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Paving the Way for Personalized Medicine

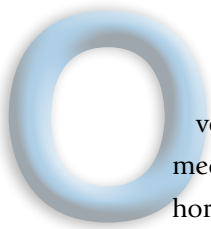
FDA's Role in a New Era of Medical Product Development



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

Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development

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Over the past few years, a number of products that signal a new era of medical product development have entered the market or come on the horizon. In just the last two years, the FDA approved four cancer drugs for use in patients whose tumors have specific genetic characteristics that are identified by a companion diagnostic test. Last year, FDA approved a new therapy for use in certain cystic fibrosis patients with a specific genetic mutation. Earlier this year, three-dimensional (3D) printing was used to create a bioresorbable tracheal splint for treating a critically-ill infant.



Each of these examples demonstrates the promise of “personalized medicine,” which is the tailoring of medical treatment to the individual characteristics, needs and preferences of each patient. The concept of personalized medicine is not new: clinicians have long observed that patients with similar symptoms may have different illnesses, with different causes; and similarly, that medical interventions may work well in some patients with a disease but not in others with apparently the same disease. What is new is that advances in a wide range of fields from genomics to medical imaging to regenerative medicine, along with increased computational power and the advent of mobile and wireless capability and other technologies, are allowing patients to be treated and monitored more precisely and effectively and in ways that better meet their individual needs.

Long before I became commissioner, FDA was attuned to the promise and potential challenges of personalized medicine. As a result of this forward thinking, the Agency moved quickly to build and shape a regulatory infrastructure to help make personalized medicine possible. I have made it a priority to continue to evolve FDA’s regulatory processes in response to—and in anticipation of—scientific developments that are critical for the development of personalized therapeutics and diagnostics.

I am pleased to offer this report, *Paving the Way for Personalized Medicine: FDA’s Role in a New Era of Medical Product Development*, as part of the Agency’s ongoing commitment to this important and emerging area of medicine. The report describes the ways in which FDA has worked to respond to, anticipate and help drive scientific developments in personalized therapeutics and diagnostics. For the first time, it provides a compendium of FDA’s many recent efforts to advance regulatory standards, methods and tools in support of personalized medicine and to further refine critical regulatory processes and policies in order to bring about personalized medical product development. This thoughtful report should serve as a useful resource for those looking toward a future where all stages of patient care—from prevention to diagnosis to treatment to follow-up—are truly personalized.

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

I. INTRODUCTION

On January 31, 2012, the FDA approved a new therapy for cystic fibrosis (CF), a serious inherited disease that impairs the lungs and digestive system. The drug, Kalydeco™ (known generically as ivacaftor), was approved for patients with a specific genetic mutation – referred to as the G551D mutation – in a gene that is important for regulating the transport of salt and water in the body. There are hundreds of known mutations that can lead to CF; the G551D mutation is responsible for only 4% of cases in the United States (approximately 1200 people). In these patients, Kalydeco works by helping to restore the function of the protein that is made by the mutated gene. It allows a proper flow of salt and water on the surface of the lungs and helps prevent the buildup of sticky mucus that occurs in patients with CF and can lead to life-threatening lung infections and digestive problems.

The Kalydeco story is compelling on several levels. First, Kalydeco is the first drug to address the underlying cause – rather than the symptoms – of CF. Skillful application of genomic science allowed researchers to understand at a molecular level the reasons why a protein fails to function, to discover and develop a medicine specifically to improve its function, and to use the results of a genetic test to select the right patients for the drug. While it is too soon to say whether Kalydeco will be an all-out cure for those eligible to receive it, patients are experiencing significantly improved lung function and weight gain.

Second, the path of development that ultimately led to the approval of Kalydeco

was patient-driven. The drug itself emerged out of a decade-long collaboration between the Cystic Fibrosis Foundation (CFF) and the drug's manufacturer, Vertex Pharmaceuticals. The Foundation had been at work several decades previously, organizing and advocating on behalf of the patient community, funding research that led to the discovery of the gene in 1989, building an extensive patient registry and clinical trial network necessary for investigating the genetics of the disease, and efficiently recruiting study participants and testing candidate drugs. Starting in the late 1990s, CFF funded a major drug screening effort that led to the discovery of the compound and invested a total of \$75 million toward the development of the drug.

Finally, FDA approved Kalydeco in a very short time. Elegant science and a well-designed program of the drug sponsor allowed the agency to apply a number of mechanisms for streamlining and expediting the review process. For one, the drug application was granted “priority review,” a designation that is given to candidate drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists. The time goal for completing a priority review is six months, but a well-prepared submission, strong evidence, and a commitment on the part of all of the parties involved enabled the review to be completed, and the drug approved, in half that amount of time.

Kalydeco is one of several “targeted therapies” approved in the past two years. Several cancer drugs – crizotinib, vemurafenib, dabrafenib, and trametinib – have each been approved

for use in patients whose tumors have specific genetic characteristics that are identified by a companion diagnostic test.

More broadly, Kalydeco is one of many medical products that point to the emergence of a new era of personalized medicine. “Personalized medicine” may be thought of as tailoring medical treatment to the individual characteristics, needs and preferences of each patient. “Personalized medicine” is not limited to pharmaceutical therapy. Advances in computational power and medical imaging are paving the way for personalized medical treatments that consider a patient’s genetic, anatomical, and physiological characteristics. The advent of mobile and wireless capability, better sensors, interoperable devices, and the Internet have led to technologies that allow for more effective patient monitoring and treatment outside of traditional medical care settings. And progress in regenerative medicine and stem cell research offers hope for some of the most personalized products imaginable – the replacement or regeneration of missing or damaged tissues.

The concept of personalized medicine is not new: The practice of medicine has always been about treating each individual patient, and clinicians have long observed that different patients respond differently to medical interventions. What is new is that paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects.

The advances of the last few years in personalized therapeutics are testament to the power of science to fundamentally

advance medical practice, yet the challenges of understanding human health and disease remain sobering. Who we are, and what illnesses we suffer, depends not only on our genes, but also on a complex intersection of environmental, genetic, social and cultural factors. We have a great deal to learn about the biological, anatomical and physiological mechanisms that underlie disease. Realizing a truly personalized approach to patient care will require fundamental advances in understanding each of these factors, as well as how they impact one another.

The purpose of this report¹ is to describe the unique and special role and responsibility that FDA has in helping to usher in the medical products that are central to this larger effort. The report describes the ways in which FDA has evolved its regulatory processes in response to – and in anticipation of – scientific developments that are critical for the development of personalized therapeutics and diagnostics. It describes in particular the ways in which FDA has worked to bridge developments in genomics and other relevant sciences to clinical practice by advancing the tools necessary for evaluating targeted therapeutics and bringing them to market more efficiently, collaborating in key research, defining and streamlining regulatory pathways and policies, and applying new knowledge in product reviews.

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II. PERSONALIZED MEDICINE FROM A REGULATORY PERSPECTIVE

We all have a stake in personalized medicine. The way we view the evolution of this area is influenced by our particular perspectives – for example, as patients, clinicians, drug or device manufacturers, information technology specialists, healthcare providers, insurers, educators, or regulators. This section describes the concept of personalized medicine and some of the ways that the term has recently been used or defined. It then turns to a discussion of personalized medicine in the regulatory context, and describes FDA’s unique perspective and responsibilities in helping to advance this important field.

1. DEFINING PERSONALIZED MEDICINE

It's far more important to know what person the disease has than what disease the person has.
– Hippocratesⁱ

The concept of personalized medicine dates back many hundreds of years. It was not until the 19th century, however, that developments in chemistry, histochemistry

and microscopy allowed scientists to begin to understand the underlying causes of disease. From here, major advancements in science and technology have allowed healthcare decisions to become increasingly granular over time. With the growth of the pharmaceutical and medical device industries in the 20th century came the rise of genetics, imaging, and data mining. Midway through the century, observations of individual differences in response to drugs gave rise to a body of research focused on identifying key enzymes that play a role in variation in drug metabolism and response and that served as the foundation for pharmacogenetics. More recently, sequencing of the human genome at the turn of the 21st century set in motion the transformation of personalized medicine from an idea to a practice. Rapid developments in genomics, together with advances in a number of other areas, such as computational biology, medical imaging, and regenerative medicine, are creating the possibility for scientists to develop tools to truly personalize diagnosis and treatment.

Despite extraordinary advances that have been made to date in medical fields, we have a long way to go in understanding why different individuals experience disease

Early Examples of Personalized Medicine

1907: Reuben Ottenberg reports the first known blood compatibility test for transfusion using blood typing techniques and cross-matching between donors and patients to prevent hemolytic transfusion reactions.

1956: The genetic basis for the selective toxicity of fava beans (“favism”) and the antimalarial drug primaquine is discovered to be a deficiency in the metabolic enzyme, glucose-6-phosphate dehydrogenase (G6PD).

1977: Cytochrome P450 2D6, a polymorphic metabolizing enzyme, is identified as the culprit for causing some patients to experience an “overdose” or exaggeration of the duration and intensity of the effects of debrisoquine, a drug used for treating hypertension.

or respond to treatment differently. Our current lack of ability to predict an individual patient’s treatment success for most diseases and conditions means that clinicians have no choice but to follow a less than optimal approach to prescribing drugs and other treatment options. A patient being treated for high blood pressure, for example, might be placed on one of a number of blood pressure medications. The patient’s doctor makes a decision about what medication to prescribe based on only general information about what might actually work for that particular patient. If the medication does not work after a few weeks, the patient might be switched to another medication. This somewhat “trial-and-error” approach can lead to patient dissatisfaction, adverse drug responses and drug interactions and poor adherence to treatment regimens. The goal of personalized medicine is to streamline clinical decision-making by distinguishing in advance those patients most likely to benefit from a given treatment from those who will incur cost and suffer side effects without gaining benefit.

The term “personalized medicine” is often

described as providing “the right patient with the right drug at the right dose at the right time.”ⁱⁱ More broadly, “personalized medicine” may be thought of as the tailoring of medical treatment to the individual characteristics, needs and preferences of a patient during all stages of care, including prevention, diagnosis, treatment and follow-up.

Several terms, including “precision medicine,” “stratified medicine,” “targeted medicine,” and “pharmacogenomics,” are sometimes used interchangeably with “personalized medicine.” “Precision medicine” is perhaps most synonymous to “personalized medicine” and has been defined by the National Academy of Sciences (NAS) as “the use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment.”ⁱⁱⁱ “Stratification” refers to the division of patients with a particular disease into subgroups, based on a characteristic of some sort, who respond more frequently to a particular drug or, alternatively, are at decreased risk of side effects in response to a certain

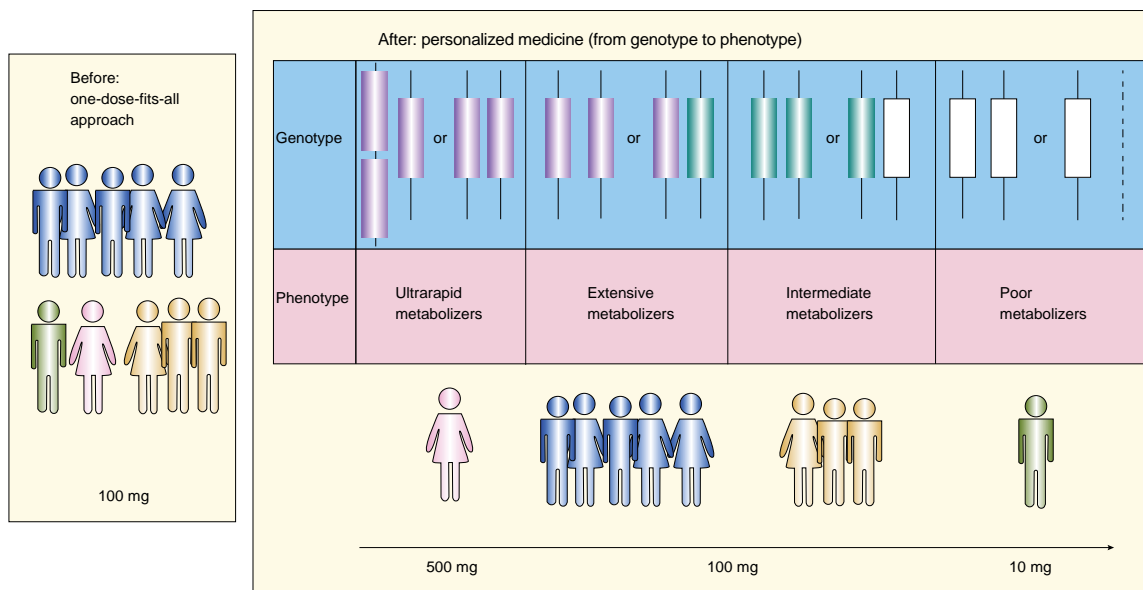


Figure 1. Representation of the trial-and-error or one-dose-fits-all approach versus personalized medicine. The left panel shows a situation in which everyone gets the same dose of a drug, regardless of genotype. The right panel shows a personalized medicine approach in which the dose of the drug is selected based upon genotypical, and therefore phenotypical, variability of the metabolizing enzyme. (Source: Xie, H., Frueh, F.W., (2005). Pharmacogenomics steps toward personalized medicine. *Personalized Medicine*, 2(4), 333.)

Describing Personalized Medicine

The definition and scope of the term personalized medicine varies widely, ranging from the extremely broad to the very narrow. These examples have been selected to demonstrate the range of definitions that have been proposed:

- “The use of new methods of molecular analysis to better manage a patient’s disease or predisposition to disease.”
– Personalized Medicine Coalition
- “Providing the right treatment to the right patient, at the right dose at the right time.” – European Union
- “The tailoring of medical treatment to the individual characteristics of each patient.” – President’s Council of Advisors on Science and Technology
- “Health care that is informed by each person’s unique clinical, genetic, and environmental information.” – American Medical Association
- “A form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.”
– National Cancer Institute, NIH

treatment. Stratification can be thought of as a core element of personalized medicine. “Pharmacogenomics” (PGx) – the study of variations of DNA and RNA characteristics as related to drug response^{iv} – is a critically important area of personalized medicine where significant progress has recently been made.

Personalized medicine generally involves the use of two medical products – typically, a diagnostic device and a therapeutic product – to improve patient outcomes. A diagnostic device is a type of medical device. Diagnostic devices include both *in vitro* tests such as assays used in measurement of genetic factors and *in vivo* tests, such as electroencephalography (EEG), electrocardiography (EKG), or diagnostic imaging equipment.

While considerable attention in personalized medicine is currently being paid to the use of genetic tests to guide therapeutic decisions, a vast variety of medical devices can be used in a personalized approach to improve patient outcomes. Many medical device therapies are now capable of being tailored to specific patient characteristics. These individual characteristics include patient anatomy (*e.g.*, size), physiology (*e.g.*, nervous and cardiovascular systems, metabolism, reproduction) and environment of use (*e.g.*, intensive care unit, home use). Additionally, physiological sensors can be used to predict treatment responses for individual patients. For example, three-dimensional (3D) printing has been used to create personalized medical devices based on imaging of a patient’s anatomy.

Pharmacogenomics

Pharmacogenomics (PGx), the study of variations of DNA and RNA characteristics as related to drug response, is one of the most exciting areas of personalized medicine today. The field arises from the convergence of advances in pharmacology (the science of drugs) and genomics (the study of genes and their functions). Patients typically have variability in response to many drugs that are currently available. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience adverse effects. PGx seeks to understand how differences in genes and their expression affect the body’s response to medications. More specifically, PGx uses genetic information (such as DNA sequence, gene expression, and copy number) for purposes of explaining interindividual differences in drug metabolism (pharmacokinetics) and physiological drug response (pharmacodynamics), identifying responders and non-responders to a drug, and predicting the efficacy and/or toxicity of a drug.

Advances in PGx have opened new possibilities in drug discovery and development. PGx has allowed for more tailored treatment of a wide range of health problems, including cardiovascular disease, cancer, and HIV/AIDS. FDA’s Center for Drug Evaluation and Research (CDER) has supported pharmacogenomics for more than a decade by providing regulatory advice, reviewing applications, and developing policies and processes centered on genomics and individualized therapeutics.

In addition, the advent of mobile and wireless capability, better sensors, interoperable devices, and the Internet have led to technologies that allow for more effective patient monitoring and treatment outside the traditional medical care settings of hospitals, chronic care facilities and physician

offices. Instead, more people are treated at home and at work and are better able to maintain their lifestyle and quality of life. As a result of these technological advances, medical diagnostics and therapeutics can be more finely tuned to better meet the needs of individual patients.

3D Printed Tracheal Splint

Physicians at the University of Michigan and Akron Children's Hospital utilized a computed tomography image, computer-aided design, and 3D printing to create a bioresorbable airway splint to treat a critically-ill infant with tracheobronchomalacia – a life-threatening condition that occurs when the airway walls are weak and the airways collapse during breathing or coughing.

The “personalized” tracheal splint for the patient was constructed based on CT images of the patient's airway and lungs. The device itself was “printed” by the 3D printer using polycaprolactone (PCL) – a degradable material that, over time, will dissolve, allowing the body to heal and grow around it. Upon receiving Institutional Review Board approval for use under FDA's emergency-use provisions, physicians successfully implanted the tracheal splint overlying the patient's airway, basically creating a placeholder for the cells to properly grow around it. One year after surgery, imaging and bronchoscopy showed an open airway while full resorption of the bioresorbable stent is expected to take 3 years.

This story serves as a powerful example of how parallel advances in multiple fields can come together to result in extraordinary advances in personalized medicine, and offers a glimpse into a future where truly individualized, anatomically-specific devices may become a standard part of patient care.

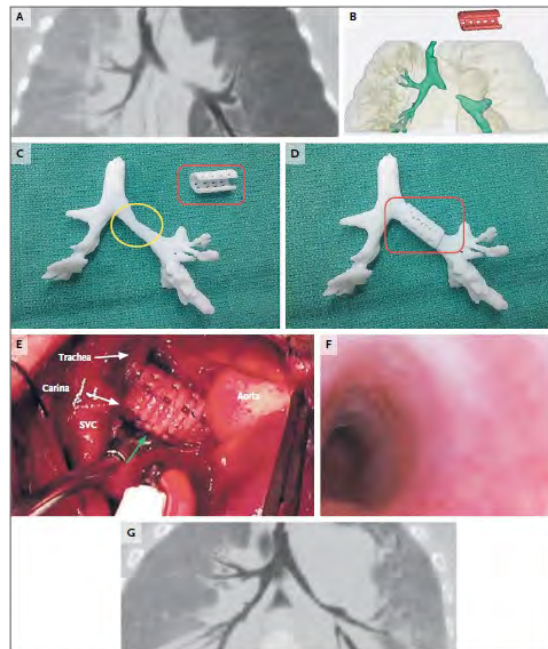


Figure 1. Placement of the Printed Airway Splint in the Patient.

Panel A shows the airway in expiration before placement of the splint; the image was reformatted with minimum-intensity projection. Panel B shows the patient-specific computed tomography-based design of the splint (red). Panel C shows an image-based three-dimensional printed cast of the patient's airway without the splint in place, and Panel D shows the cast with the splint in place. Panel E shows intraoperative placement of the splint (green arrow) overlying the malacic left mainstem bronchial segment. SVC denotes superior vena cava. Panel F shows the bronchoscopic view, from the carina, of the left mainstem bronchus after placement of the splint. Panel G shows the airway in expiration 1 year after placement of the splint; the image was reformatted with minimum-intensity projection.

From: Bioresorbable Airway Splint Created with a Three-Dimensional Printer N Engl J Med 2013; 368:2043-2045.

Examples of “Personalized” Medical Devices

- **Tinnitus masker** is personalized by the manufacturer to patient tinnitus. The tinnitus treatment custom-tailors the audio signals to suit the individual patient’s hearing requirements
- **Pedicle screw spinal systems**- Spinal systems consisting of a rod/screw/hook/connector kit are assembled by a surgeon to accommodate a patient’s unique anatomy/physiology using MRI/CT imaging.
- **Software-based quantitative EEG analysis** to predict an individual’s response to various psychotropic drugs. The device provides the probability of response to various medications to guide clinician in decision making.
- **The Zenith Fenestrated AAA Endovascular Graft** is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysms having morphology suitable for endovascular repair. The fenestrated device allows for treatment of patients with shorter proximal neck lengths (i.e., length of healthy aorta between the renal arteries and the aneurysm) as compared to those who can be treated using other endovascular grafts. Each device is tailored to the patient’s individual aortic anatomy with openings in the graft material placed appropriately to maintain blood flow to branch vessels of the aorta.
- **The Artificial Pancreas Device System** is a device under clinical investigation that automatically monitors patient glucose levels and delivers patient-tailored insulin doses in people with diabetes. A computer-controlled algorithm connects the continuous glucose monitoring system and an insulin infusion pump to allow continuous communication between both devices and deliver a personalized treatment based on individual glucose patient readings.

The success of personalized medicine depends on the development of accurate and reliable diagnostics and, in some cases, on the identification of predictive biomarkers. Diagnostics used in personalized medicine are generally intended to identify the presence, absence, or amount of a biomarker (as in the case of *in vitro* diagnostics) or to assess physiological or anatomical patient characteristics (as in the case of EKG tracings or imaging technologies). If the diagnostic test is inaccurate, then the treatment decision based on that test may not be optimal. For example, with an incorrect diagnostic result, an unsuitable drug may be given to a patient who will as a result, be harmed or will not benefit, because the drug will cause an otherwise avoidable side effect, will be ineffective for that patient, or both.

In the long run, personalized medicine seeks to reduce the burden of disease by targeting prevention and treatment more effectively. With the help of personalized medicine, the health care management paradigm will focus on prevention, moving from illness to wellness, and from treating disease to maintaining health. By improving our ability to predict and account for individual differences in disease diagnosis, experience, and therapy response, personalized medicine offers hope for diminishing the duration and severity of illness, shortening product development timelines, and improving success rates. At the same time, it may reduce healthcare costs by improving our ability to quickly and reliably select effective therapy for a given patient while minimizing costs associated with ineffective treatment and avoidable adverse events.

2. FDA'S UNIQUE ROLE AND RESPONSIBILITIES IN PERSONALIZED MEDICINE

FDA's mission is to protect and promote the health of all Americans through assuring the safety, efficacy, and security of drugs, biologics (such as blood products and vaccines), and medical devices, and the safety and security of foods, cosmetics, and many other consumer goods. In the U.S., FDA-regulated products account for about 20 cents of every dollar spent by American consumers each year. In the case of medical products, FDA determines that products are safe and effective before marketing through a careful evaluation of benefits and risks that considers the available scientific data in the context of the underlying condition or disease. FDA also requires manufacturers to follow quality manufacturing practices and processes, and conduct post-market surveillance. In addition FDA strives to advance the public health by helping to speed access to innovative medical products.

FDA's responsibility for ensuring that drugs, devices, and biologics are safe and effective provides the agency with a unique perspective on both the successes and failures that occur in medical product development and special insight into the emergence and direction of the field of personalized medicine. Consistent with FDA's core mission are a series of institutional responsibilities that are key to the emergence and direction of the field of personalized medicine. These include responsibilities to:

- Carefully consider benefits and risks when evaluating medical products to appropriately foster innovative product development while assuring adequate patient protections;
- Stay abreast of rapid advances in innovative science and technology;
- Provide clarity, predictability, and guidance to industry in order to help encourage development in promising new areas of medical product development;
- Help ensure that information about the latest science and technology is being used appropriately and rationally to inform clinical trial design, drug and device development, and clinical practice;
- Work together with university scientists, government agencies, including NIH, companies, standards organizations, practicing physicians, and patients to evaluate and validate new diagnostics and therapeutics;
- Help address the "pipeline" problem for drugs and medical devices by identifying opportunities for streamlining regulatory processes and advancing the science and tools that will help drive innovation.

From FDA's perspective, personalized medicine promises to increase benefits and reduce risks for patients by improving both the safety and efficacy of medical products. Every product has inherent risks, but FDA's job is to determine if the likely benefit exceeds the risk in the targeted populations as a whole. A medical product can be approved as "safe and effective" if there is scientific evidence

that the product is effective for its intended use and its demonstrated benefits outweigh its known and potential risks. But the actual safety and effectiveness of the product may vary from one individual to the next as a result of genetic and environmental factors, as well as the interaction of these factors. As a result, there is considerable room for improvement in overall efficacy rates for many products. For example, a 2001 study showed that the response rates of patients to medications from different therapeutic classes ranged from ~80%

(analgesics) to ~25% (oncology).^v In addition, an estimated 2.2 million adverse drug reactions occur each year in the United States, including more than 100,000 deaths.^{vi} By further elucidating why some patients respond or do not respond to a drug, and why some experience adverse reactions while others do not, we may be able to use this information to tailor drug indications to certain populations, thus improving safety and efficacy of drugs by specifying the population(s) in which they should be used.

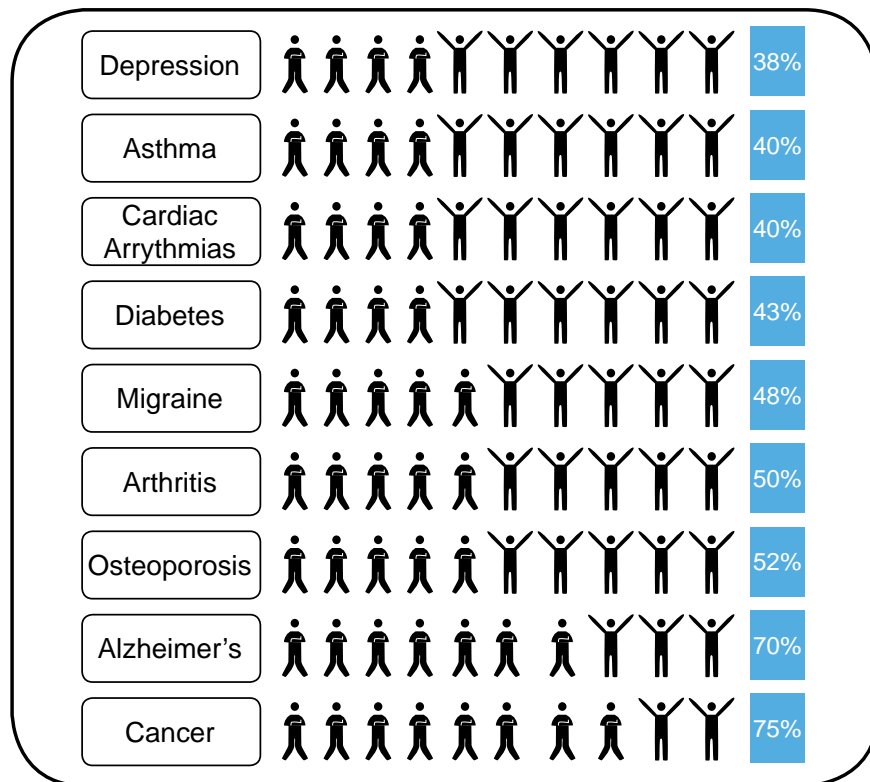


Figure 2. Percentage of patients for whom drugs are ineffective. (Source of data: Spear, B.B., Heath-Chiozzi, M., & Huff, J. (2001). Clinical application of pharmacogenetics. *TRENDS in Molecular Medicine*, 7(5), 201-204.) (Note that lack of efficacy in a given patient may reflect a complex interaction of factors and can also result from inadequate or inappropriate dosing regimens of a drug that would otherwise be effective, as well as lack of adequate patient compliance.)

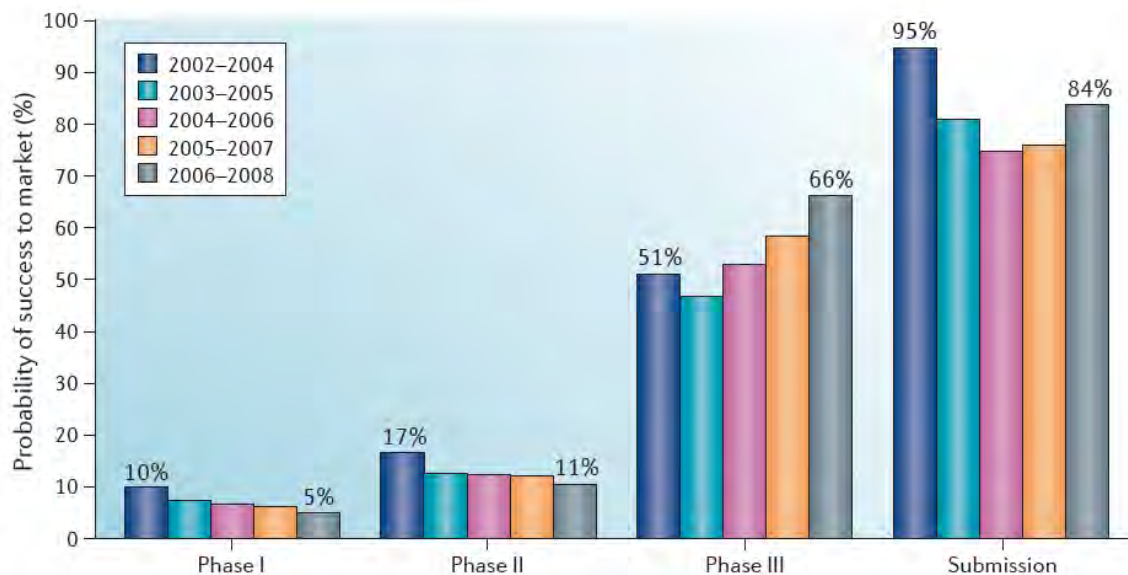


Figure 3. Probability of success from stage of development. This figure shows the probability of drugs successfully making it to market according to key milestones in the development process. (Source: Arrowsmith, J. (2012). A decade of change. *Nature Reviews Drug Discovery*, 11, 17-18.)

Personalized medicine also promises to enhance medical product development by improving the probability of success. For example, many drugs under development never reach the stage of being submitted to FDA in an application requesting approval for marketing. High attrition rates stem largely from failure of drugs to meet expected efficacy

levels, to demonstrate improved outcomes over a comparator drug, or to demonstrate sufficient safety to justify their use. Improving our understanding of the underlying causes of variability in patient response should catalyze an increase in the numbers of drugs that are shown to be safe and effective and make it to the market.

III. DRIVING TOWARD AND RESPONDING TO SCIENTIFIC ADVANCES

For well over a decade, personalized medicine has changed the FDA while the FDA, in turn, has changed personalized medicine. Beginning in the 1980s, a series of important breakthroughs in the molecular characterization of disease paved the way for new and exciting possibilities in tailored therapeutics. Important discoveries about the role of cell growth and oncogenes in cancer set the stage for the development and approval in 1998 of trastuzumab (Herceptin®), the first genetically-guided therapy for the treatment of HER2 positive metastatic breast cancers. A few years later, the International Genome Sequencing Consortium announced that it had completed the first sequencing of the human genome. While there was considerable speculation in the scientific community about the pace at which this fundamental information might be applied in medical product development, there was no question that completion of the human genome project would unleash an explosion of genetic information related to complex diseases, pharmacogenomics associations important for drug development, and rapidly advancing sequencing and information technologies.

Herceptin made clear the promise of personalized medicine. Translating genomic and other discoveries into personalized

therapeutics, however, requires overcoming a number of significant scientific, technical, economic and social challenges. From FDA's perspective, those challenges are, to begin with, scientific. Our understanding of the mechanistic underpinnings of health and disease was, and still is, in its infancy. At the same time, the human genome project has created an explosion of information—how to make sense of it and utilize it responsibly and effectively in the design of new diagnostics and therapeutics has raised many new questions. In addition, translation of our increasing understanding of biological indicators of disease or disease risk into new diagnostics brings considerable challenges related to accuracy and performance of these tests. How to validate the clinical and analytical performance of emerging biomarkers and diagnostic assays in the context of an explosion of information that is anticipated to continuously evolve presents extraordinary challenges. Finally, the prospects for co-developing two or more medical products – such as an *in vitro* diagnostic and a drug – in tandem raise a number of regulatory, policy, and review management challenges, since such products are usually regulated by different FDA Centers, and are usually owned by separate companies.

The Story of Herceptin

The story of trastuzumab (Herceptin®, made by Genentech, Inc.) began with the identification by Robert Weinberg in 1979 of “HER-2,” a gene involved in multiple cancer pathways. Over the next two decades, UCLA researcher Dennis Slamon worked to understand the link between HER2 and specific types of cancer. Slamon observed that changes in the HER2 gene caused breast cancer cells to produce the normal HER2 protein, but in abnormally high amounts. Overexpression of the HER2 protein appeared to occur in approximately 20-25% of breast cancer cases, and seemed to result in an especially aggressive form of the disease. These observations made it clear that HER2 protein overexpression could potentially serve as both a marker of aggressive disease as well as a target for treatment.

In May 1998, before an audience of 18,000 attendees of the annual meeting of the American Society for Clinical Oncology (ASCO), Slamon presented evidence that Herceptin, a novel antibody therapy he had developed in collaboration with researchers at Genentech, was highly effective in treating patients with this extraordinarily aggressive and intractable form of breast cancer. What was so revolutionary about Herceptin was that it was the first molecularly targeted cancer therapy designed to “shut off” the HER2 gene, making the cancerous cells grow more slowly and without damaging normal tissue. This precision also meant that patients taking the new treatment generally suffered fewer severe side effects as compared with other cancer treatments available at that time.

*In September 1998, FDA approved Herceptin for the treatment of HER2 positive metastatic breast cancers. On that same day, the Agency granted approval to DAKO Corp for HercepTest, an **in vitro** assay to detect HER2 protein overexpression in breast cancer cells. Simultaneous approval of the gene-targeting drug and assay for the drug’s potential effectiveness marked the beginning of what many hoped would be an exciting trend toward co-development of gene-based therapies with tests to detect the drug targets, in order to identify the right therapies for the right patients.*

Today, HER2 testing is a routine part of clinical diagnosis for breast cancer patients. Testing methods for HER2 have evolved and FDA has approved several different tests for HER2 detection. Herceptin is not beneficial, and may cause harm, to patients with cancers that do not overexpress HER2, so the availability of a well-validated assay is critical for the use of the therapy. Herceptin generated more than \$5 billion in sales for Genentech/Roche in 2011. In 2012, Genentech was awarded approval by FDA for Perjeta®, a drug with a similar HER2-binding mechanism of action as Herceptin, that has been found to result in improved outcomes when used in combination with Herceptin and another chemotherapy medication, Taxotere®, in patients with HER2 positive breast cancers. Perjeta is believed to work by targeting a different part of the HER-protein than Herceptin, resulting in further reduction in growth and survival of HER2-positive breast cancer cells.^{vii}

Development and approval of Herceptin marked the dawn of a new era of cancer treatment by bringing an emerging understanding of cancer genetics out of the laboratory and to the patient’s bedside. The story of Herceptin also emphasized a profound lesson: not all cancers are the same. Breast cancer – as well as other cancers – cannot be viewed as a single disease, but rather as a group of several subtypes, each with its distinct molecular signature. A growing appreciation of the biological diversity of cancer challenges us to embrace the inherent complexity of the disease and underscores the importance of ensuring that our treatment regimens are designed with an understanding of a cancer’s underlying biologic features.

1. BUILDING THE INFRASTRUCTURE TO SUPPORT PERSONALIZED MEDICINE

In order to help usher in a new era of tailored medical products – and especially, drugs, biologics and medical devices targeted to particular sub-populations together with genetic or other biomarker tests for use in identifying appropriate patients for those treatments – the Agency needed to evolve with – and anticipate – the science. As a result, shortly following the announcement of the completion of the human genome project, each of the FDA’s medical product centers – the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation

and Research (CBER), the Center for Devices and Radiological Health (CDRH) – as well as the National Center for Toxicological Research (NCTR) – took steps to begin to put into place regulatory processes, policies, and infrastructure to meet the challenges of regulating these complex products and coordinating their review and oversight.

In 2002, CDER, in collaboration with the Drug Industry Association (DIA) and the pharmaceutical and biotechnology industries, organized a series of workshops to discuss scientific developments in pharmacogenomics. These workshops served to catalyze guidance and policy development, to build an infrastructure for regulatory review and to provide pharmacogenomics principles in drug development. They also led

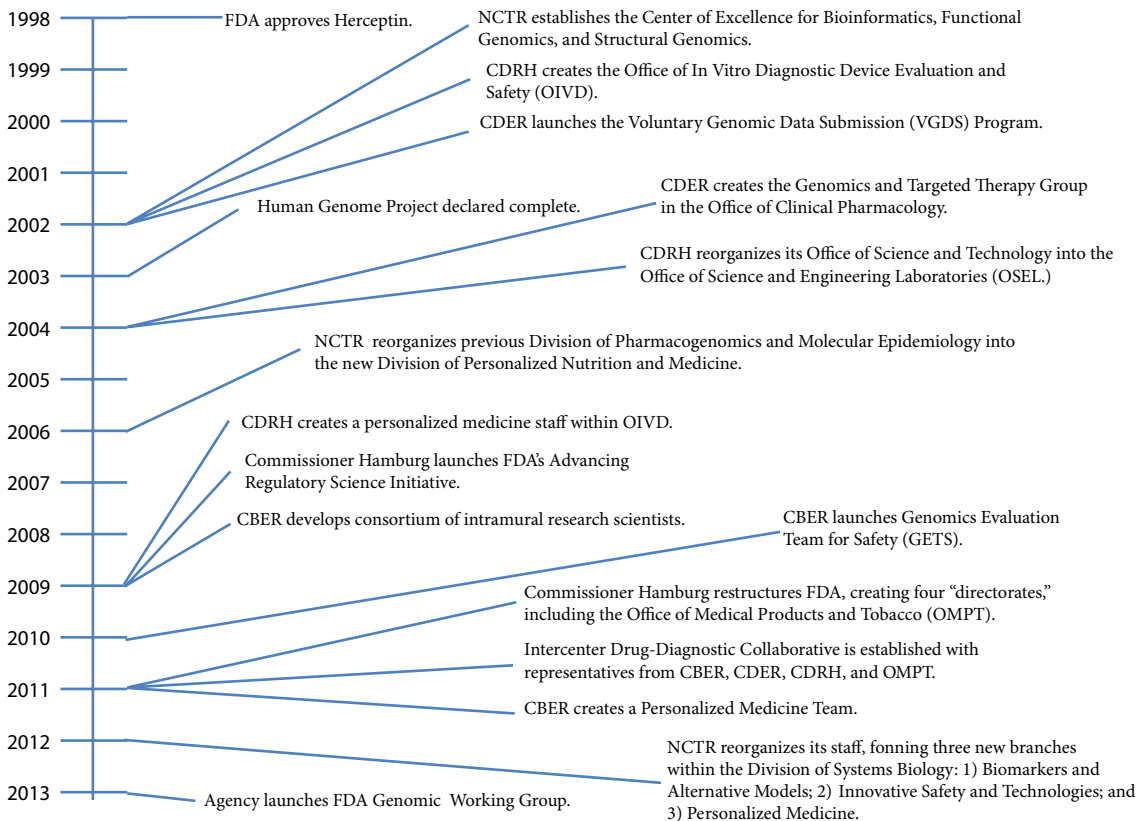


Figure 4. Organizational Transformation to Support Personalized Medicine

to the creation of the Voluntary Genomic Data Submission (VGDS) Program (later renamed the Voluntary Exploratory Data Submission Program (VXDS)), a program that provided companies the opportunity to discuss genetic information with the FDA in a forum separate from the product review process. This program, governed by the Interdisciplinary Pharmacogenomics Review Group and utilizing expertise from across the medical product centers and NCTR, has proven critical for encouraging scientific exchange between sponsors and the FDA about exploratory genomic data and in furthering successful integration of novel biomarker data in drug development.

Likewise, leadership in FDA's CDRH recognized that biological insights stemming in part from the completion of the draft human genome would give rise to a diagnostic revolution in medicine, including rapid

expansion of molecular testing as targets became established and new molecular technologies were developed. Safe and effective diagnostic tests – and especially, *in vitro* diagnostic tests – would be key for driving personalized medical treatment. In 2002, CDRH created the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) as a single organizational unit for comprehensive regulation of *in vitro* diagnostic devices (IVDs) and organized it into three divisions – Immunology and Hematology; Chemistry and Toxicology; and Microbiology. In 2013, OIVD incorporated products related to radiological health and was renamed as the Office of In Vitro Diagnostics and Radiological Health (OIR). Combining the three key regulatory programs for IVDs and radiological health (premarket review, compliance, and post-market safety monitoring) into a single geographic unit

The Genomics and Targeted Therapy Group in FDA's CDER

The Genomics and Targeted Therapy Group in the Office of Clinical Pharmacology, Center for Drug Evaluation and Research (CDER) has played a key role in establishing FDA on the leading-edge of personalized medicine and pharmacogenomics. This group works to advance the application of pharmacogenomics in the discovery, development, regulation, and use of medications. At its inception in 2004, the Group spearheaded CDER's hallmark Voluntary Genomic Data Submission (VGDS) Program and established an interdisciplinary review committee for the program. The Group also worked to modernize the labeling of approved therapeutics with pharmacogenomic information when appropriate. Over time, the Group has increased its capacity and become more integrated with drug product review divisions throughout CDER. Today, the Group, consisting of 8 full time employees and many affiliates across the Center, is committed to maximizing the impact of individualized therapeutics. Through pre-market review of therapeutics, policy development, regulatory research, and education, the Group ensures that pharmacogenomic and targeted development strategies are appropriately promoted and proactively applied in all phases of drug development.

ensures that all diagnostic device activity related to these products would spring from a common consolidated technical and regulatory base. In addition, in 2004, CDRH reorganized its Office of Science and Technology into the Office of Science and Engineering Laboratories (OSEL), which performs regulatory science research at FDA and collaborates with academia, healthcare providers, other government agencies, and industry, to better align and integrate its organizational structure with its premarket review offices. In 2007, CDRH consolidated its scientific laboratories with its pre-market and post-market staffs on FDA's White Oak Campus in Silver Spring, MD.

Many of CBER's early efforts to expedite the development of innovative and complex biological products, such as gene therapies, cell-based and tissue-engineered products, and new technologies to enhance the safety and availability of blood products, similarly arose out of extraordinary advances in genomics and proteomics. CBER has launched a number of initiatives that seek to integrate genomics, proteomics, high sensitivity gene sequencing, and other cutting-edge scientific technologies into regulatory oversight. Stem cell-based treatments and new technologies involving the introduction into the body of manipulated cells to fight disease, restore normal function, repair injuries, or regenerate failing organs present exciting possibilities, but also present significant challenges for CBER in its commitment to facilitate the development of new products while helping to ensure their safety and effectiveness. To address these challenges, CBER has developed a consortium

of intramural research scientists who also work collaboratively with scientists in other government agencies, such as NIH, to develop new methods and knowledge for reducing uncertainty with regard to safety and efficacy of these exciting new therapies.

The National Center for Toxicological Research (NCTR) is a laboratory research center that supports FDA's agency-wide needs. NCTR fosters national and international research collaborations and communications to promote rapid exchange of theories and emerging sciences with promise to inform FDA's regulatory decisions. NCTR's early research efforts towards personalized medicine included: the identification of genetic polymorphisms that influence drug and carcinogen metabolism, individual cancer susceptibility and therapeutic drug efficacy; the conduct of epidemiological studies for post-market surveillance of chemical toxicants found in foods, drugs, cosmetics, and medical devices; and the development and validation of DNA Microarray Technology for human diagnostics. In 2002, NCTR established the Centers of Excellence (for Bioinformatics, Functional Genomics, and Structural Genomics) in which a wide variety of studies related to personalized medicine were conducted, including the Microarray Quality Control (MAQC) project. These Centers of Excellence were subsequently combined to form the Division of Systems Biology to apply genomics, proteomics, and metabolomics to biomarker development. The new division played a key role in the VGDS program by providing technology expertise and a database and analysis tools (ArrayTrack™) to manage the large datasets

provided by industry groups. In 2006, the previous Division of Pharmacogenomics and Molecular Epidemiology was reorganized into the new Division of Personalized Nutrition and Medicine for which the overall goals were

to develop and implement research strategies that account for genetic, environmental, and cultural diversity that influence expression of genetic makeups and produce knowledge for improving personal and public health.

FDA's Office of Special Medical Programs

The Office of Special Medical Programs (OSMP), which serves as an agency focal point for special programs and initiatives that involve multiple medical product centers and are clinical, scientific, and/or regulatory in nature, also plays a role in supporting FDA's personalized medicine efforts. Within OSMP, the Office of Orphan Products Development (OOPD) implements statutorily mandated incentives, including orphan drug and humanitarian use device designations and multi-million dollar grant programs, to promote the development of products for rare diseases. In the case of drugs, rare disease is defined as a disease or condition affecting fewer than 200,000 people in the United States; in the case of devices, it is defined as one that affects fewer than 4,000 people in the United States. Development of products that fit under the umbrella of personalized medicine will more likely qualify for the incentives associated with the development of products for rare diseases since such products are generally targeted for use in small populations. For example, the number of products eligible for orphan drug designation has been increasing in recent years. As the science and tools of personalized medicine evolve and facilitate identification of new sub-populations, FDA expects to see this trend continue.

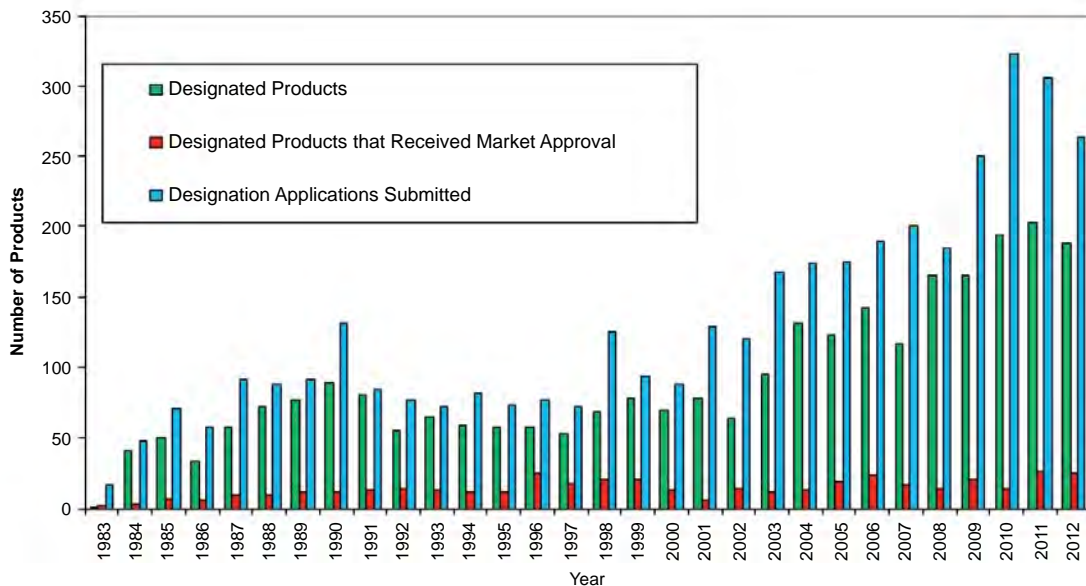


Figure 5. Number of Orphan Drug Designation Applications, Designations, and Approved Orphan Products by Year.

2. RECENT ORGANIZATIONAL EFFORTS

Under the leadership of FDA Commissioner Margaret A. Hamburg, M.D., FDA has intensified its commitment to furthering personalized medicine. In 2011, Dr. Hamburg unveiled a restructuring of the Commissioner's Office and the Agency's programs into four "directorates." As part of this effort, a new position of Deputy Commissioner for Medical Products and Tobacco and accompanying office were established to provide high-level coordination and leadership across the Centers for drugs, biologics, medical devices and tobacco products and to oversee the Office of Special Medical Programs. The new management structure was designed out of recognition of the agency's responsibilities, subject matter expertise, and mandates in an ever more complex world, where products and services do not fit into a single category. By tying together programs that share regulatory and scientific foundations, FDA could be a consistently powerful catalyst for innovation and address the scientific and regulatory challenges posed by truly transformative areas, including personalized medicine.

Each of the medical product centers has intensified its efforts related to personalized medicine under the current Administration.

The Genomics and Targeted Therapy Group in CDER has significantly increased its capacity, and the Offices of Biostatistics, New Drugs, and Translational Sciences have established leads for pharmacogenomics and biomarker development. In 2009, CDRH created a Personalized Medicine Staff dedicated to addressing the opportunities and challenges associated with diagnostics used in personalized medicine [*see text box, pg. 22*]. In addition, CDRH's OSEL has established a high-performance computer facility to support data- and computationally-intensive calculations and modeling. Other efforts are focused on identifying and characterizing biomarkers "beyond genomics." For example, imaging technologies (*e.g.*, intravascular ultrasound, intravascular near infrared spectroscopy, magnetic resonance spectroscopy, magnetic resonance imaging, CT imaging, and PET imaging) are being studied to evaluate atherosclerotic plaque characteristics to determine its vulnerability to rupture, and to identify the best stent to treat individual patients. Finally, CDRH's Office of Surveillance and Biometrics (OSB) provides statistical support and epidemiological expertise for pre-market and post-market issues associated with the design and evaluation of diagnostic studies in personalized medicine.

The Personalized Medicine Staff in CDRH's OIR

To improve focus on cross-cutting personalized medicine issues, in 2009 FDA received funding to create a Personalized Medicine Staff within OIVD (now called OIR). This group was created out of a recognition that there would be regulatory challenges inherent in developing effective mechanisms to synchronize reviews of therapeutics with IVDs used to personalize treatment, evaluating IVDs for use in guiding treatment, and the importance of clarifying and resolving regulatory oversight challenges. The Personalized Medicine Staff is charged with addressing the important and unique issues for diagnostics used in personalized medicine, including policy- and process-related issues and helping to coordinate regulatory oversight between centers to ensure efficient review of personalized medicine products.

CBER has continued to integrate genomics, proteomics, high sensitivity gene sequencing, and other cutting-edge scientific technologies into regulatory oversight programs, which ensure the consistency and purity of biological products and expedite product development and review. In 2010, CBER created a Genomics Evaluation Team for Safety (GETS) with the goal of enhancing biological product safety by identifying possible human genetic contributions to adverse reactions [see text box]. CBER also created a Personalized Medicine Team to address complex issues associated with the regulation of drug/device combinations,

including new *in vitro* diagnostic devices and novel uses of medical devices for compatibility testing in organ and cellular therapies.

Recognizing that most personalized medicine products will require review by more than one center, a cross-center working group has been established with representatives from CDER, CDRH, CBER, and the Office of Medical Products and Tobacco to frame anticipated issues and questions for both internal and public discussion, and to develop long-range policies. FDA has also organized an expert seminar and educational series where speakers address issues related to pharmacogenomics

CBER's Genomics Evaluation Team for Safety

In 2010, as part of its goal to enhance biological product development and safety by better integrating genomics and related sciences, CBER launched a new multidisciplinary Genomics Evaluation Team for Safety (GETS). GETS supports research, education, and policy activities related to genomics. Currently comprised of researchers from diverse backgrounds who have an advanced knowledge of biology, bioinformatics, and statistical analysis of genomic data, GETS focuses on identifying possible human genetic contributions to adverse reactions and works collaboratively with CBER product offices to leverage "omics" resources at FDA, NIH, CDC, academia, and industry in order to influence and shape optimal policy, education, and research.

The FDA Genomic Working Group

In anticipation of future regulatory submissions that include High-Throughput Sequencing (HTS), and to be able to develop the tools to evaluate such data, the Agency launched the FDA Genomic Working Group. This group is charged to prepare the FDA to address IT and scientific challenges to facilitate FDA readiness for HTS data submission, including: 1) how to store, transfer, and perform efficient computation on large and complex HTS data sets, 2) assess bioinformatics needs, expertise, and resources, 3) how to evaluate data quality and data interpretation for regulatory decision making. The working group includes representatives from each FDA Center, Office of Chief Scientist, Senior Science Council, and Science Computational Board.

in drug development. These and other organizational developments throughout the agency have been key to assuring that FDA's scientific and clinical staff keep abreast of the evolution of the science and are able to carry out the research, policy development, and review activities as described in the following section.

In June 2012, NCTR reorganized its science staff into divisions that work as cross-functional teams on NCTR research projects. The reorganization formed three new branches within the Division of Systems Biology and has better positioned NCTR to support the larger personalized medicine efforts of the Agency. The three new branches of the Division of Systems Biology are: 1) Biomarkers and Alternative Models; 2) Innovative Safety and Technologies; and 3) Personalized Medicine.

In May 2013, NCTR established a new Division of Bioinformatics and Biostatistics to ensure that NCTR bioinformatics and statistics capabilities are integrated with FDA's business processes, and that NCTR linkages with product centers are strengthened to support emerging fields including personalized medicine and pharmacogenomics. Indeed, this division has developed various bioinformatics tools, such as ArrayTrack™ and SNPTrack, to support review of VXDS submissions. This division has also led the MicroArray Quality Control (MAQC) consortium effort, with support from other FDA centers, to address the technical issues and application of pharmacogenomics tools in biomarker development and personalized medicine.

IV. DEFINING AND CLARIFYING REGULATORY PATHWAYS AND POLICIES

The development and regulatory review of personalized medicine products raise a number of regulatory, policy, sponsor coordination, and review management challenges. First, the success of personalized medicine fundamentally depends on safe and effective diagnostics. Extraordinary advances across multiple scientific fields are leading to an explosion in diagnostic tests, but questions concerning appropriate evidentiary standards and regulatory oversight of these tests remain. In addition, personalized medicine generally involves the use of two or more products – such as the performance of a diagnostic test

to determine whether a patient may or may not benefit from a particular therapeutic intervention, requiring considerable coordination in the development and review of the different products. The FDA's three medical product review centers – the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) – along with the Office of Special Medical Programs (OSMP), are primarily responsible for establishing regulatory pathways and policies for addressing these challenges.

FDA's Office of Combination Products

Many innovative combination products also fit under the personalized medicine umbrella. Combination products are therapeutic and diagnostic medical products that combine drugs, devices, and/or biological products when both are necessary to achieve the indication. Because of the complexities associated with combination product regulation, the Office of Combination Products (OCP), within OSMP, was created under Medical Device and User Fee Modernization Act of 2002 to enhance transparency, predictability, and consistency of combination product regulation and also to ensure timely approval of combination products. OCP accomplishes these goals by collaborating with experts from all three product centers and the regulated industry to develop guidance documents and regulations to assist the developers of these innovative combination products.

Over the past decade, the Agency has issued a number of guidance documents and regulations that seek to clarify regulatory requirements, coordinate premarket reviews, delineate the activities and responsibilities of

the different centers, and provide consistency and timeliness in the oversight of personalized medicine products. Together, these policies provide guidance on a broad range of topics, such as guidance on incorporating genetic

and other biomarker information in drug development programs, designing clinical trials to incorporate biomarker data, coordinating cross-labeling activities, evaluating pharmacogenomics data, and demonstrating companion diagnostic test performance.

A list and brief description of the main policies issued to date that relate to personalized medicine are provided in Table 1. Many of these policies are aimed at fostering the use of applied genomics and biomarker

information in drug development. Early guidances focused on when and how to submit data to FDA. More recently, the Agency has issued a guidance on generating those data broadly in early phase studies, and even in specific contexts. FDA's most recent guidances on companion diagnostics and enrichment strategies, along with its evolving guidance on co-development, speak to core issues in personalized medicine product development.

TABLE 1: Select FDA Guidances That Relate To Personalized Medicine (cont.)

Year Issued	Guidance	Description
2005	Pharmacogenomic Data Submissions	Promotes the use of pharmacogenomic data in drug development and provides recommendations to sponsors on: 1) when to submit pharmacogenomic data to the Agency during the drug or biological drug product development and review processes; 2) what format and content to provide for submissions; and 3) how and when the data will be used in regulatory decision making. Encourages voluntary genomic data submission (VGDS) as a means to gaining a greater understanding of issues surrounding the use of pharmacogenomic data in drug development. Companion guidance issued in 2007 to reflect experience gained in VGDS.
2007	Pharmacogenomic Tests and Genetic Tests for Heritable Markers	Aims to facilitate progress in the field of pharmacogenomics and genetics by helping to shorten development and review timelines, to facilitate rapid transfer of new technology from the research bench to the clinical diagnostic laboratory, and to encourage informed use of pharmacogenomic and genetic diagnostic devices. Recommends a basic framework for the types of data and regulatory issues that should be addressed in a genetic test submission and provides a common baseline from which both manufacturers and scientific reviewers can operate.
2007	Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests	Describes statistically appropriate practices for reporting results from different studies evaluating diagnostic tests and identifies common inappropriate practices. The recommendations in this guidance pertain to diagnostic tests where the final result is qualitative (even if the underlying measurement is quantitative), with a focus on <i>discrepant resolution</i> and its associated problems.
2008	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories	Clarifies the definitions of key terms in the discipline of pharmacogenomics and pharmacogenetics, namely genomic biomarkers, pharmacogenomics, pharmacogenetics, and genomic data and sample coding categories in an effort to develop harmonized approaches to drug regulation.

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TABLE 1: Select FDA Guidances That Relate To Personalized Medicine (cont.)

Year Issued	Guidance	Description
2010	Adaptive Design Clinical Trials for Drugs and Biologics (Draft Guidance)	Describes how designing clinical trials with adaptive features (i.e., changes in design or analyses guided by examination of the accumulated data at an interim point in the trial) may make studies more efficient, more likely to demonstrate an effect of the drug if one exists, or more informative. Provides advice to sponsors on special considerations that arise with the use of adaptive design trials in drug development programs, and when to interact with FDA in planning and conducting these studies and what information is required.
2010	Qualification Process for Drug Development Tools (Draft Guidance)	Describes the qualification process for DDTs – including but not limited to biomarkers and patient reported outcomes (PRO) instruments – intended for potential use, over time, in multiple drug development programs. Provides a framework for identifying data needed to support qualification and creates a mechanism for formal review. Once qualified, the DDT can be used by drug developers for the qualified context in new submissions without having to reconfirm the suitability of the tool, helping to speed therapy development and evaluation.
2011	Clinical Considerations for Therapeutic Cancer Vaccines	Provides recommendations for the design of clinical trials for cancer vaccines conducted under an IND to support a subsequent BLA for marketing approval. Discusses considerations common to phase 1, 2, and 3 clinical trials, as well as considerations that are unique to specific stages of clinical development of therapeutic cancer vaccines. The products discussed in this guidance are therapeutic cancer vaccines intended to result in specific responses to a tumor antigen and are intended for the treatment of patients with an existing diagnosis of cancer.
2011	<i>In Vitro</i> Companion Diagnostic Devices (Draft Guidance)	The development of therapeutic products that depend on the use of a diagnostic test to meet their labeled safety and effectiveness claims has become more common. These technologies – including IVD companion diagnostic devices – are making it increasingly possible to individualize, or personalize, medical therapy by identifying patients who are most likely to respond, or who are at lower or higher risk for a particular side effect. This guidance defines IVD companion diagnostic devices, provides information for industry and FDA on possible premarket regulatory pathways and FDA’s regulatory enforcement policy, and describes certain statutory and regulatory approval requirements relevant to therapeutic labeling.
2011	Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions (Draft Guidance)	The marketing of unapproved and uncleared “research use only” (RUO) and “investigational use only” (IUO) IVD products for purposes other than research or investigation has led in some cases to diagnostic use of laboratory tests with unproven performance characteristics and manufacturing controls that are inadequate to ensure consistent manufacturing of the finished product. Use of such tests for clinical diagnostic purposes may mislead healthcare providers and cause serious adverse health consequences to patients. This guidance is intended to clarify the types of IVD products that are properly labeled RUO or IUO, and provide responses to some frequently asked questions about how such products should and should not be marketed.

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TABLE 1: Select FDA Guidances That Relate To Personalized Medicine (cont.)

Year Issued	Guidance	Description
2011	E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions	The use of biomarkers has the potential to facilitate the availability of safer and more effective drug or biotechnology products, to guide dose selection, and to enhance their benefit-risk profile. Qualification is a conclusion that, within the stated context of use, the results of assessment with a biomarker can be relied upon to adequately reflect a biological process, response, or event, and support use of the biomarker during drug or biotechnology product development, ranging from discovery through post approval. This guidance creates a harmonized recommended structure for biomarker qualification applications that fosters consistency of applications across regions and facilitates discussions with and among regulatory authorities.
2011	Evaluation of Sex Differences in Medical Device Clinical Studies (Draft Guidance)	This guidance outlines CDRH's expectations regarding sex-specific patient enrollment, data analysis, and reporting of study information. The intent is to improve the quality and consistency of available data regarding the performance of medical devices in women. This information can be of benefit to patients and their medical providers, as well as clinical researchers and others. The specific objectives of this guidance are to: 1) better communicate the balance of risks and benefits of FDA-approved or cleared medical devices; 2) identify sex-specific questions for further study; and 3) encourage the consideration of sex and associated covariates (e.g., body size, plaque morphology) during the trial design stage.
2011	Applying Human Factors and Usability Engineering to Optimize Medical Device Design (Draft Guidance)	This guidance is intended to assist the medical device industry to address the needs of users in the design of devices, particularly to minimize the occurrence of use errors that could result in harm to the patient or device user. The guidance discusses human factors and usability engineering processes used in the design and evaluation of medical devices and provides details about methods to use to generate validation data to show that the device is safe and effective for the intended users, uses and use environments.
2012	Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products (Draft Guidance)	Enrichment is increasingly used as a strategy for increasing study efficiency. This document describes three enrichment strategies that can be used in clinical trials intended to support effectiveness and safety claims in new drug applications and biologics license applications, including: 1) decreasing heterogeneity (practical enrichment); 2) identifying high-risk patients (prognostic enrichment); and 3) choosing patients most likely to respond to treatment (predictive enrichment).
2012	Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and <i>De Novo</i> Classifications	This guidance document explains the principal factors that FDA considers when making benefit-risk determinations in the premarket review of certain medical devices. The guidance sets out the principal factors FDA considers when making these determinations, including consideration of patient tolerance for risk and evidence relating to patients' perspectives of what constitutes a meaningful benefit when determining if the device is effective.

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TABLE 1: Select FDA Guidances That Relate To Personalized Medicine (cont.)

Year Issued	Guidance	Description
2012	The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems	This guidance informs industry and agency staff of FDA’s recommendations for analytical and clinical performance studies to support premarket submissions for artificial pancreas systems. The guidance outlines considerations for development of clinical studies and recommends elements that should be included in IDE and PMA applications for artificial pancreas systems, including threshold suspend systems, single hormonal control systems, and bihormonal control systems. The guidance focuses on critical elements of safety and effectiveness for approval of this device type, while keeping in mind the risks diabetic patients face everyday.
2013	Mobile Medical Applications	Describes the need for regulatory oversight of mobile medical applications that pose potential risks to public health. Clarifies that FDA plans to focus its regulatory oversight on a subset of mobile apps that either are used as an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.
2013	Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling	This guidance is intended to assist the pharmaceutical industry and other investigators engaged in new drug development in evaluating how variations in the human genome, specifically DNA sequence variants, could affect a drug’s pharmacokinetics (PK), pharmacodynamics (PD), efficacy, or safety. It provides recommendations on when and how genomic information should be considered to address questions arising during drug development and regulatory review, focusing on general principles of study design, data collection, and data analysis in early-phase trials. It also provides recommendations for labeling.
2013	FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations (Draft Guidance)	This guidance was developed to promote the initiation of clinical investigations to evaluate medical devices under FDA’s IDE regulations. The guidance provides clarification regarding the regulatory implications of the decisions that FDA may render based on review of an IDE and a general explanation of the reasons for those decisions. In an effort to promote timely initiation of enrollment in clinical investigations in a manner that protects study subjects, FDA has developed methods to allow a clinical investigation of a device to begin under certain circumstances, even when there are outstanding issues regarding the IDE submission. These mechanisms, including approval with conditions, staged approval, and communication of outstanding issues related to the IDE through study design considerations and future considerations, are described in this guidance.
2013	Molecular Diagnostic Instruments with Combined Functions (Draft Guidance)	Molecular diagnostic instruments are critical components of certain in vitro diagnostic devices (IVDs). These types of instruments cannot generally be approved alone, (i.e., without an accompanying assay), because their safety and effectiveness cannot be evaluated without reference to the assays that they run and their defined performance parameters. However, the same instruments may also be used for additional purposes that do not require FDA approval or clearance, such as for basic scientific research. This draft guidance communicates FDA’s policy regarding the regulation of molecular diagnostic instruments with combined functions, including recommendations on the type of information that applicants should include in a premarket submission for a molecular diagnostic instrument that measures or characterizes nucleic acid analytes and has combined functions.

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TABLE 1: Select FDA Guidances That Relate To Personalized Medicine (cont.)

Year Issued	Guidance	Description
2013	Providing Information about Pediatric Uses of Medical Devices Under Section 515A of the Federal Food, Drug, and Cosmetic Act (Draft Guidance)	Section 515A(a) of the FD&C Act requires persons who submit certain medical device applications to include, if readily available: 1) a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and 2) the number of affected pediatric patients. This guidance document describes the type of information that FDA believes is readily available to the applicant, and the information FDA believes should be included in a submission to meet the pediatric use information requirements of the law.
2013	Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA (Draft Guidance)	For a combination product that is approved under one application, there may be uncertainty on the part of the sponsor in determining the appropriate regulatory pathway for submitting a post-market submission for a change to a constituent part or to the combination product as a whole. This document provides guidance to industry and FDA staff on the underlying principles to determine the type of marketing submission that may be required for postapproval changes to a combination product, as defined in 21 CFR 3.2(e), that is approved under one marketing application, (i.e., a biologics license application (BLA), a new drug application (NDA), or a device premarket approval application (PMA)).
2013	Current Good Manufacturing Requirements for Combination Products Final Rule	While CGMP regulations that establish requirements for drugs, devices, and biological products have been in place for many years, until 2013, there were no regulations that clarified and explained the application of these CGMP requirements when these drugs, devices, and biological products are constituent parts of a combination product. This rule is intended to promote the public health by clarifying which CGMP requirements apply when drugs, devices, and biological products are combined to create combination products. In addition, the rule sets forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with CGMP requirements for “single-entity” and “co-packaged” combination products.

The remainder of this section describes in more detail some of the fundamental challenges posed by the development and regulatory review of personalized medicine products – with an emphasis on *in vitro* diagnostics that are used together with

therapeutic products – and the steps the agency has taken in recent years or is currently taking to help shepherd products through the review process and monitor their safety post-market.

1. ENSURING THE AVAILABILITY OF SAFE AND EFFECTIVE DIAGNOSTICS

The success of many personalized medicines fundamentally depends on the identification of biomarkers and the successful development of diagnostic tests that can be used to accurately stratify the patient population. While scientific discoveries across multiple fields have led to an explosion of biological information, the development of diagnostics and their translation into clinical practice pose a number of scientific and regulatory challenges. Inadequate performance of a diagnostic test that is used to guide treatment decisions can have severe therapeutic consequences. For example, with an incorrect diagnostic result, an unsuitable drug may be given to a patient who will, as a result, be harmed or will not benefit, because the drug will cause an otherwise avoidable adverse event, will be ineffective for that patient, or both.

Diagnostic tests are intended to measure (as in the case of *in vitro* diagnostics), or evaluate (as in the case of electrocardiogram tracings or imaging technologies), an indicator of a normal biological process, pathogenic process, or response to a therapeutic intervention.^{viii} In the case of *in vitro* diagnostic test development, biomarker discovery and evaluation of the biomarker are critical initial steps. If the biomarker is not significantly correlated with the clinical state – for example, a particular genetic mutation with a disease – a diagnostic test that measures that biomarker will not produce meaningful results for that disease.

Diagnostic tests generally fall under the

FDA's medical device authority and are classified and regulated in a risk-based manner.² Risk determination includes the risk of an erroneous result, and the harm to a patient that might be incurred based on an incorrect test result when the test is used as intended. Diagnostic test results can be incorrect in two major ways: they can report a positive result when the result is actually negative (false positive), or they can report a negative result when the actual result was positive (false negative). Tests that measure the amount of a substance can report values that are falsely high or low. False test results and their consequences are evaluated for their risk of harm to patients. For example, a false positive test result that could lead to a patient undergoing an invasive medical procedure or a therapy with toxic side effects would generally be considered high risk. Similarly, a false negative test result that might alter medical management and delay appropriate intervention for a life-threatening condition might also be considered high risk.

In evaluating a diagnostic device, FDA looks at its *analytical validity* as well as its *clinical validity*. Analytical validity refers to how well the test measures what it is supposed to measure, whereas clinical validity looks at how well the test predicts who has or does not have a disease or condition for which it is being tested. In personalized medicine, where

²"Device" is defined as "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is [among other things]... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals ... and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." Section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 321(h).

the diagnostic test is often a biomarker-based assay, such as a genetic test, the clinical validity of the test refers to how well the test works in helping to identify people who will or will not respond to a therapy (or who will or will not suffer adverse consequences).

In addition to analytical and clinical validity, stakeholders in personalized medicine are also interested to know the clinical utility of new diagnostics. “*Clinical utility*” is a term that describes the relevance and usefulness of an intervention in patient care; in other words, how much value does it add? When a diagnostic test informs the use of a medical treatment, the test has clinical utility if its use improves the treatment outcome. While the accuracy of a diagnostic test used to individualize treatment or an intervention is evaluated by measuring its analytical and clinical validity, the usefulness of the test is typically evaluated by its clinical utility. There is considerable debate about the methods of demonstrating clinical utility and the level of evidence – in terms of quantity, quality, and type – that should be obtained for any new diagnostic test to be introduced into routine clinical practice.^{ix}

Many of the diagnostic tests used in personalized medicine are *in vitro* diagnostic devices (IVDs), also called clinical laboratory tests, which test body substances from patients for alterations in levels of biomarkers (*e.g.*,

proteins) and the presence/absence of genetic susceptibility biomarkers. The development and validation of IVDs for use in guiding therapeutic treatment pose a number of particular challenges. First, the sheer pace of the development of IVDs over the past decade has been staggering. Volumes of information arising out of the human genome project combined with a dramatic decrease in costs of DNA sequencing, for example, are giving way to an explosion of publications linking particular genetic markers to diseases or conditions and a rapid application of this information in the development of new molecular diagnostic tests. How best to integrate rapidly evolving genomic information into clinical care while ensuring safety and efficacy is a topic of considerable public debate and discussion. For FDA, the evaluation of these tests, and the development of standards for levels of evidence required to demonstrate the validity of the test, are especially complicated when the meaning of a given genetic association may be poorly understood or change over time. Moreover, the complexity of these tests is ever evolving, as single marker tests have given way to tests that measure multiple markers simultaneously, such as complex gene panels. Extensive DNA and RNA sequencing across multiple genes or the whole genome are already being used in clinical practice.

Challenges for Regulating Whole Genome Sequencing

High-throughput genomic sequencing technologies are used extensively in research and have started to enter clinical practice. Whole genome sequencing (WGS), in which the entire human genome can be sequenced at a reasonable cost in a reasonable amount of time, is expected to bring transformative public health applications, yet WGS platforms are still evolving rapidly, and there are currently no agreed-upon approaches to analytically assess their performance. FDA approval or clearance of diagnostic tests generally requires demonstration of their analytical and clinical validity. However, in the case of WGS, sequence-based assays, and extensive gene panels, tests will involve the analysis of many alleles (3 billion base pairs in the case of WGS), so that demonstrating the validity of each and every variant may not be practical or even feasible, since the significance of most of these variants is currently unknown. In addition, many variants detected by these methods are exceedingly rare, so that it is difficult to find enough patients to run a clinical trial to determine whether they are significant.

FDA has taken a number of steps toward developing a new method for evaluating these tests. In June 2011, the Agency sponsored a public workshop on approaches to evaluating the technical performance of a new generation of sequencing and on the bioinformatics data analysis needed to interpret the data generated by the technologies. The Agency has since started to assess sequence-based tests using a strategy that focuses on validating the analytical performance of the sequencing platform – whether it measures what it is supposed to measure accurately and reliably and precisely. While it will be impossible for the Agency to assess the platform's performance for every single variant, the Agency is looking at possibilities for identifying a representative set of markers that could be assessed in order to develop an understanding of the performance of the platform as a whole.

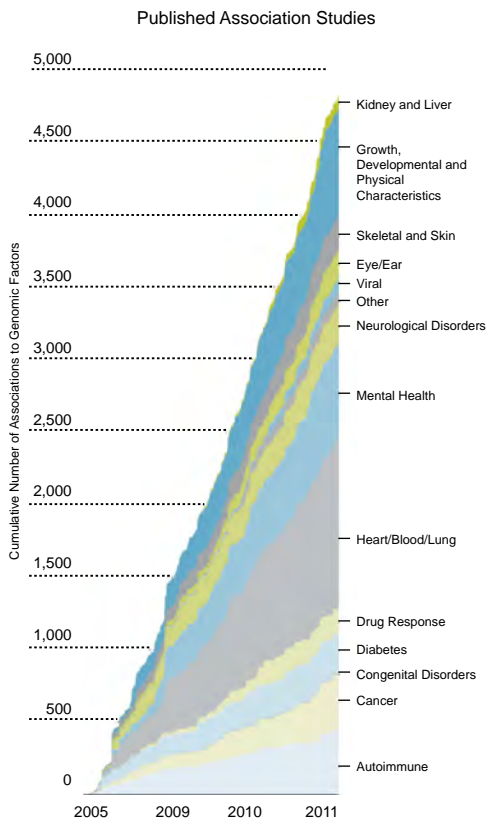


Figure 6. Knowledge about associations between genomic factors and disease has rapidly accumulated. (Source: Raskin, A. Casdin, E. (2011). *The Dawn of Molecular Medicine: The Transformation of Medicine and Its Consequences for Investors*. New York, NY: Alliance Bernstein.)

Another challenge associated with ensuring the safety and reliability of IVDs is that they may be marketed in one of two ways: as IVD kits or as laboratory developed tests (LDTs). IVD kits are those developed by a conventional device manufacturer and sold to labs, hospitals and physicians offices where the test kit is used to run the tests, whereas LDTs are those that are designed, manufactured, and used by a single laboratory. While FDA has had the authority to regulate all IVDs since 1976, it has generally exercised enforcement discretion (withheld active enforcement) over LDTs.

If administration of a therapeutic depends upon identifying appropriate patients through use of a diagnostic test, then confidence in the therapeutic can only be assured if the diagnostic test is properly validated in the *specific therapeutic context of use*. Today, however, many *in vitro* diagnostic tests that are used to guide treatment are being developed and offered as LDTs without FDA pre-market review. Often, where an FDA-cleared or approved test is available, laboratories continue to develop and use their own LDT that may not be an equivalent test. For example, two tests that measure the same biomarker may produce different results if they use different technologies, are interpreted differently, or are conducted under different laboratory conditions.

The increasing reliance on diagnostic tests in clinical decision making, combined with the dramatic shift in the number and complexity of LDTs being offered, are posing increasing risks to patients. FDA has been made aware of a number of examples where clinical decisions made on the basis of faulty tests resulted in harm to patients. As a

result, FDA has been developing a risk-based framework for regulatory oversight of LDTs that would assure that tests, regardless of the manufacturer, have the proper levels of control to provide a reasonable assurance of safety and effectiveness, while also fostering innovation and progress in personalized medicine. FDA believes that clarifying the regulatory oversight framework for IVDs would facilitate the development of *in vitro* diagnostic tests for use in providing optimized treatment for patients.

2. PRODUCT INTERDEPENDENCY

Personalized medicine generally involves the use of two or more medical products, such as a diagnostic test to determine whether a patient may or may not benefit from a particular therapeutic intervention, and the therapeutic product itself. Often, these products are: (1) regulated under different regulatory authorities (*e.g.*, drugs vs. devices); (2) regulated by different FDA Centers (*e.g.*, CDER vs. CDRH); and (3) owned and manufactured by different companies.^x The different regulatory authorities that oversee these products have been in place for many years and were not intentionally designed to address situations where different types of medical products are dependent upon one another to achieve safety and effectiveness. FDA has been working to develop processes and policies that delineate the activities and responsibilities of the different centers and that address the inherent regulatory and scientific complexities of these products.

The specific challenges for any particular set of products depend in part on the nature of

their relationship to each other. For example, many personalized medicines require diagnostic tests that identify appropriate patients for a given therapy or patients who should not receive a particular therapy because of an increased risk of a serious side effect. Other tests help to characterize a disease or condition – such as cancer – to determine what type of treatment is potentially most appropriate. In cases where a test is *essential* for the safe and effective use of a corresponding therapeutic product, it is termed a “companion diagnostic.”

A companion diagnostic impacts the ability of a specific therapeutic product to achieve its established safety and effectiveness. FDA believes that companion diagnostics should be subject to oversight with appropriate controls, and has recently issued a draft guidance that clarifies the definition and approval requirements that apply to the development and marketing of this particular category of diagnostic tests.^{xi} Generally, if a companion diagnostic is required for safe and effective use of a therapeutic product, through selection of patients or dose, then an FDA-approved or cleared test must be available at the time that the drug is approved.^{xii} Companion diagnostics are often (and ideally) developed concurrently with a therapeutic, but can also be developed to optimize treatment with a therapeutic that has already been approved.³

Pharmaceutical and device sponsors have become increasingly interested in pursuing “co-development” strategies for the

development of a therapeutic product and an accompanying IVD companion diagnostic device. As described earlier, the concept of co-development was first applied in 1998, when the approval of the therapeutic Trastuzumab (Herceptin), was paired with approval of an immunohistochemical IVD companion diagnostic device (HercepTest™) that measures expression levels of human epidermal growth factor receptor 2 (HER-2) in breast cancer tissue.

Co-development is recognized as essential for the success of personalized medicine. Development of companion diagnostics together with therapeutics should in theory allow for more efficient studies with smaller patient populations while also leading to more focused therapies that offer better outcomes, less toxicity, and fewer treatment delays. However, these strategies raise considerable technical, conceptual, organizational, and procedural challenges.

First is the challenge of timing and alignment of the development strategies of the two products: if the diagnostic is going to be used to select patients for the trial, an analytically validated test should be available at the time of initiation of the trial. This can be challenging, since sometimes the need for the companion diagnostic may not be evident until late in the development of the drug, or the need to change the test might arise during the course of the trial. The purpose of the trial is not only to assess the safety and effectiveness of the drug, but also to investigate the performance of the diagnostic in that specific therapeutic context. A test that does not perform adequately may negatively impact the outcome of the trial and harm patients. Changes made to the test after

³A list of companion diagnostics that have been approved to date can be viewed at: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>

initiation of the trial can make it difficult if not impossible to interpret the study results.

Second is the design of the trial itself. Identifying patients at the beginning who are most likely to benefit from a drug or biological product (or excluding those likely to suffer toxicities) can allow for smaller, faster, and less expensive clinical trials with a higher likelihood of success. However, there are some challenges associated with designing very small trials, such as being able to build in sufficient statistical power to yield convincing results. Designing a trial to test whether a drug is effective for a subpopulation of patients also sometimes raises complex technical and ethical questions about whether to include marker-negative patients (*i.e.*, those that are not

expected to benefit from the drug) in the trial. These and other issues are discussed at length in a draft guidance on employing “enrichment strategies” in clinical trials that was issued by FDA in 2012.

Reviews of co-developed products pose a number of challenges to the Agency, since they require expertise from and careful coordination between the Centers to ensure consistent reviews and contemporaneous approval of the two products. Challenges stem from the co-developed products falling within the purview of multiple FDA centers each operating under different laws, regulations, systems for tracking submissions, and timelines. The products also have different development cycles and regulatory

Enrichment Strategies for Clinical Trials

In December 2012 the FDA published a draft guidance on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. Enrichment is prospective use of any patient characteristic – demographic, pathophysiologic, historical, genetic, and others – to select patients for study to obtain a study population in which detection of a drug effect is more likely than it would be in an unselected population. Enrichment strategies fall into three broad categories:

- *Strategies for decreasing heterogeneity - for example, selecting patients with baseline measurements in a narrow range or excluding patients whose disease or symptoms improve spontaneously.*
- *Prognostic enrichment strategies – choosing high-risk patients (those with a greater likelihood of having a disease-related endpoint event or a substantial worsening in condition).*
- *Predictive enrichment strategies – choosing patients more likely to respond to treatment than other patients with the condition being treated.*

The main reason for use of enrichment is study efficiency – increasing the chance of success, often with a smaller sample size. However, it also provides benefits of individualization, directing treatment where it will do the most good and sparing people who cannot respond to potential harm. Utilization of enrichment strategies – particularly predictive enrichment strategies – is commonplace in the development of personalized medicines. FDA’s draft guidance describes and illustrates enrichment strategies, discusses study design options and their advantages and disadvantages, and addresses issues of interpretation of the results of enrichment studies.

requirements. And of course, each diagnostic-drug pair may raise unique regulatory and scientific issues. Finally, often the diagnostic and therapeutic products are developed by different companies, each with its own commercial interest. As such, cooperation, coordination, and communication between Centers and between sponsors throughout the process are essential for ensuring a successful co-development program.

FDA has developed a process for helping to shepherd co-development programs through the regulatory channels. The process involves

early communication with the sponsors to ensure that they understand what will be required, frequent and ongoing consultations both internally and externally throughout the process, and close coordination among the relevant product centers involved. Staff in the three relevant centers are working together to develop guidance that outlines principles for the co-development process, and are also developing recommendations for inter-center coordination to maximize the efficiency of co-reviews.

Personalized Cancer Medicine: Recent Successes with Co-Development

The value of co-development has been demonstrated by the recent successful development and approval of targeted cancer therapies.

Vemurafenib/BRAF V600E: In August 2011, FDA simultaneously approved the drug vemurafenib (Zelboraf) along with its companion diagnostic, the Cobas 4800 BRAF V600E mutation test, for use in treating metastatic or unresectable melanoma. Metastatic melanoma is a highly aggressive form of skin cancer with a 5-year survival rate of only 15%. Vemurafenib works by inhibiting the BRAF V600E mutation that is found in approximately 50% of melanoma patients. Melanomas that lack the mutation are not inhibited by the drug; therefore, using a test to identify the population of patients who would more likely benefit from the treatment accelerated development of the drug, facilitated a successful regulatory review, and led to an improved therapeutic profile. Vemurafenib was approved by FDA in near record time (3.6 months) through an expedited process.

Crizotinib/ALK testing: Also in August 2011, FDA approved crizotinib (Xalkori), a drug along with an ALK FISH probe companion diagnostic for the treatment of non-small cell lung cancer. Crizotinib targets tumors with an abnormal ALK gene, which occurs in approximately 5% of non-small cell lung cancer patients. Crizotinib's safety and effectiveness was established through a clinical trial involving only 255 patients, and the approval process for the drug and its associated test took only 4.9 months, well below average review times for priority drugs.

Tafinlar/Mekinist/THxID BRAF test: In May 2013, FDA approved Tafinlar (dabrafenib) and Mekinist (trametinib) for patients with advanced or unresectable melanoma, the leading cause of death from skin disease. The FDA approved Tafinlar and Mekinist with a genetic test called the THxID BRAF test, a companion diagnostic that will help determine if a patient's melanoma cells have the V600E or V600K mutation in the BRAF gene. Approximately half of melanomas arising in the skin have a BRAF gene mutation. Tafinlar is intended for patients whose tumors express a single BRAF gene mutation, V600E. Mekinist is intended for patients who express that mutation or the V600K mutation.

3. PRODUCT LABELING

Medical product labeling must provide adequate information about the product and its use. Drug labeling, for example, is “intended to provide a summary of the essential scientific information needed for the safe and effective use of the drug.”^{xiii} As such, labeling provides healthcare practitioners with information that is critical for treating patients. FDA requires product labeling to be balanced, scientifically accurate and not misleading, and that clear instructions be communicated to healthcare practitioners for drug prescribing and/or administration. Personalized medicines that may only be safe and effective in particular sub-populations, or must be administered in different doses in different sub-populations, must be labeled accordingly.

In cases where a therapeutic product is approved together with a companion diagnostic device, the labeling of the two products must be consistent. In cases where an IVD companion diagnostic is developed for use with an already approved therapeutic product, it may be necessary to update the therapeutic product’s labeling with appropriate test-related information if such information is essential to the safe and effective use of the product. Diagnostic tests may also be developed that provide information that is helpful for determining whether a drug is appropriate for a patient

or not, but is not essential for the safe and effective use of the therapeutic product.

Therapeutic product labeling may also be revised to reflect this additional information.

The decision of whether, and when, to revise labeling of already-approved therapeutic products in light of new information can be complicated and often involves a highly deliberative process. Great care must be taken in assessing the therapeutic benefits and risks for changing a labeling, since a decision to adjust a labeling to incorporate the use of a diagnostic device narrows the range of the population for which the drug is considered to be appropriate, effectively limiting access to that drug. FDA can only compel a labeling change in circumstances where FDA identifies new safety information that becomes available after approval of the drug or biological product. FDA or sponsors may request to change labeling to reflect updated safety or efficacy information.

To date, the labeling of **more than 100 approved drugs** contain information on genomic biomarkers (including gene variants, functional deficiencies, expression changes, chromosomal abnormalities, and others).^{xiv} Some, but not all, of the labeling include specific actions to be taken based on genetic information. Pharmacogenomic information can appear in different sections of the labeling (*e.g.*, Therapeutic Indications, Warnings and Precautions).

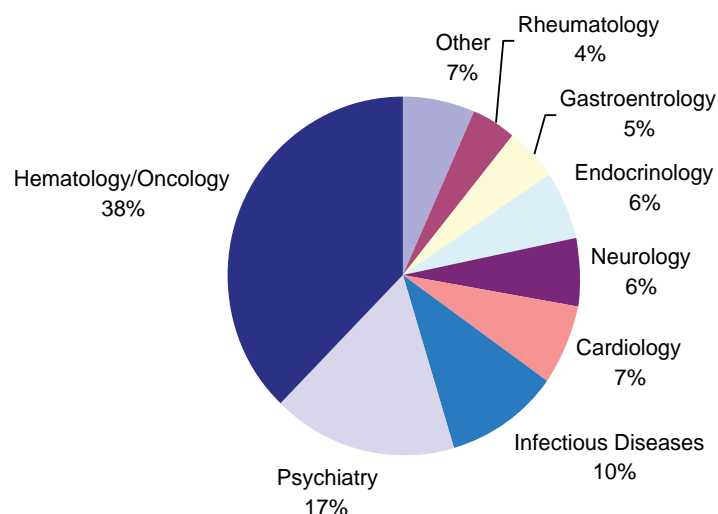


Figure 7. Pharmacogenomic Biomarker Information in Drug Labeling.

TABLE 2: Selected drugs with specific actionable guidance in labeling (i.e., indications, contraindications, dosing). (cont.)

Drug	Original Approval Date	Therapeutic Area	Biomarker
Arsenic Trioxide	2000	Oncology	PML/RAR α
Tretinoin	1995		
Brentuximab Vedotin	2011	Oncology	CD30
Capecitabine	1998	Oncology	DPD
Fluorouracil	1998		
Cetuximab	2004	Oncology	EGFR; KRAS
Panitumumab	2006		
Crizotinib	2011	Oncology	ALK
Denileukin Diftitox	1999	Oncology	CD25/IL2
Exemestane	1999	Oncology	ER/PR
Fulvestrant	2002		
Letrozole	1997		
Imatinib	2003	Oncology	C-Kit, PDGFR, FIP1L1
Lapatinib	2007	Oncology	HER2
Pertuzumab	2012		
Trastuzumab	1998		
Everolimus	2009	Oncology	Ph Chromosome
Nilotinib	2007		
Dasatinib	2006		
Imatinib	2003		

continued on next page

TABLE 2: Selected drugs with specific actionable guidance in labeling (i.e., indications, contraindications, dosing). (cont.)

Drug	Original Approval Date	Therapeutic Area	Biomarker
Rasburicase	2002	Oncology	G6PD
Tositumomab	2003	Oncology	CD20 antigen
Vemurafenib	2011	Oncology	BRAF
Citalopram	1998	Psychiatry	CYP2C19
Valproic Acid	1978	Psychiatry	UCD
Pimozide	1984	Psychiatry, Neurology	CYP2D6
Aripiprazole	2002		
Iloperidone	2009		
Tetrabenazine	2008		
Thioridazine	1962		
Ivacaftor	2012	Pulmonary	CFTR
Celecoxib	1998	Analgesics	CYP2C9
Maraviroc	2007	Antivirals	CCR5
Lenalidomide	2005	Hematology	Chromosome 5qdeletion

FDA’s framework for adjusting therapeutic product labeling applies a “totality of evidence” approach that considers a range of factors, such as public health need, strength of the association, whether clinical variables can be identified that may help identify subgroups of patients for which testing would be most

beneficial, and whether a clear clinical course of action exists once the pharmacogenomics information is available. The impact that the incorporation of pharmacogenetic information in product labeling may have on medical practice must also be considered, such as whether the test is required.

Examples of Labeling Updates

- *In 2009, FDA approved labeling changes to the drugs cetuximab (Erbix) and panitumumab (Vectibix) to advise against their use in patients with metastatic colorectal cancer whose tumors have certain mutations in the KRAS gene. The changes were based on the retrospective analysis of several clinical trials that revealed that the drugs provide no benefit to patients with those mutations. Approximately 35-40% of colorectal cancers contain a mutated KRAS gene at a level measurable by the companion diagnostic and associated with poor outcome. Using the companion diagnostic to stratify patients with respect to KRAS mutation spares some patients from an ineffective treatment, and not using either of these drugs as first-line treatments in inappropriate patients could save approximately \$600 million a year.^{xv}*
- *In 2008, FDA approved labeling changes to abacavir-containing products to recommend HLA testing prior to initiating abacavir therapy. Abacavir is an antiviral used in the treatment of HIV infection and was first approved in 1998. Studies showed that patients who carry the HLA-B*5701 allele are at high risk for experiencing serious and sometimes fatal hypersensitivity reactions to the drug.^{xvi} The labeling was changed to recommend against its use in at-risk patients based on the results of a prospective randomized controlled clinical trial that compared a prospective screening strategy vs. standard of care. Clinicians who were hesitant to prescribe abacavir do so more readily as a result of the improved understanding of the risk associated with the drug and the availability of the test. The incidence of abacavir hypersensitivity reactions has diminished worldwide and the drug has enjoyed a significant resurgence in sales in response to the adoption of HLA testing.*
- *In 2007, FDA approved labeling changes to warfarin, an anticoagulant that is prescribed to people who are at high risk for the formation of blood clots due to conditions such as deep vein thrombosis, heart valve disease or replacement, and irregular heart beat, or to prevent recurrence of pulmonary embolism, heart attack, and stroke. Warfarin has a narrow therapeutic window and a wide range of inter-individual variability in response, requiring careful clinical dose adjustment for each patient. The “precautions” section of the labeling was updated to include information to alert physicians that people with variations in two genes, CYP2C9 and VKORC1, may require a lower initial dose of the drug. The labeling did not provide specific dosing recommendations. In 2010, FDA updated the “Dosage and Administration” section of the labeling, to include specific initial dosage recommendations for patients with different variant combinations.*

4. POST-MARKET SURVEILLANCE

The post-market surveillance of medical products is ever more important in an era of personalized medicine. One of the most exciting promises of personalized medicine is that it will allow for more focused clinical trials, the most expensive phase of drug development, by increasing the proportion of responders in the trial, increasing the average effect size, or both. While clinical trials for blockbuster drugs typically enroll somewhere on the order of 7,000 patients, clinical trials for crizotinib involved only 255 patients. For Kalydeco, the main trial involved only 161 patients; a second tested the drug in 52

children. One implication of dramatically smaller pre-market exposure, however, is a general increase in the importance of and emphasis on post-market monitoring, because relatively rare adverse events, in particular, are unlikely to show up when a drug is being tested in a small population, but will arise when a broader population is treated.

Post-market surveillance, then, is critical to the success of personalized medicine. FDA's ongoing efforts to refine methods for analysis of post-market data, including data mining of spontaneous reports and analysis of electronic health records from accessible, large healthcare databases, will benefit all medical products, including personalized medicines.

Sentinel Initiative

In 2008, FDA launched the Sentinel Initiative, a multi-year effort to create a national, integrated, electronic system (the Sentinel System) for monitoring the safety of FDA-regulated medical products. Although FDA has a highly rigorous pre-approval process, well-conducted, randomized, controlled clinical trials cannot uncover every safety problem, nor are they expected to do so.

In the past FDA has used administrative and insurance claims databases to investigate safety questions about Agency-regulated products, but generally it has only worked with one particular healthcare system at a time to evaluate a given safety issue. The Sentinel System, which is being developed and implemented in stages, will ultimately enable the Agency to access the capabilities of multiple existing data systems (e.g. electronic health record systems and medical claims databases) to augment the Agency's current structure. The System will enable the FDA to query distributed data sources quickly and securely for relevant de-identified product safety information, thereby strengthening the Agency's ability to eventually monitor the performance of a product, throughout its entire life cycle. This need for additional post-market surveillance becomes increasingly important in this new era of personalized medicine as more and more products are approved on the basis of very small clinical trials.

Much of the development of FDA's Sentinel System is being conducted via FDA's Mini-Sentinel pilot program, a large-scale working model of the eventual full-scale System. The Mini-Sentinel System provides secure access to the electronic health care information of more than 125 million patients, provided by 17 data partners nationwide.

National System for Medical Device Post-market Surveillance

Medical device post-market surveillance presents unique challenges compared to that of drugs and biologics due to the iterative nature of medical product development, the learning curve associated with technology adoption, and the relatively short product life cycle. In April 2013, CDRH issued an update to its September 2012 report entitled “Strengthening Our National System for Medical Device Post-market Surveillance.” FDA’s vision for medical device post-market surveillance is the creation of a national system that serves four primary functions: 1) communicates timely, accurate, systematic, and prioritized assessments of the benefits and risks of medical devices throughout their marketed life using high quality, standardized, structured, electronic health-related data; 2) identifies potential safety signals in near real-time from a variety of privacy protected data sources; 3) reduces the burdens and costs of medical device post-market surveillance; and 4) facilitates the clearance and approval of new devices, or new uses of existing devices.

CDRH is pursuing four key proposed actions to help fulfill the vision for a National System: 1) establish a unique device identifier (UDI) system and promote its incorporation into electronic health information; 2) promote the development of national and international device registries for selected products; 3) modernize adverse event reporting and analysis; and 4) develop and use new methods for evidence generation, synthesis, and appraisal.

One of the challenges with tracking, investigating, and understanding adverse events associated with the use of personalized therapeutic products is that adverse events must be traced for multiple products that are used together, *e.g.*, a diagnostic and a therapeutic product. For example, an adverse event associated with the use of a therapeutic product may have arisen as a result of failure of the test to identify the optimal subset of patients due to design deficiencies, manufacturing deficiencies, or operator error. It may be challenging for FDA to identify these deficiencies, especially since FDA’s current IT systems do not allow for easy sharing of information relevant to products regulated in different Centers. In addition, post-approval changes to personalized therapeutic products and related diagnostic devices can raise concerns about whether

changes that could affect the ability of one product to perform safely and effectively also implicate changes in the companion product.

Patient follow-up and registries may play an increasingly important role in shedding light on potentially drug-related events. One of the benefits of creating therapeutics tailored to smaller populations is that it can allow for close monitoring of patient outcomes. The Kalydeco story – involving a highly organized patient community, a well-run registry, and a small set of doctors – represents not only a remarkable success in targeted drug development, but also a possible model for generating follow-on knowledge in an era of personalized medicine. The opportunity it presents for accurate tracking and monitoring of every patient taking the drug allows for a true “life cycle approach” to drug safety.

V. ADVANCING REGULATORY SCIENCE IN SUPPORT OF PERSONALIZED MEDICINE

In 2010, the FDA announced its “Regulatory Science Initiative,” a four-part strategic framework to lead a major effort to advance regulatory science within the agency and around the nation.^{xvii} The Initiative was developed out of the recognition that FDA must play an increasingly active role in the scientific research enterprise directed towards new treatments and interventions and must also modernize its evaluation and approval processes to ensure that safe and effective innovative products reach the patients who need them, when they need them. One of the key priority areas for the Regulatory Science Initiative, as outlined by a 2011 strategic plan, is to “stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes.”^{xviii} The following section provides an overview of some of the ways that the FDA is working to advance the fundamental science, research, technology, and tools that are required for the Agency’s ability to assess the safety, quality, and performance of personalized medicine products.

1. DEVELOPING REGULATORY STANDARDS, RESEARCH METHODS, AND TOOLS

Advances in genomics together with widely accessible biological information, sophisticated bioinformatics tools, and high

throughput screening methods have led to rapid identification of potential biomarkers and therapeutic targets. Yet, the translation of new scientific findings into safe and effective medical products remains a major challenge.

FDA is working to help speed the development of promising new therapeutics by developing regulatory science standards, reference libraries, research methods, and tools that are needed for integrating genetic and other biomarker information into drug and device development and clinical decision making.

- **Biomarker Qualification Program:** The Biomarker Qualification Program was established to support CDER’s work with external scientists and clinicians in developing biomarkers. The program aims to provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development, facilitate integration of qualified biomarkers in the regulatory review process, and encourage the identification of new and emerging biomarkers. As part of this program, CDER developed a formal process for qualifying biomarkers for use in drug development. Once qualified, a biomarker can be used by drug developers within a qualified context of use in investigational and marketing submissions without requesting that the relevant agency review group reconsider and reconfirm the suitability of the biomarker.

- MicroArray and Sequencing Quality Control Project (MAQC/SEQC):^{xix} New diagnostics emerging out of advances in genomics are evolving with extreme rapidity and are creating the need for new standards. Microarrays and next-generation sequencing represent core technologies in pharmacogenomics, toxicogenomics, and personalized medicine. However, for regulatory decision making and utilization in clinical practice, development of standards, quality measures, and guidance for these technologies is

necessary. Implemented, organized, and run by NCTR scientists, the FDA-led MAQC/SEQC project seeks to advance translational and regulatory sciences by assessing technical performance and practical utility of emerging molecular biomarker technologies for clinical application and safety evaluation. By helping to develop standards for industry, this collaborative effort will help to ensure that the field of personalized medicine will benefit from high quality diagnostic tests.

MAQC/SEQC: The MicroArray and Sequencing Quality Control Project

Initiated by the FDA with active participation of hundreds of scientists from the genomics and bioinformatics communities, the MAQC/SEQC project is expected to enhance our capacity to understand, predict, and eventually prevent idiosyncratic and serious adverse drug reactions by reliably utilizing patient-specific genomic information at the single-base resolution level. The project has been carried out in three phases. Phase I, completed in 2006, evaluated the technical performance of multiple microarray platforms and the advantages and limitations of various bioinformatic data analysis methods in identifying differentially expressed genes (or biomarkers). The findings^{xx} informed FDA's updated guidance on the submission of pharmacogenomics data to the agency. Phase II evaluated methodologies for developing and validating classification models based on high-dimensional microarray data to predict clinical and toxicological endpoints, and also evaluated the technical performance of genome-wide association study platforms and different data-analysis methods.^{xxi} Phase III aims at assessing the technical performance of next-generation sequencing platforms by generating large benchmark datasets with reference samples and evaluating advantages and limitations of various bioinformatics strategies in RNA and DNA analyses.

- Genomic Reference Library for Evaluating Whole Genome Sequencing Platforms: Whole genome sequencing (WGS) is widely used as a research tool and is starting to become commercially available

for other uses. Multiple sequencing instrumentation systems have been introduced, yet it is not clear how well sequencing works on an individual patient level, and there are no agreed-

upon approaches to establishing the measurement characteristics or the clinical application of results provided by these instruments. In partnership with the National Institute of Standards and Technology (NIST), FDA's Office of *In Vitro* Diagnostics and Radiological Health (OIR) in CDRH is developing genomic reference materials for evaluating WGS instrument systems. The reference materials will allow FDA and external users to understand overall system performance, the variation between instrument types and uses, the types of errors each system may make, and specific measurement performance for individual sequences of interest. In addition, the project will generate products and testing methods that can be used with any technology or application. The resulting reference materials will be available for purchase by industry and researchers and will serve as a national resource in understanding how WGS systems work.

- Virtual Physiological Patient: Advances in medical imaging and computational modeling have allowed incorporation of patient-specific simulations into clinical practice and medical device development. This can allow for personalized, custom-built medical devices designed for individual patient anatomic and physiological characteristics. CDRH is currently developing a publicly available digital library of such models and simulations for evaluation, modification, sharing, and incorporation into medical device development. Source data will also be available for users to develop

models *de-novo*. Allowing such pre-competitive collaboration and sharing of modeling knowledge will likely help advance personalization of medical device development and use.

- High-Performance Integrated Virtual Environment (HIVE) for Next-Generation Sequencing Analysis Infrastructure: The High-performance Integrated Virtual Environment (HIVE) is a cloud-based environment optimized for the storage and analysis of extra-large data, primarily Next Generation Sequencing (NGS) data. This environment will provide secure web access for authorized users to deposit, retrieve, annotate, and compute High-Throughput Sequencing (HTS) data, and to analyze the outcomes using web-interface visual environments appropriately built in collaboration with research scientists and regulatory personnel. Developed by CBER, HIVE is a multicomponent cloud infrastructure where the distributed storage library and the distributed computational powerhouse are linked seamlessly. The novel paradigm of moving computations to the data instead of moving data to computational nodes implemented in HIVE has proven to be significantly less taxing for hardware and network infrastructure. FDA's medical product centers are beginning to use HIVE for regulatory submissions.
- Development of High Resolution Human Leukocyte Antigen (HLA) Typing: The Human Leukocyte Antigen (HLA) system refers to a large number of genes and protein products that are related to

immune system function. HLA typing is the process of testing patient or donor blood or other tissue samples for HLA antigens. The results can then be used to determine compatibility between the donor and patient (HLA matching). More precise HLA matching through the application of molecular-based typing methods has been shown to significantly improve transplant outcomes and is especially critical for bone marrow transplant outcomes, where poor matches can result in catastrophic health consequences. However, ambiguous results occur even with the use of current “gold standard” DNA-based HLA typing methods, in part due to the extraordinary variability and complexity of the HLA genes. CBER scientists, along with others in industry and academia, are working to apply cutting-edge technologies to develop a high resolution HLA typing method that achieves results without ambiguities.

- Development of Molecular Tools to Facilitate Blood Group Typing: Blood group typing by molecular methods is of great and increasing interest for use in predicting highly specific red blood cell (RBC) types and to enable the transfusion of compatible blood products. Molecular typing has certain benefits over traditional techniques and can increase the possibility of identifying suitable blood donors in complex patient

cases.⁴ As red blood cell molecular typing kits are approved and become available for use, there will be a need for quality control standards. CBER’s Division of Blood Applications is working to develop quality control DNA reference panels with broad coverage of approximately 90 genotypes from 17 blood groups that can be used in the evaluation, validation, and standardization of RBC molecular testing devices.

- Clinical Trial Designs and Methodologies: The core capability of personalized medicine – the ability to select patients for whom therapy is most likely to provide a benefit – can also be leveraged in the design of clinical trials. FDA is working to refine clinical trial design and statistical methods of analysis to address issues such as missing data, multiple endpoints, patient enrichment, and adaptive designs that often arise in the development of targeted therapeutics. FDA is also looking specifically at clinical trials for oncology drug development. Development of cancer drugs is complicated in part by the fact that many cancers are heterogeneous, meaning that cancers in the same organ can have very different origins and characteristics, each with their own specific genetic makeup. This heterogeneity is one reason why

⁴For example, the availability of molecular typing has proven to be valuable in cases where patients require multiple transfusions throughout their lifetime, such as patients with sickle cell anemia. These patients often develop immune antibodies to donor blood, making finding compatible blood for transfusion very difficult. High-throughput, multiplex molecular typing technologies create the possibility of large-scale donor screening for multiple antigens, including rare antigen combinations or genotypes. This will assist in providing well-matched RBC units for transfusion for these patients.

different people with cancer in the same organ respond differently to therapies. The I-SPY 2 trial, a highly collaborative initiative developed under a unique public-private partnership and involving

the participation of more than 20 cancer centers, attempts to account for this heterogeneity and complexity of cancer at the outset [*see text box*].

I-SPY 2 Trial

The “I-SPY 2 Trial,” launched in March 2010, represents a groundbreaking new clinical trial model that will help scientists quickly and efficiently test the most promising drugs in development for women with higher risk, rapidly growing breast cancers. Designed to reduce the cost, and speed the development, of promising new drugs for women with high-risk, aggressive breast cancers, the I-SPY 2 trial focuses on biomarkers from individual patients’ tumors and personalized treatments. During the trial, drugs in development are individually targeted to the biology of each woman’s tumor using specific genetic or other biomarkers. By applying an adaptive trial design, researchers will use data from one set of patients’ treatments to treat other patients – more quickly eliminating ineffective treatments and drugs and allowing for knowledge learned throughout the course of the trial to be used in individualizing treatment. The I-SPY 2 trial was developed under the Biomarkers Consortium, a unique public-private partnership that includes the FDA, the National Institutes of Health (NIH), and major pharmaceutical companies, led by the Foundation for NIH. Approximately 20 cancer centers are recruiting and treating patients as part of this collaborative effort.

- Study Design Considerations for HLA Genotyping Devices: The HLA region is the most variable part of the human genome. HLA typing is critical for tissue transplant matching, and sponsors face significant challenges developing and evaluating devices used to determine a patient’s HLA type. These devices are highly multiplexed and hundreds to thousands of analytes need to be detected, making traditional approaches to the assessment of diagnostic devices unwieldy and burdensome. CBER has created an HLA genotyping working group that is developing study design considerations for both clinical and analytical performance, essential components of an HLA diagnostic device submission.
- Statistical Methods for Analyzing Genomic Data: Working with scientists at Booz Allen Hamilton and the FDA supercomputer center, the Genomics Evaluations Team for Safety (GETS) and the Office of Vaccines Research and Review (OVRR) in CBER are comparing different methods for analyzing genomic data for use in a predictive or prognostic fashion. By simulating full sized genomes for tens of thousands of humans and assigning medically-relevant phenotypes in a realistic manner, they have been able to determine which methods, under

which circumstances, may provide the highest predictive accuracy. In addition, they are better able to estimate necessary sample sizes and the maximal expected benefits of genomic information for predictive purposes.

- Novel Device Diagnostics for Improving Drug Safety: In the 1990s, multiple drugs were removed from the market because they increased the risk of a potentially fatal abnormal heart rhythm called Torsade de Pointes. Drugs that cause the abnormal heart rhythm also increase a measurement on the electrocardiogram called the “QT interval”. However, not all drugs that prolong the QT interval cause Torsade de Pointes. Screening for drug-induced QT prolongation early in drug development may be preventing some effective new drugs (that are benign QT prolonging drugs) from reaching the market. An inter-center collaborative team from CDER and CDRH is assessing new device-based algorithms and biomarkers that can distinguish benign (not harmful) from malignant (harmful) drug-induced QT prolongation.
- Novel Methodological Approaches to Studying Medical Device Performance and Clinical Outcomes: Through the Medical Device Epidemiology Network (MDEpiNet) Partnership, CDRH has begun developing a Formal Evidence Synthesis Framework that combines existing data sources, including clinical trials, observational studies, patient registries, published literature, administrative claims data, and other known data sources. This framework

will allow CDRH to have a targeted, comprehensive, up-to-date benefit-risk profile for a specific medical device for subgroups of patients at any point of a life cycle, thus enabling us to make optimally informed decisions and provide more useful information to practitioners, patients, and industry.

2. CONDUCTING AND COLLABORATING IN RESEARCH

Regulatory practice and policy must incorporate in-depth scientific understanding. The rate and pace of development of the field of personalized medicine are driven most fundamentally by our understanding of basic science and the integration and translation of that science into product development. FDA has a responsibility to maintain an understanding of rapidly evolving science and technology. It is also uniquely positioned to identify critical gaps in that scientific understanding and to conduct research to fill those gaps. For example, FDA often conducts large combined analyses (meta-analyses) of multiple clinical trials when a question arises about the safety of a product or a class of products. By participating in research, FDA scientists maintain critical expertise in their fields while contributing directly to the generation of knowledge. Following are a selection of examples of current research activities that relate to personalized medicine.

- Biomarker Identification and Development: NCTR’s Division of Systems Biology works to identify important translational biomarkers

and pathways of response that provide predictive, diagnostic, and prognostic value in both the preclinical testing of compounds and the management of patients. The Personalized Medicine Branch, in particular, is focused on 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. The classifications include: genetics, sex, age, epigenetics, and life-style and environmental factors such as smoking and obesity. Preventions and therapies can then be chosen that maximize benefits while minimizing side effects and unnecessary treatments and tests.

- Biology of Cancer: NCTR's Division of Genetic and Molecular Toxicology performs research to improve understanding of cancer's underlying biologic features. A research project focused on the KRAS oncogene, for example, established that many tumors carry subpopulations of KRAS mutant cells, which can contribute to acquired resistance to some cancer therapeutics. A goal of this work is to establish experimental approaches to identify efficacious treatments that block the development of acquired drug resistance in tumors with defined genetic profiles.
- Pharmacogenetics and Immunogenicity of Protein Therapeutics: There has been a steady shift towards the use of recombinant human proteins in the treatment of human diseases, such as hemophilia. However, the safety and

efficacy of these therapies are affected by the fact that proteins can elicit an immune response in the form of the production of inhibitory antibodies. Genetic variability may lead some individuals, racial/ethnic groups, or other sub-populations to develop inhibitory antibodies at a higher frequency. Development of inhibitory antibodies to therapeutic proteins is a life-threatening adverse event, which requires expensive clinical intervention that can cost up to several million dollars per patient. Researchers at CBER are working to establish pharmacogenetic determinants of immunogenicity in patients with Hemophila A. This research may eventually allow for a patient's risk of immunological response to a given protein therapy to be predicted in advance of treatment.

- Understanding the Effects of DNA Modifications on the Quality of Protein Products: Over the last decade, it has become apparent that single nucleotide polymorphisms (SNPs) are a significant cause for genetic variability in the population, including variation in individual response to prescribed medications. Evaluating the safety of protein-based therapeutics that mimic human proteins is inherently complex, in part because several possible sequences of the protein exist in the normal population, any one of which could be developed as a drug. In addition, there has recently been a surge in protein and DNA engineering that allow improved therapeutic protein product yields. A second generation of therapeutics involves

Pharmacogenetic Determinants of Immunogenicity in Patients with Hemophilia A

Hemophilia A, also known as “Factor VIII deficiency” is the most common form of hemophilia and occurs in one of every 5,000 males in the United States. In patients with this disease, one of the proteins involved in blood clotting (Factor VIII) is missing or not functional, causing patients to have longer bleeding episodes after trauma or serious injury, or in more severe cases, episodes that occur spontaneously. In the treatment of hemophilia A, about 20% of patients develop inhibitory antibodies against life-saving therapies. In addition, the prevalence of this life-threatening reaction among patients of Black African descent is almost twice to that observed in patients of Caucasian descent.

Researchers at CBER are working to establish the pharmacogenetic determinants of immunogenicity, using Factor VIII as a model system. The long-term goal of their research is to identify and utilize biomarkers to ensure the safety and efficacy of medications for all populations. They have developed an algorithm that considers three critical parameters – mutations in Factor VIII, HLA type of the patients/recipients, and sequence of therapeutic Factor VIII agent – to generate an immunogenicity score that appears to predict a patient’s risk of immunological response to a given protein therapy and has proven to be consistent with clinical reports of immunogenicity. Validation of this tool could pave the way for the development of therapeutics that are closely matched to the target population. The approach used in this research is also useful in accessing the potential immunogenicity of bioengineered protein therapeutics.

engineering the protein to achieve desirable therapeutic outcomes. All of these manipulations can potentially affect the efficacy and safety of protein therapeutics but predicting how different manipulations can alter safety and efficacy remains a challenge. CBER researchers have initiated a research project that seeks to better understand the effects of DNA modifications on the quality of protein products. Using proteins that are involved in blood clotting as models, the researchers have demonstrated that while “synonymous” or “silent” mutations [*see text box, pg. 53*] do not affect the protein sequence, they may affect protein levels as well as protein folding and function. The researchers are also looking to understand which mutations are deleterious and which may be safely employed in design of

therapeutic protein products, and aim to develop tools and methodologies to evaluate protein properties from gene sequence. This research could have wide implications for the development and evaluation of safe and effective protein therapeutics, including biosimilar products.

- Identification of Genetic Risk Factors for Vaccine Reactions: CBER’s Office of Vaccines Research and Review (OVRR) together with the Genomics Evaluations Team for Safety (GETS) are involved in several research collaborations that focus on identification of genetic risk factors associated with adverse reactions to vaccines. For example, a project with Harvard Pilgrim Healthcare and Georgia Kaiser Permanente attempts to identify genetic risk factors associated with “idiopathic thrombocytopenia

Understanding ‘Silent’ Mutations

The genetic code governs how a cell translates DNA instructions, via RNA, into functional proteins. Inside the cell nucleus, DNA is transcribed into RNA and then edited to remove segments that do not code for amino acids. In the process of translation, RNA nucleotides spell out the sequence of amino acids in an encoded protein using three-letter “codes” (called codons) each of which correspond to one of 20 amino acids. With an alphabet of four nucleotide bases, 64 codon triplets are possible, resulting in several codons that specify the same amino acid. Thus one can frequently have a mutation in the DNA that does not result in an amino-acid change in the resulting protein. These single nucleotide changes that do not result in a change in the amino acid in the translated protein are referred to as “synonymous mutations or “silent mutations.”

Scientists long assumed that because synonymous mutations do not alter the sequence of the protein they had no functional or clinical consequences. However, it is now understood that such changes may not be ‘silent,’ after all, and instead can impact protein expression, conformation, and function. To date, more than 50 diseases have been shown to be caused entirely or in part by synonymous mutations. While only one synonymous mutation could cause disease, codon optimization more often than not results in the employment of synonymous mutations in more than half of the entire codon.

Researchers at FDA’s CBER are working to understand the extent to which synonymous mutations occur genome-wide, the mechanisms by which they can affect protein function, and their global importance in human health and disease. Advancements in our understanding in these areas could have broad applications in drug development as well as in the practice of clinical medicine. For example, synonymous mutations are routinely introduced into protein therapeutics by way of genetic engineering as a strategy for increasing protein production. In recent years, new approaches, novel technologies and genomic data are helping us to elucidate the “rules” by which synonymous codons affect protein folding, structure and function that may have broad applicability.

purpura” – a condition of having an abnormally low platelet count – following measles-mumps-rubella (MMR) vaccination in children. A second study in collaboration with CDC and Northern California Kaiser looks at genetic risk factors of febrile seizures after MMR vaccination. Another study, in collaboration with the Innovation Center for Biomedical Informatics (ICBI) at Georgetown University, seeks to identify genes associated with vaccines, vaccine

components, and several autoimmune diseases of interest in order to help assess plausibility of autoimmune diseases as adverse reactions to vaccines. Pathway models derived from this data may help predict autoimmune reactions to vaccines and other medical products in the future.

- Evaluation of Personalized Cell-Based Products: Mesenchymal or Multipotent Stem Cells (MSC): Stem cell-based treatments hold great promise to provide cells, tissues, and perhaps organs to treat

a variety of clinical indications from cardiovascular disease to repairing or regenerating injured organs or limbs. However, these products are complex and raise a number of questions with regard to use in clinical trials, such as what are the critical product attributes to measure, will they form tumors in patients, and will they go to the wrong place in the body and cause harm? In order to regulate them effectively, CBER has a consortium of scientists using a systems biology approach to identify the critical product characteristics that are measurable and correlated to desired clinical outcome using nonclinical functional assays. The outcome of these studies will be new or improved assays to characterize these cells as well as improved guidance to sponsors performing studies to evaluate MSC-based products, thus facilitating development of this new class of medical products.

- Genetics of Drug Induced Hypersensitivity Reactions: Understanding genetic susceptibilities to drug responses (*i.e.*, adverse reactions and efficacy) is critical to the implementation of personalized medicine. Genetic variants have been associated with severe adverse reactions to carbamazepine, a common drug used primarily in the treatment of epilepsy and trigeminal neuralgia. In particular, two HLA-related variants (HLA-B* 1502 in Asian populations and HLA-A* 3101 in Caucasian populations) have been associated with an increased risk of developing Stevens-Johnson (SJS) syndrome and toxic epidermal necrolysis (TEN), two forms of a life-

threatening skin condition. However, these HLA variants predict only a portion of individuals who will develop these conditions. This suggests that other rare or non-HLA related variants may also play an important role. Scientists at NCTR, in collaboration with scientists at the University of Liverpool (UK) and the Huashan Hospital (China) are performing whole genome sequencing and genetic analysis to identify susceptibilities to carbamazepine-induced SJS or TEN. The researchers hope that by identifying additional factors that help to explain variation in patient response, they will be able to better predict in advance who will have an adverse reaction to the drug.

- Genetics and Cardiovascular Risk: In collaboration with researchers at the University of Maryland, scientists at NCTR are conducting research that seeks to identify genetic factors that interact with common lifestyle factors to contribute to heart disease. Research subjects were recruited from the Amish community in Lancaster, Pennsylvania. The volunteers were examined for metabolic responses to various diets and drugs that are associated with cardiovascular risk, specifically: blood triglyceride response after a high fat meal, blood pressure response after a high salt meal, and platelet aggregation response after aspirin or clopidogrel administration. The DNA from subjects who showed abnormal responses was sequenced using NGS technology and genetic association studies were conducted. This work is ongoing, and as candidate genetic markers are discovered,

they are being validated in another cohort. Identification of genetic factors that interact with dietary and drug exposures to increase risks of cardiovascular disease or efficacy of treatment will allow patients and their doctors to utilize personalized medicine to improve health.

- Role of Genetics in Response to Clopidogrel Doses: Clopidogrel (sometimes marketed under the trade name Plavix®) is a drug that inhibits aggregation of blood platelets, and is commonly used in patients to prevent heart attacks or strokes caused by blood clots. Although clopidogrel works in many individuals, some people do not respond well to the drug. This variation in treatment response may be linked to genetics. Clopidogrel is converted to an active drug in the human body through an enzyme encoded by the gene named CYP2C19. Individuals with genetically-impaired CYP2C19 metabolism have lower capacity to convert the drug to its active form. Consequently, these individuals have lower blood levels of the activated form of the drug, diminished antiplatelet responses, and higher rates of cardiovascular events and stent thrombosis. Researchers at FDA, in collaboration with the National Cancer Institute (NCI), the National Institute of General Medical Sciences (NIGMS) and the University of Maryland, conducted a study to evaluate whether increasing the dose of clopidogrel increases antiplatelet responses and active metabolite exposure in individuals with genetically reduced CYP2C19 metabolism relative to those

with normal CYP2C19 metabolism.

- Personalized Medicine for Heart Devices: Researchers in the Office of Science and Engineering Laboratories at CDRH have made major advances in understanding the underlying biology of heart disease. They have used new methods for analysis of the electrocardiogram to identify the underlying causes of heart disease and to predict which patients will benefit from cardiovascular therapies such as cardiac resynchronization therapy. Specifically, this work has resulted in new methods to diagnose electrical conduction problems and to quantify scar tissue in the heart, with different criteria for women and men. These new methods are being used by outside research groups and are helping decipher why women benefit significantly more than men from cardiac resynchronization therapy. This example of personalized medicine diagnostics helps to explain why the efficacy and safety of medical products differs in patient subgroups and can be used to design more efficient clinical trials.
- Role of Body Fluid Interaction Testing and Adaptive Optics in Personalized Medicine: The Office of Science and Engineering Laboratories at CDRH is collaborating with George Washington University to develop a microfluidic, high-throughput microchip to test the interaction of tears with contact lenses, care products, and microbes. The goal is to use individual testing results to guide patient prescription of lens materials and hygiene products. Moreover, in the area of personalized eye research, scientists

at OSEL are working on adaptive optics where a patient's ocular aberrations are measured and used to either provide custom photorefractive surgery (e.g., LASIK), a custom contact lens, a custom intraocular lens, or a superhigh resolution imaging to diagnose retinal disease down to the cellular level (as well as other novel gene-based applications). The first three enable a customized treatment; the last enables disease diagnosis and tailored treatment.

- Centers for Excellence in Regulatory Science and Innovation (CERSI): In support of their activities facilitating collaborative regulatory science research, FDA's Office of the Chief Scientist (OCS) has established a program to fund academic Centers of Excellence in Regulatory Science and

Innovation (CERSI). To date, centers have been established at Georgetown University and the University of Maryland. One of the major focuses of the Georgetown University CERSI is on pharmacogenomics research – understanding what genetic variants predict response to therapy, building gene and protein based pathways models to understand adverse event mechanisms, and better understanding genetic variant information across ethnic groups to evaluate usefulness and thoroughness of clinical trial data. On September 3, 2013, the University of Maryland CERSI facilitated a discussion between FDA scientists, academic scientists, industry, and other stakeholders regarding rate-limiting regulatory issues in personalized medicine and pharmacogenomics.

VI. A NEW ERA OF MEDICAL PRODUCT DEVELOPMENT: OPPORTUNITIES AND CHALLENGES AHEAD

From FDA's vantage point, the era of personalized medicine has clearly arrived. Of the new drugs approved since 2011, approximately one-third had some type of genetic or other biomarker data included in the submission to characterize efficacy, safety, or pharmacokinetics. Since 2010, CBER has licensed Provenge,[®] an autologous cancer vaccine, Laviv,[®] an autologous fibroblast product, and five cord blood products for hematopoietic reconstitution, which require careful matching of donor and recipient. Personalized medicine submissions to CDRH's Office of In Vitro Diagnostics and Radiological Health (OIR) have increased by more than an order of magnitude since 2007. Review

activity in CDER's Genomics and Targeted Therapy Group has steadily increased over the past five years. Recombinant protein therapeutics, which are particularly suited for a personalized approach, are the fastest growing segment of the pharmaceutical repertoire and are increasingly used to treat or manage some of the most complex medical conditions. Data from the last few years indicate that more and more drugs are being designed for small populations, a trend that is consistent with the increasing use of stratification in drug development. Multiple examples of targeted approaches to drug development have demonstrated that such approaches can dramatically shorten overall drug development and review times.

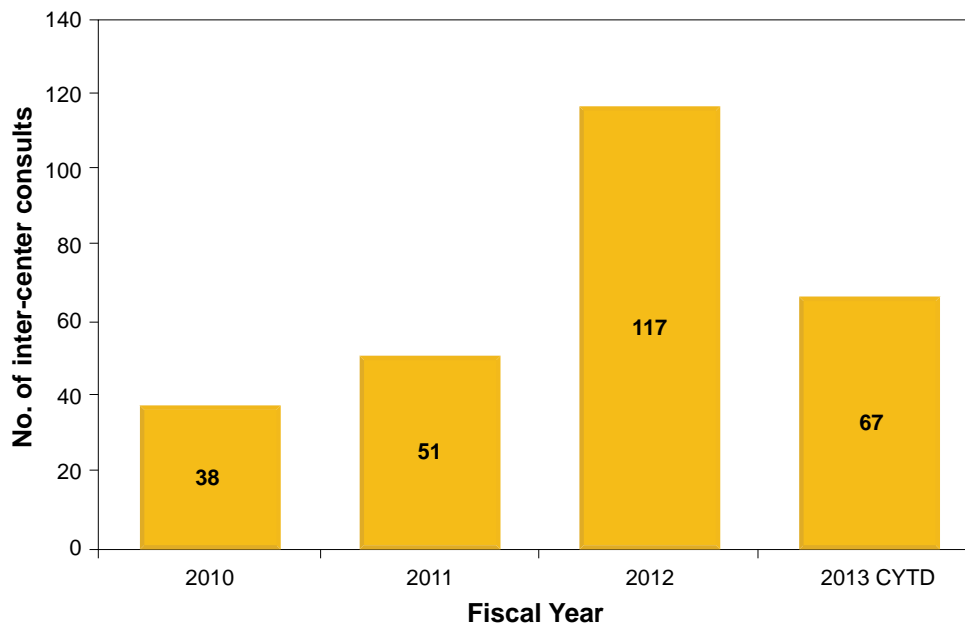


Figure 8. Office of In Vitro Diagnostics and Radiological Health inter-center consults FY 2010-2013

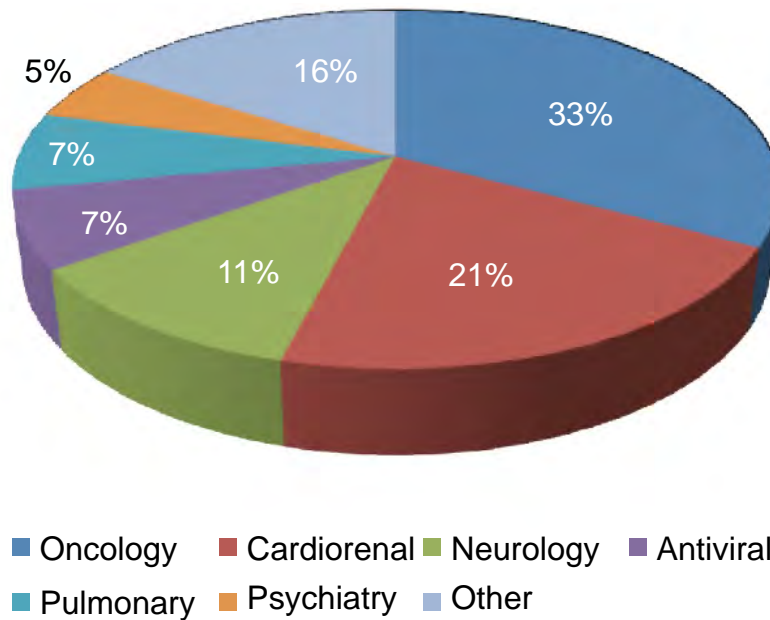


Figure 9. Review Activity in the Personalized Medicine Space - 2012^{xvii}

Today, patients with breast, colorectal, and lung cancers, as well as melanoma and leukemia are routinely offered a “molecular diagnosis,” allowing their physicians to select treatments that are more likely to improve their chances of survival. These cancers are no longer considered single diseases, but instead sub-classified on the basis of their genetics. Advancements in HLA genotyping are improving transplant outcomes and dramatically improving our ability to predict the potential for a patient to experience a severe hypersensitivity reaction to a drug, including drugs used to treat HIV, hemophilia, epilepsy, and bipolar disorder. The genotyping of drug-metabolizing enzymes has led to dramatic improvements in our ability to identify proper dosing schedules for drugs, and has helped thousands of patients avoid harmful side effects, drug interactions, and ineffective treatments.

Similarly, “personalized” medical devices, tailored to individual and unique patient characteristics, are becoming increasingly common.

All trends signal continued growth in the development and use of personalized therapeutics. For example, the numbers of published gene-disease association studies continue to grow each year. DNA sequencing and characterization of the human genome have unveiled thousands of new drug targets. Translating new knowledge about pharmacogenomic biomarkers into routine clinical practice has become a reality rather than a futuristic vision. As companies shift pharmacogenomics investigations to early phase development, we can only expect to see the generation of more prospective biomarker applications and the development and approval of more drugs tailored by biomarker use. A recent report by the Tufts Center for the

Study of Drug Development notes that more than 90% of pharmaceutical companies now utilize at least some genomic-derived targets in their drug discovery program. The same study found that personalized medicines comprise 12-50% of company pipelines.^{xxiii}

While there is growing optimism, even the most groundbreaking personalized therapies are not “magic bullets,” and significant scientific, medical, educational, business, regulatory, and policy challenges remain before personalized medicine can reach its potential and be fully integrated into patient care. A future where personalized therapeutics are standard in medical practice and supported by continual learning systems that allow for adequate clinical decision support and the use of electronic medical records linked with personal genome sequences, while ever more plausible from a technical perspective, is still quite a ways off. The most significant challenges include:

- Limited understanding of the intrinsic biology of disease: The tools of the last two decades have left us awash in data, yet we still have a relatively limited understanding of what it all means. Scientific understanding will likely remain the most important limiting factor for the momentum of this field.
- Common conditions involving multiple genes/biomarkers: Common conditions are often influenced by multiple genetic, as well as environmental and social factors, in ways that are not yet well understood. Realization of the benefits of personalized patient management for common conditions affected by multiple genes will be a complex process that

will depend on substantial investment in clinical research well beyond the initial demonstration of gene-disease correlations.

- An outdated disease classification system: Currently used disease classification systems define diseases primarily on the basis of their signs and symptoms. These systems do not easily accommodate emerging information about disease mechanisms, particularly when it is at odds with traditional physical descriptions. As a result, many disease subtypes with distinct molecular causes are still classified as one disease, while multiple, different diseases that share a common molecular cause are not properly linked. The failure of our outdated disease classification systems to incorporate optimally new biological insights serves as a fundamental barrier to progress in personalized medicine. The National Academy of Sciences has called for the creation of a “New Taxonomy” of disease that is designed to advance our understanding of disease pathogenesis and improve health and that defines and describes diseases on the basis of their intrinsic biology in addition to traditional signs and symptoms.^{xxiv}
- Lack of infrastructure: Costs of genetic sequencing have plummeted over the past decade, resulting in an explosion of information. Yet, while information is becoming easier and easier to obtain, the infrastructure to collect, analyze, integrate, share, and mine that information remains lacking.

- Clinical implementation of new diagnostics: Many clinicians have been reluctant to use new diagnostics. Part of this reluctance may be due to the ongoing controversy over clinical utility and the fact that biomarker clinical utility can often be a moving target. Clinicians also commonly face the general problem of “information overload,” making adoption of new tests difficult without decision-support tools in place that could be accessed to help the clinician to identify, order, and interpret the appropriate tests.
- Investment uncertainties: One of the disincentives to developing personalized therapies is the perceived lower return on investment that targeted drugs will provide because of smaller patient populations and therefore lower sales. While these concerns may be offset by the increased safety and effectiveness of these medicines that in turn allows for smaller trial designs and leads to rapid uptake, premium pricing, and increased patient compliance, the relative costs and rewards of these investments will clearly vary from one product to the next, and uncertainties will likely remain for some time.
- Access to personalized therapeutics: Even though personalized medicine is bringing great benefit to those who have disease with a diagnostic characteristic of interest, patients who do not have the characteristic are not benefitting. Additional work to target all sub-classifications of a disease is needed to assure that many patients will not be “left out” of the sea change that personalized medicine brings.

While many of these and other challenges are well beyond the scope of FDA’s set of roles and responsibilities, the Agency is committed to working in concert with all key stakeholders to finding solutions that will help move this promising field forward. Moreover, the Agency will continue to facilitate the development of the personalized medicine field by advancing the science and tools that will drive innovation, collaborating with scientists worldwide in important research activities, providing clarity and guidance to industry in order to help shepherd new products through regulatory review, and continuing to identify opportunities to streamline regulatory processes.

GLOSSARY OF TERMS

- Analytical Validity.** The accuracy of a test in detecting the specific characteristics that it was designed to detect, often measured by sensitivity and specificity.
- Biomarker.** Characteristics that can be scientifically measured and evaluated as indicators of normal biologic processes, disease, or response to therapeutic intervention. Biomarkers include genes and their protein products and other metabolic intermediates and endpoints. A biomarker is typically measured using a diagnostic test (e.g. an *in vitro* diagnostic test, imaging diagnostic, etc.) or other objective measurement method.
- Clinical Utility.** The relevance and usefulness of an intervention in patient care; the likelihood of an intervention to improve patient outcomes.
- Clinical Validity.** The accuracy with which a test identifies or predicts a patient's clinical status.
- Combination Product.** A product comprised of two or more regulated components, *i.e.*, drug/device, biologic/device, drug/biologic, or drug/device/biologic. Combination Products are uniquely subject to 21 CFR Part 3 and Part 4.
- Companion Diagnostic.** An *in vitro* diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
- Enrichment.** The prospective use of any patient characteristic – demographic, pathophysiologic, historical, genetic, and others – to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.
- Genetic Test.** A test for DNA, RNA, or protein mutations with a target population composed of those who are suspected of having, or are at risk of developing, a particular disease or condition.
- Genomic Biomarker.** A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions; for example, the expression of a gene, the function of a gene, the regulation of a gene.
- Immunogenicity.** The ability of a substance to provoke an immune response or the degree to which it provokes a response.
- In Vitro* Companion Diagnostic Device.** An *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
- In Vitro* Diagnostic (IVD).** A reagent, instrument, or system intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.
- Laboratory Developed Tests (LDTs).** A subset of *in vitro* diagnostic devices which are designed, manufactured, and offered for clinical use by a single laboratory.

Metabolomics. The study of small-molecule metabolites in cells, tissues, and organisms that are present in biofluids such as plasma and urine.

Molecular Diagnostics. Laboratory tests that can be used on blood, tissue, or other biological samples to identify the presence of specific molecular biomarkers. Molecular diagnostics can be used to assess the likely efficacy of specific therapeutic agents in specific patients, identify patients who may suffer disproportionately severe adverse effects from a given treatment or dosage, determine optimal dosages for drugs whose therapeutic effect is known to vary widely, assess the extent or progression of disease, examine surrogate measures for clinical outcomes, or identify patients who can benefit from specific preventive measures.

Next-Generation Sequencing. Technologies that parallelize the genetic sequencing process, allowing for the production of thousands or millions of sequences concurrently (also referred to as “high-throughput sequencing”).

Pharmacogenetics (PGt). The study of variations in DNA sequence as related to drug response. Pharmacogenetics is a subset of pharmacogenomics.

Pharmacogenomics (PGx). The study of variations of DNA and RNA characteristics as related to drug response.

Pharmacodynamics. Drug response; all of the effects of the drug on any physiologic and pathologic processes, including those related to effectiveness and those related to adverse reactions; “what the drug does to the body.”

Pharmacokinetics. Drug exposure; a readily measured feature of the drug, including: absorption, distribution, metabolism (including formation of active metabolites), and excretion; “what the body does to the drug.”

Protein therapeutics. Proteins used in the treatment of human diseases that are purified from animal or human sources or, increasingly, manufactured by recombinant DNA technology.

Proteomics. A large-scale comprehensive study of a specific proteome, including information on protein abundances, their variations and modifications, along with their interacting partners and networks, in order to understand cellular processes.

Single Nucleotide Polymorphism. A single nucleotide polymorphism, frequently called SNPs (pronounced “snip”), is a variation at a single position in a DNA sequence among individuals. SNPs occur normally throughout a person’s DNA, and are the most common type of genetic variation among people. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome. Most of these genetic differences appear to have no effect on health or development, but some may be used to help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases.

Stratified Medicine. Using a biomarker to match a patient to a cohort that has exhibited a differential response to a treatment.

Synonymous SNPs. Single nucleotide changes that do not result in a change in the amino acid in the translated protein.

Whole Genome Sequencing. A laboratory process that determines the complete sequence of DNA in an individual’s cells.

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