors, Center Directors, and the Commissioner's Office), OCP coordinates such meetings to address the issue. OCP also routinely provides briefings to senior staff in all three Centers on significant combination product issues.

Each Center has its own electronic databases for storing and tracking premarket submissions. These electronic databases allow for accessibility across centers at the reviewer level; "read-only" access can and is granted on an as-needed basis. Currently, OCP is beginning an information technology assessment to enhance cross-center "read and write" access to facilitate premarket review and post-market oversight.

In addition, the Office of the Chief Scientist (OCS) provides strategic leadership, coordination, and expertise to support scientific excellence, innovation, and the capacity to achieve FDA's public health mission. OCS serves as a hub for cross-agency scientific coordination that involves multiple agency components. For example, the Senior Science Council (SSC), comprised of senior Agency scientists, is coordinated through OCS. The SSC provides advice and guidance to the Agency and Center leadership on cross-cutting regulatory science planning, reporting, programs, policies, and communication. The SSC's responsibilities include:

- Creating an environment for enhanced communication and coordination on cross-cutting regulatory science activities at FDA.
- Providing input on strategic planning and reporting for regulatory science.
- Providing input into the development of intramural and extramural competitive regulatory science grants funded through OCS, and facilitating scientific and programmatic review of resulting proposals.
- Drafting or providing input on Agency-wide regulatory science policies for consideration by Agency leadership; and
- Providing input on cross-cutting regulatory science activities managed within OCS, such as professional development, training, and scientific integrity.

Routine collaboration is also achieved through Agency-level working groups or task forces that address specific needs of the Agency. Examples include the Nanotechnology Task Force (NTF) and the Genomics Working Group. The NTF, which includes representatives from each of the Centers, was formed to identify and recommend ways to address scientific knowledge gaps to better enable FDA to evaluate FDA-regulated products that may contain nanomaterials or otherwise involve the application of nanotechnology. The FDA Genomics Working Group strives to enable FDA to address IT and scientific challenges to facilitate FDA's capacity to receive, analyze, and interpret "High Throughput Sequencing" data, also known as "Next Gen

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combination-products

<sup>18</sup> <http://www.fda.gov/regulatoryinformation/guidances/ucm346727.htm>

Sequencing.” These new methods allow parallelized sequencing to simultaneously generate thousands of sequences in a relatively short time for significantly lower cost than conventional sequencing methods, such as Sanger sequencing (also known as dideoxy or dye-termination methods).

OCS encourages and enables collaboration through intramural funding programs, such as the Chief Scientist’s Challenge Grants and the Collaborative Nanotechnology grants program. The Chief Scientist’s Challenge Grants program provides funding to enable exceptional, innovative, and collaborative (i.e., involving more than one Center) research that might not otherwise be done and shows strong promise to address major regulatory science needs that will advance public health. The Collaborative Nanotechnology grants program has funded 18 projects since 2011 at a total of \$2.5M. These projects have not only increased FDA knowledge on nanotechnology but have also led to the development of vital regulatory science tools such as assays, assessment methodologies, and test protocols that the Agency is using to evaluate nanotechnology in FDA-regulated products. The Collaborative Nanotechnology grants program has increased overall collaboration across FDA and continues to strengthen the Agency’s relationship with academia and across the U.S. government.

Thank you for your interest in these important issues. If you have further questions, please let us know. The same letter has been sent to Senator Burr.

Sincerely,

A handwritten signature in black ink, appearing to read 'Thomas A. Kraus', with a long horizontal flourish extending to the right.

Thomas A. Kraus  
Associate Commissioner for Legislation



## Attachment A

### FDA's Public-Private Partnerships

	Center for Drug Evaluation and Research		
Consortia <sup>1</sup>	Partners and Participants	Mission	FY 2014 Funding
<u>The Analgesic Clinical Trial Translations, Innovations, Opportunities and Networks Initiative (ACTION);</u>	Supports strategic collaborations among a broad spectrum of stakeholders — including, but not limited to, academia, the FDA and other government agencies, industry, professional organizations, patient advocacy groups, foundations, and philanthropic organizations	Streamline the discovery and development process for new analgesic drug products for the benefit of the public health.  Address major gaps in scientific information which can slow down analgesic clinical trials and analgesic drug development.	Cooperative Agreement \$500,000
<u>Biomarkers Consortium (BC)</u>	Stakeholders across the health enterprise, including government, industry, academia, patient advocacy, and other non-profit private sector organizations	Discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics.	No funding provided
<u>Coalition Against Major Disease (CAMD) Consortium</u>	Scientists from pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors and representatives from regulatory agencies	Develop new tools (biomarkers and disease progression models) and methods that can be applied during the development of new treatments for neurodegenerative diseases.	See note at the end of the table:  Grant with parent 501(c)(3)

<sup>1</sup> The CDER list is limited to PPPs that focus on “examining novel regulatory science questions, accelerating innovation, and assisting in the development of medical products” and does not include all PPPs or partnerships (e.g. organizations like GS1, RX-360 not included in this list).

Center for Drug Evaluation and Research			
Consortia <sup>1</sup>	Partners and Participants	Mission	FY 2014 Funding
<u>Coalition For Accelerating Standards and Therapies (CFAST);</u>	CDISC (Clinical Data Interchange Standards Consortium) and Critical Path Institute	Accelerate clinical research and medical product development by facilitating the creation and maintenance of data standards, tools and methods for conducting research in therapeutic areas important to public health.	Cooperative agreement granted to CDISC for a standards project under CFAST \$220,742
<u>Clinical Trials Transformation Initiative (CTTI)</u>	U.S. and international government agencies; pharmaceutical, biotech, device manufacturers; clinical research organizations; patient advocacy groups, professional societies and academic institutions	Identify practices that through broad adoption will increase the quality and efficiency of clinical trials.	Grant \$7,500,000
<u>Critical Path to TB Drug Regimens (CPTR Consortium)</u>	Bill & Melinda Gates Foundation , the Global Alliance for TB Drug Development, and the Critical Path Institute	Accelerate the development of new TB regimens by catalyzing innovative testing methods, product development partnerships and novel development strategies to develop innovative tools that will significantly accelerate development of new TB medicines.	See note at the end of the table:  Grant with parent 501(c)(3)
<u>Critical Path to TB Therapies</u>	International and domestic foundations, government, industry, and others	Accelerate the development of new multidrug regimens to treat TB.	Pursuant to FDAAA, FDA provides infrastructure support to the Reagan-Udall Foundation, the 501(c)(3) that runs this PPP, but currently does not provide separate funding for this project.
<u>Critical Path Institute Patient Reported Outcome (PRO) Consortium</u>	Pharmaceutical companies along with representatives from the FDA, EMA, NIH, patient advocacy organizations and academic advisors	To develop qualified and publicly available PRO instruments for use in clinical trials in order to support labeling claims	FDA funding provided  <a href="http://www.prnewswire.com/news-releases/us-food-and-drug-administration-continues-funding-critical-path-">http://www.prnewswire.com/news-releases/us-food-and-drug-administration-continues-funding-critical-path-</a>

	Center for Drug Evaluation and Research		
Consortia <sup>1</sup>	Partners and Participants	Mission	FY 2014 Funding
			<a href="http://www.fda.gov/oc/2014/02/institute-275440441.html">institute-275440441.html</a>  See note at the end of the table: Grant with parent 501(c)(3)
<u>Cardiac Safety Research Consortium (CSRC)</u>	Stakeholders from industry, academia, and government	Advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the FDA's Critical Path Initiative as well as other public health priorities.	No funding provided
<u>ILSI Health and Environment Sciences Institute</u>	Academic institutions, government agencies, Industry, other public sector organizations	Engage scientists from academia, government, industry, research institutes, and NGOs to identify and resolve global health and environmental issues. FDA participates in working groups.	No funding provided
<u>Innovation in Medical Evidence Development and Surveillance (IMEDS) program;</u>	Industry, academia, consumer groups, and regulatory and other government agencies	Advance science and tools to support post-market evidence generation on regulated products, including safety surveillance and evaluations, and to facilitate utilization of a robust electronic healthcare data platform for generating better evidence on regulated products in the post-market settings	Pursuant to FDAAA, FDA provides infrastructure support to the Reagan-Udall Foundation, the 501(c)(3) that runs this PPP, but currently does not provide separate funding for this project.
<u>International Serious Adverse Events Consortium (ISAEC);</u>	Representatives of the pharmaceutical industry, the Wellcome Trust, regulatory authorities and academic centers	Identify DNA-variants useful in understanding the risk of drug-	No funding provided

	Center for Drug Evaluation and Research		
Consortia <sup>1</sup>	Partners and Participants	Mission	FY 2014 Funding
		related serious adverse events.	
<u>Kidney Health Initiative (KHI);</u>	Patient organizations, health professional organizations, research institutions, foundations, pharmaceutical, biotechnology and device manufacturers, dialysis providers, and US and international government agencies	Advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and foster development of therapies for diseases that affect the kidney	Grant \$430,000
<u>Multiple Sclerosis Outcome Assessments Consortium (MSOAC);</u>	Industry, academia, patient representatives, regulatory and other government agencies, the National MS Society	Develop standards for assessing outcomes in clinical trials of MS therapies.  Collect, standardize, and analyze data about MS with the goal of qualifying a new clinician-reported outcome measure of disability as a primary endpoint for future MS trials.	See note at the end of the table:  Grant with parent 501(c)(3)
<u>National Institute for Pharmaceutical Technology and Education (NIPTe);</u>	Pharmaceutical science and engineering programs across 13 major research universities.	Improve human health through a multi-university collaboration on leading scientific research to advance the quality, safety, affordability, and speed to market of medicines through interdisciplinary research and education in pharmaceutical technology.	Grant \$1,400,000
<u>Patient Reported Outcome (PRO) Consortium;</u>	Scientists from pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors and representatives from (FDA, EMA), and NIH	Develop, evaluate, and qualify PRO instruments with the FDA for use in clinical trials	See note at the end of the table:  Grant with parent 501(c)(3)

	Center for Drug Evaluation and Research		
Consortia <sup>1</sup>	Partners and Participants	Mission	FY 2014 Funding
		designed to evaluate the safety and effectiveness of medical products.	
<u>PredicTox</u>	Government, academia, industry and patients	Use the science of systems biology to better understand the mechanisms driving the cardiac side effects of Tyrosine Kinase inhibitors (a common class of cancer drug	Pursuant to FDAAA, FDA provides Infrastructure support to the Reagan-Udall Foundation, the 501(c)(3) that runs this PPP, but currently does not provide separate funding for this project.
<u>Product Quality Research Institute</u>	academia, industry, and FDA	Generate and share timely, relevant, and impactful information that advances drug product quality and development.	No funding provided
<u>Polycystic Kidney Disease Outcome Consortium (PKDOC)</u>	Scientists from pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors and representatives from FDA, EMA, and NIH	Develop CDISC data standards for PKD and to use clinical data from ADPKD patients in patient registries and observational studies to support the FDA and EMA qualification of an imaging biomarker, Total Kidney Volume (TKV), for use in drug development trials	See note at the end of the table:  Grant with parent 501(c)(3)
<u>Predictive Safety Testing Consortium (PSTC)</u>	FDA, EMA and PMDA, and representatives of the pharmaceutical industry	Qualify new biomarkers for the detection and monitoring of drug-induced toxicity in preclinical and clinical studies.	See note at the end of the table:  Grant with parent 501(c)(3)
<u>SmartTots</u>	The International Anesthesia Research Society, regulatory agencies (FDA), professional societies, academic research institutions, patient advocacy groups, industry and other government and nonprofit organizations	Address major gaps in scientific information concerning the safety of anesthetics and sedatives in pediatric age groups. This initiative focuses on the safety of	Cooperative Agreement \$200,000

	Center for Drug Evaluation and Research		
Consortia <sup>1</sup>	Partners and Participants	Mission	FY 2014 Funding
		Inhaled and intravenous drugs in pediatrics.	
Medical Device Innovation Consortium (MDIC) <a href="http://mdic.org/">http://mdic.org/</a>	MDIC's membership has grown to 43 members with broad representation including large and small companies, non-profit organizations such as the Patient-Centered Outcomes Research Institute (PCORI) and Pew, patient advocacy organizations such as the National Organization for Rare Disorders (NORD), and other government agencies such as NIH and CMS	MDIC is working on regulatory science questions in clinical trial design for therapeutic and diagnostic devices, patient centered benefit-risk, computational modeling and simulation, and case for quality.	FDA has provided funding to MDIC for(Patient Centered Benefit-Risk ( \$500,000) and Case for Quality(FDA Total: \$642,000- \$442,000 from CDRH and \$200,000 from ORA)
Medical Device Epidemiology Network (MDEpiNet) Initiative  <a href="http://www.fda.gov/medicaldevices/scienceandresearch/epidemiologymedicaldevices/medicaldeviceepidemiologynetworkmdepinet/default.htm">http://www.fda.gov/medicaldevices/scienceandresearch/epidemiologymedicaldevices/medicaldeviceepidemiologynetworkmdepinet/default.htm</a>	MDEpiNet is comprised of professional organizations, academic centers, insurance companies, hospitals, patients, and medical device manufacturers	A public-private partnership to evaluate clinical evidence and develop new approaches for studying devices in use. Clinical studies that are performed before a device is marketed are often limited in size and short-term and cannot always detect long-term outcomes and rare adverse events. Also, it can be difficult to generalize the results of these studies to the broad range of patients that may use the device after it is marketed. To overcome these limitations, this partnership helps all stakeholders ensure data and methods developed can be monitored for the proper evolving	Since 2010, FDA has invested \$12 million through contracts and cooperative agreements. These funds have been used to establish MDEpiNet centers of excellence for: Methodology (Harvard University), Science and Infrastructure (Weill Cornell Medical College), and Partnership Management (Duke University). Pilot projects have been performed by these centers and other collaborators to establish International consortia of registries dedicated to orthopedic and cardiovascular devices, new methods for working with missing an Incomplete data, linking registry data to administrative claims to lower the burden of follow-up reporting, developing new registries for pelvic floor disorders, breast implants, automated external defibrillators, pediatric



## Attachment B

### Examples of FDA Accomplishments and Activities Organized by Priority Areas from the Strategic Plan for Regulatory Science

#### 1. Modernize Toxicology to Enhance Product Safety

FDA researchers have invested resources in closing gaps in predicting toxicity or safety issues of FDA-regulated products. This work includes the development and use of new computational modeling, *in silico* (i.e. a computer simulation), *in vitro* and *in vivo* approaches to predict patient responses, the identification of potential biomarkers for monitoring adverse reactions in preclinical species and in humans, and using computational tools to develop data mining tools and build knowledge bases.

The following are examples of these approaches:

- Computational approaches include research in physiologically based pharmacokinetic (PBPK) modeling to improve dosimetry correlations between nonclinical species and individuals who are difficult to study, such as pregnant woman and neonates.
- Computer modeling of cells includes the use of the DILIsym® model in a collaborative study between the FDA, the Hamner Institute for Health Sciences, and others.
- Improved and patented methods of *in silico* modeling have been used to build new models to predict drug toxicity to inform population-based safety risks; one approach might enable personalized medicine by identifying patient-specific genetic susceptibilities to individual drugs.
- *In vitro* approaches were used to study developmental toxicity, cardiotoxicity, etc. Models included the zebrafish and human induced pluripotent (iPS) stem cells.
- Bioimaging offers a non-invasive assessment of toxicity and, coupled with cognitive function tests, has been used to demonstrate in non-human primates, neurotoxicity of anesthetics routinely used in neonates .
- Organ specific toxicities, such as drug-induced pancreatitis, are being studied to improve the predictive utility of pre-clinical animal models.
- Technologies, including genomics, metabolomics, proteomics, and epigenetics have been used to identify new biomarkers of toxicity; work to date includes the identification of potential translational biomarkers of drug-induced liver injury in animals and humans.

- Next-generation sequencing, bioinformatics, resistomics, transcriptomics, and metagenomics are being applied to monitor trends and better understand the mechanism, emergence, persistence, and spread of antibiotic resistance.
- Bioinformatic approaches have been used to develop tools to assist reviewers and create knowledge bases of divergent information that can be queried to identify previously unknown associations.

## **2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes**

Evaluating the safety and effectiveness of medical products remains one of the most challenging steps in the translation of new scientific discoveries into viable medical treatments. Working with the clinical trial community, patient organizations, and other stakeholders, FDA has made significant contributions to advancing the science of clinical trials on several fronts.

Clinical trial designs that incorporate adaptive designs and enrichment strategies are being used to generate data that identify which patients benefit from an experimental therapy. Trials suited for the device development arena are incorporating Bayesian designs and using non-randomized controlled trials to do the same. New bioequivalence methods and clinical study requirements for determining biosimilarity are being developed. FDA statisticians have contributed to the design of efficient master protocols for cancer and antimicrobial therapies. These protocols incorporate biomarker information and reduce the number of patients required. Additional new tools that aid in the design and analysis of clinical trials include pharmacometric models to optimize dosing strategies, disease models that inform the design of trials, models that inform bioequivalence determinations and models that predict device performance.

New biomarkers and clinical outcome assessments have been developed and integrated into the regulatory process by formal qualification processes for drugs and devices. FDA has enhanced infrastructure for receipt, storage, and analysis of digital applications by specifying data standards for preclinical and clinical studies, building digital preclinical and clinical trial repositories, and developing data mining and analysis tools to make the review process more efficient and effective.

FDA's significant advances in facilitating the realization of personalized medicine are detailed in an October 2013 report entitled "Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development."<sup>1</sup> Advances include a focus on pharmacogenomics, personalized devices, and clinical trials designs focused on defined subgroups.

Some recent examples of FDA advances in clinical evaluation strategies and personalized medicine include:

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<sup>1</sup> Report available at:

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf>.

- Worked with Friends of Cancerto help develop a master multi-drug, multi-arm protocol for lung cancer which will involve large-scale screening through which patients are assigned to treatment based on biomarker status;
- Incorporated improvements in device trials as one of three major areas of focus for the Medical Device Innovation Consortium;
- Qualified an electronically administered patient-reported outcome (PRO) to measure symptoms of acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease;
- Created a clinical trials repository and integrated data mining and analysis tools to facilitate regulatory analysis and research;
- Developed disease progression models for Parkinson's disease to inform design trials to discern disease modifying effects; and
- Developed through analysis of multiple development programs earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies.

### **3. Support New Approaches to Improve Product Manufacturing and Quality**

FDA has made concerted efforts to understand how new science and technology could be applied to increase the efficiency, accuracy, and quality of manufacture of FDA-regulated products. The safety and effectiveness of FDA regulated products depend on a number of factors, including design, manufacture, quality assurance, packaging, labeling, storage, installation, and servicing. Research in these areas focuses on improving the initial product design and manufacturing processes as well as techniques to detect problems when they arise.

The following examples illustrate the range of accomplishments and ongoing activities in this area of regulatory science:

- Investigated the ability of next-generation sequencing data to evaluate product purity and quality, for example, for vaccine consistency of live virus vaccines or for screening vaccine cell substrates and other vaccine manufacturing intermediates for contamination with infectious agents;
- Developed and evaluated methods to use high-resolution NMR, mass spectrometry, aptamers and other high resolution analytic methods to identify structural determinants of recombinant therapeutic proteins to prepare for evaluation of biosimilars;
- Developed and evaluated novel analytic methods to assess product purity and identity of nanotechnology-based regulated products;
- Developed laboratory analytical and field examination procedures addressing various attributes of higher risk medical devices and radiation-emitting products;

- Used next-generation sequencing data to detect and track the source of foodborne outbreaks and human pathogens with antimicrobial resistance markers in food animals and animal feed;
- Developed and implemented hand-held monitors based on Raman spectrometry to screen imported FDA-regulated products for evidence of contamination or to identify counterfeit products;
- Determined root-cause failures of device safety issues in devices such as Huber needles, ventilators, and infusion pumps; and
- Developed standards to prevent misconnection of different sets of small-bore connectors used for IV, feeding, tracheotomy, and discharge tubes to prevent contamination and serious adverse events.

#### **4. Ensure FDA's Readiness to Evaluate Innovative Emerging Technologies**

FDA has invested heavily in regulatory science to support readiness to evaluate emerging technologies. To ensure readiness, FDA needs to recruit the scientific expertise needed to address new areas as well as provide resources to train/retrain existing staff to provide up-to-date knowledge of new technologies. By performing its own research on emerging technologies, FDA can identify and fill the knowledge gaps necessary to support regulatory decision-making.

The following examples illustrate the range of accomplishments and ongoing activities in this area of regulatory science:

- Evaluated and used 3-D printers to understand the limits and capabilities of this new technology in developing regulated products;
- Developed fatigue test methods for medical devices composed of bioresorbable polymers including peripheral and coronary stents, bone screws and related components;
- Developed analytical and field test protocols for automated non-invasive bloodp monitors (sphygmomanometers) for imported devices labeled for home and public use;
- Created a general testing protocol and test methods for automated external defibrillators (AEDs);
- Developed methods to evaluate and characterize new test equipment for suitability in x-ray compliance testing;
- Created new approaches to identify and understand critical product quality attributes of complex products, such as stem cell-derived products (both animal and human) and complex systems of medical devices;
- Developed methods and models to assess the toxic effects of FDA-regulated products containing engineered nanomaterials;

- Evaluated the health impact of probiotic nutritional supplementation;
- Developed analytic methods and preclinical models for assessment of hemoglobin-based oxygen substitutes;
- Established genomic sequencing reference material and constructing a library of definitive sequences for common pathogens to serve as a foundational body of data that could be used in the creation of future diagnostic tools, devices, and therapies; and
- Developed strategies to ensure the credibility of computational models to inform product design before the products are tested in patients.

## **5. Harness Diverse Data through Information Sciences to Improve Health Outcomes**

In the last several years, FDA scientists have greatly expanded the development and use of new methods and tools for data mining, modeling, simulation, data visualization, active surveillance and risk assessment, applying them in a variety of regulatory contexts. FDA has worked actively to expand access to a broad range of new external data sources while improving capabilities for mining in-house data for knowledge building, analysis, modeling, and simulation. New methods and tools for the analyses of large datasets have been applied to understanding clinical endpoints, dose estimation in special populations, safety assessment and prediction, and product performance. Some efforts are exploratory, some are providing practical, auditable tools to aid reviewers, and others are being used to inform regulatory decisions. The following examples illustrate the range of accomplishments in this area of regulatory science:

- Used the Mini-Sentinel pilot program to leverage electronic health care records from over 150 million patients across 18 data partners to support hundreds of queries related to post-marketing surveillance of the safety of medical products;
- Developed a computational Virtual Family of anatomically correct models to investigate how various devices interact with the body;
- Implemented natural language text mining tools to interrogate FDA drug product labels, MEDLINE abstracts, and gene/protein databases to find causal interactions between drug pharmacology and unexpected clinical adverse events;
- Developed and applied risk-based models to guide selection of facility and clinical trial sites for inspection;
- Explored the potential for mining social media and other web sources to detect adverse event and safety signals;
- Applied data mining and natural language processing of free text to multiple information sources to refine post-market surveillance;
- Expanded the available quantitative structure-activity models to predict toxicity;

- Developed models to bridge existing clinical data to guide dosing recommendations in pediatric populations;
- Worked to develop and validate an *in silico* model of the human ventricular myocyte for regulatory use as a potential replacement for the Thorough QT study, which is used to evaluate proarrhythmic risk (partnership with HESI, the pharmaceutical industry and CSRC); and
- Launched the CERES (Chemical Evaluation and Risk Estimation System) database to enhance chemical evaluation and risk estimation for pre- and post-market review of food ingredients (The system will enable FDA to fully leverage available data through modern computational and predictive methods for pre-market review and post-market monitoring of food ingredients and packaging materials).

## **6. Implement a New Prevention-Focused Food Safety System to Protect Public Health**

In 2011, the Food Safety Modernization Act (FSMA) was signed into law and gave FDA new and enhanced mandates and authorities to protect public health, redefining the role of FDA's Food and Veterinary Medicine Program (FVM) in safeguarding America's food supply. FSMA directs FDA to build a new food safety system based on the public health principles of comprehensive prevention, an enhanced focus on risk-based resource allocation, and partnership across the public and private sectors to minimize hazards from farm-to-table. To accomplish new mandates under FSMA, FDA continues to build and sustain high-quality, focused intramural and extramural scientific research programs which are providing the foundation for sound regulatory policy, as well as compliance and enforcement actions. Research is needed to fill critical data gaps in our scientific knowledge regarding both the assessment and management of food safety hazards (e.g., microbial and chemical), and to support the development and application of the analytical tools to manage and prevent those food safety risks. This research is critical because it is not conducted by other public or private entities, but is fundamental to the fulfillment of FDA's statutory responsibilities to protect and promote the public health under FSMA.

The following examples illustrate the range of accomplishments in this area of regulatory science:

- Released FDA's 2012–2016 Food and Veterinary Medicine Program Strategic Plan, which identifies key goals and objectives to advance food safety, nutrition, and animal health (This strategic plan includes a new vision and mission statement, a cross-cutting goal, and seven program goals requiring action and dedicated effort over the next five years.);
- Created a Science and Research Steering Committee (SRSC), which includes science and research leaders from relevant FDA operating units, offices, and centers (The SRSC's primary role is to lead, coordinate and unify research and methods development strategies across the Foods and Veterinary Medicine program.);
- Developed new validation guidelines for chemical methods and analytical methods for detecting microbial pathogens in foods to ensure they meet the highest analytical



performance standards for their intended purpose (These criteria now apply to all FDA laboratories that develop and participate in the validation of analytical food methods for Agency-wide implementation in a regulatory capacity.);

- Expanded FDA's network of veterinary diagnostic laboratories (Vet-LIRN) from the original 16 members in 2010 to 34 laboratories in 2014, which has also been heavily involved in CVM's investigation of the illness in dogs associated with eating pet jerky treats (Since 2011, Vet-LIRN has conducted more than 1,000 tests on jerky pet treat samples.);
- Enhanced the National Antimicrobial Resistance Monitoring System (NARMS) to test outbreak strains, link with other federal food safety surveillance programs, expand retail meat testing, enhance collaborative research, and develop new IT tools for data management and analysis (Surveillance and testing is also being extended to isolates from animal production facilities, to cover the complete spectrum from farm to fork.);
- Developed and evaluated software tools that can perform non-targeted screening using data from a wide range of analytical instruments, to determine the presence of unexpected adulterants and contaminants in FDA-regulated products;
- Developed FDA-iRISK®, an interactive tool that can compare and rank public-health risks from contaminants (chemical and microbial) in foods (This risk assessment tool generates results relatively quickly and is available to the public at [www.foodrisk.org](http://www.foodrisk.org).);
- Developed approaches to use new and emerging technologies for the detection and confirmation of veterinary drug residues in food derived products including animal feeds;
- Created the GenomeTrakr project, a collaboration between FDA, seven state public health laboratories and ten FDA field laboratories to use whole genome sequencing (WGS) for characterization of foodborne bacteria ; and
- Established the Coordinated Outbreak Response and Evaluation (CORE) Network to manage not just outbreak response, but also surveillance and post-response activities related to incidents involving multiple illnesses linked to FDA-regulated human and animal food and cosmetic products.

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

Since 2010, with the launch of MCMi, FDA has greatly expanded its efforts to advance regulatory science related to this category of FDA-regulated products to create the tools that can support regulatory decision-making. Priority research areas include: developing animal models and tools to evaluate product safety and efficacy; identifying and qualifying biomarkers for safety and efficacy; using protein engineering to stabilize vaccine proteins; developing methods to assess MCM product quality and related product release assays; validating next-generation *in vitro* diagnostics platforms; assessing the performance of emergency medical equipment; and enhancing emergency preparedness and response capabilities, including risk communication and tracking and evaluating the safety and clinical benefit of MCMs used during public health emergencies.

The following examples illustrate the range of cutting-edge research being supported in this area of regulatory science:

- Developing models of radiation damage in lung, gut, and bone marrow organs-on-chips and then used these models to test candidate MCMs to treat such damage;
- Mapping immune responses to certain biothreat agents and MCMs in humans and animal models to create species-specific immune function maps;
- Examining the scientific basis for the instability of the protective antigen that has hindered efforts to develop next-generation anthrax vaccines and used protein engineering to stabilize the antigen;
- Developing new approaches for measuring the quality of next-generation smallpox vaccines;
- Developing new methods for evaluating the purity and sterility of novel cell substrates that can be used to produce vaccines;
- Developing new and improved tests to detect viruses and mycoplasma in biological samples including cell substrates and other starting materials to support assessment of product quality, safety, and consistency;
- Developing methods for real-time detection of medical device surface contamination to decrease the potential for the transmission of infection between patients as well as between patients and health care workers;
- Assessing the feasibility of using electronic health record systems to conduct near real-time monitoring of health outcomes, including serious or unexpected adverse events associated with MCMs used during public health emergencies; and
- Developing a high-density microarray for detection of over 4,000 antimicrobial resistance genes from bacterial pathogens to accelerate treatment decision making and improve MCMs in the event of a deliberate release of bacterial threat agents or an emerging bacterial disease outbreak.

## **8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions About Regulated Products**

FDA social and behavioral scientists have expanded and deepened our use of social science methods of inquiry to understand our target audiences and how to communicate effectively with them. We test how the public responds to various potential communication formats, including nutrition labels, educational videos, and placement of information in print and broadcast advertising, using Internet panels as well as in-person participation. In addition to traditional surveys and focus groups, we also are exploring structured qualitative data gathering methods in open meetings to understand the knowledge, values and concerns of the public. By applying social science methods in the context of internal quality improvement exercises, we leverage our own dedicated workforce to improve our communication products

and processes. We are developing new methods to integrate quantitative and qualitative social science results with pharmacoepidemiological data to assess communication effectiveness in the use of regulated products, while also expanding our analytical capacity to learn the extent and effect of FDA communications in social as well as traditional media. The results of our inquiries inform our communications about regulated products with the public including health care professionals, and our communication to regulated industry about labeling and advertising.

The following examples illustrate the range of accomplishments in this area of regulatory science:

- Conceptualized a novel integrated, multidisciplinary approach to assessing communication effectiveness followed throughout a unified health care system, from FDA release of safety information, through traditional and social media uptake, to patient awareness assessed qualitatively and quantitatively, and finally to quantitative changes in drug dispensing and rates of health outcomes of interest in comparison to controls and compared to rates observed prior to communication issue;
- Conducted a research program on facilitating audience understanding of a legally required list of harmful and potentially harmful constituents of tobacco products, starting with focus groups, then using the findings to develop an experiment comparing lists in different formats for three different types of products (cigarettes, smokeless, or roll-your-own), or no list at all (control);
- Completed a randomized study assessing whether quantitative information could be successfully added to television and print advertisements to maximize audience understanding of benefit information in the piece, including the type of benefit information, different combinations of statistical format, and different graphic representations;
- Examined the effects of changing the Nutrition Facts label on foods to help consumers identify healthier choices, particularly for products listed as having 1 or 2 servings per container, but likely to be eaten as one serving (9,493 participants and 10 format variations);
- Examined usage and preferences regarding device labeling among both home caregivers (using a web-based survey) and health care providers (focus groups followed by web-based survey);
- Facilitated dozens of analyses of publicly available social media traffic on topics of FDA communications; and
- Released a second, updated edition of the Bad Bug Book, a compendium of pathogens that are found as contaminants of foods. The revised online edition provides updated scientific and technical information about the major pathogens and toxins that cause foodborne illness.

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