

Preparing For A “New Era of Medical Product Development”

FDA report demonstrates support for personalized medicine and more efficient regulatory pathways.

In a new report issued by the Food and Drug Administration (FDA) on October 28, 2013, Commissioner of Food and Drugs Margaret Hamburg declared her priority is “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.”¹ The report, titled *Paving the Way for Personalized Medicine: FDA’s Role in a New Era of Medical Product Development*, describes “the unique and special role and responsibility that FDA has in helping to usher in the medical products that are central” to the practice of personalized medicine.² Reinforcing the Agency’s commitment to support the development of personalized medicine and emphasizing the Agency’s intent to provide further “clarity and guidance to industry,”³ the report reviews the potential benefits and current challenges presented by the trend towards personalized medicine, and details steps the Agency has taken to both prepare for and facilitate this fundamental change in patient care.

The Goals of Personalized Medicine: FDA’s Perspective

FDA’s report broadly defines “personalize medicine” 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.”⁴ FDA emphasizes that personalized medicine is not limited to pharmaceutical treatments, and describes wireless technologies, advances in computational power and medical imaging, stem cell research and the Internet as all playing a role in the development of personalized medicine.

To illustrate the potential benefits of personalized medicine, the report explains that under the traditional approach to medical care, a patient may receive any one of a number of possible therapies to treat an illness. In a “somewhat ‘trial-and-error’ approach,” doctors prescribe one course of therapy based on “only general information.”⁵ If that treatment proves ineffective, a second therapy is attempted. The results of this therapy-to-therapy strategy may include drug interactions, adverse reactions, patient dissatisfaction or poor treatment adherence.

In contrast, personalized medicine seeks to identify patients who may benefit from a particular treatment, or those who may experience side effects from a particular treatment, before the treatment begins. Personalized medicine therefore has the potential to more effectively prevent and treat diseases by anticipating individual patient differences. Benefits that may stem from this approach include:

- Reducing illness duration
- Reducing illness severity

- Reducing product development timelines, by allowing for smaller and more targeted clinical trials
- Improving treatment success rates
- Reducing healthcare costs by enabling patients to avoid ineffective treatments and preventable adverse events

In addition, personalized medicine may help shift the focus of “the health care management paradigm... from illness to wellness, and from treating disease to maintaining health.”⁶

FDA believes that personalized medicine is central to the Agency’s duties. The report explains that FDA must determine whether the expected benefits of a product exceed the risks in a particular patient population. The report further notes that personalized medicine may make products both safer and more effective by pairing patients with their optimal treatments. In addition, personalized medicine may facilitate the success of medical product development efforts, as “[h]igh attrition rates [in medical product development] 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.”⁷

Facilitating and Responding to the Development of Personalized Medicine: FDA’s Strategy

The bulk of FDA’s report surveys the wide range of activities the Agency has pursued so as to better regulate personalized medical products and stimulate the development of personalized medicine. After the completion of the human genome project in 2003, the FDA centers responsible for regulating medical products began crafting “regulatory processes, policies, and infrastructure” and coordinating review and oversight activities to optimally regulate “tailored medical products.”⁸ FDA has also pursued research collaborations to develop new technology and scientific knowledge in support of the shift towards personalized medicine. The Agency’s extensive activities can be grouped into the following three categories: early stage development; regulatory pathways and policies; and product use.

Early Stage Development:

Many of FDA’s activities focus on the development of scientific standards, reference libraries, research methods, and research tools that may speed the emergence of personalized medical products. In addition, FDA has engaged in outreach and collaboration with industry in various forms. A sampling of these activities, as described in FDA’s report, includes:

- **The National Center for Toxicological Research (NCTR):** The NCTR is an FDA laboratory research center that supports the Agency’s research needs. NCTR has pursued research efforts geared towards the development of personalized medicine. In addition, the NCTR reorganized its scientific staff in 2012 to form three cross-functional divisions. One of those divisions, the Division of Systems Biology, is further divided into three branches, including a Personalized Medicine Branch.
- **Seminars and Educational Series:** FDA has coordinated expert seminars and educational series that enable interested parties to hear speakers discuss issues involving the use of pharmacogenomics in drug development.
- **Biomarker Qualification Program:** The Biomarker Qualification Program supports the efforts of the Center for Drug Evaluation and Research (CDER) to develop biomarkers with external scientists and

clinicians. FDA's report describes three primary functions of the program: (1) to provide a framework for the development of biomarkers for use in drug development; (2) to facilitate the integration of qualified biomarkers in regulatory reviews; and (3) to encourage the identification of new biomarkers. The program includes a formal process by which to qualify biomarkers for use in drug development. Drug developers may then use such qualified biomarkers within specific contexts, without additional assessment by the FDA group responsible for reviewing the specific product.

- **Genomic Reference Library for Evaluating Whole Genome Sequencing Platforms:** According to FDA's report, it remains unclear whether genomic sequencing performed by recently-developed multiple sequencing instrumentation systems works on an individual-patient level. Moreover, there are no universally accepted criteria for setting the measurement characteristics for such instruments, nor is there agreement regarding the clinical application of the results. FDA's Office of In Vitro Diagnostics and Radiological Health (OIR) in the Center for Devices and Radiological Health (CDRH) is therefore working with the National Institute of Standards and Technology (NIST) to develop reference materials for evaluating whole genome sequencing platforms.

Regulatory Pathways and Policies:

Over the past decade, FDA has issued numerous guidance documents designed to assist industry and staff in navigating the challenges associated with the regulation of personalized medical products. In addition, FDA has engaged in significant reorganization in response to the development of personalized medicine, including the formation of new units and attempts to improve coordination within the Agency. FDA explains that the practice of personalized medicine often requires the use of two or more medical products, such as the pairing of a targeted therapy with a diagnostic test to determine whether a particular patient falls within the category of individuals who may benefit from the treatment. This pairing requires "considerable coordination" in the development of the products, as well as in their review by FDA.⁹ FDA's report notes that absent organizational changes within the Agency, targeted therapeutic products and their applicable diagnostic tests would often be (1) subject to different regulatory authorities, such as the different requirements and policies that apply to drugs versus devices; (2) regulated by different divisions within FDA, such as CDER versus CDRH; and (3) owned and manufactured by different companies. Many of FDA's recent actions have been designed to address these challenges, including, among others:

- **Establishment of a Cross-Center Working Group:** FDA has assembled a working group with representatives from CDER, CDRH, the Center for Biologics Evaluation and Research (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" with respect to personalized medicine.¹⁰
- **Significant Expansion of the CDER Genomics and Targeted Therapy Group**
- **CDRH Personalized Medicine Staff:** In 2009, the Personalized Medicine Staff was formed in CDRH to address "the opportunities and challenges associated with diagnostics used in personalized medicine."¹¹
- **CBER Personalized Medicine Team:** Similarly, CBER established 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."¹²
- **Guidance Documents:** Since at least 2005, FDA has issued multiple guidance documents that describe regulatory requirements, detail the different activities and responsibilities of FDA's medical

product centers, and otherwise articulate policies related to personalized medicine. For example, FDA issued a draft guidance in 2011 on in vitro companion diagnostic devices, which addresses the oversight of tests essential for the safe and effective use of corresponding therapeutic products. FDA's report lists more than 20 guidance documents in a table that provides the title, the year issued and a description of each document.

Product Use and Marketing:

FDA's report emphasizes the importance of ensuring that products which are only safe and effective in certain patient populations, or which require different dosage regimens in different patient populations, are labeled appropriately. Similarly, products designed to be used together should be labeled consistently. FDA has therefore focused attention on designing an effective framework for labeling personalized medical products. In addition, FDA is developing mechanisms that will enable improved postmarket evaluation of personalized medical products. According to FDA, "post-market surveillance of medical products is ever more important in an era of personalized medicine," as smaller clinical trials will result in significantly reduced pre-market exposure to the product and will therefore require greater post-market monitoring.¹³

- FDA's report notes that the Agency applies a "totality of evidence" approach in its "framework for adjusting therapeutic product labeling."¹⁴ The factors to be considered include, but are not limited to, the public health need for the product, the strength of the relevant evidence, "whether clinical variables can be identified that may help identify subgroups of patients for which testing would be most beneficial," and whether there exists a "clear clinical course of action" after pharmacogenomic information is obtained.¹⁵
- CDRH's Office of Surveillance and Biometrics (OSB) provides statistical and epidemiological support to help resolve issues associated with diagnostic studies involving personalized medicine, including post-market issues.
- FDA is engaged in a variety of efforts to improve the Agency's post-market data analysis, including "data mining of spontaneous reports" and "analysis of electronic health records from accessible, large healthcare databases."¹⁶ FDA's report explains that these efforts "will benefit all medical products, including personalized medicines."¹⁷

Other Sections of the Report

In addition to articulating FDA's perspective on personalized medicine and enumerating the many actions that the Agency has taken in this area, the report provides a brief overview of the history of personalized medicine, including early examples of personalized medical products. In addition, the report surveys different definitions of personalized medicine and highlights recent examples of personalized medicine practice.

FDA's report also features multiple short sections, set apart from the main text, which discuss "Enrichment Strategies for Clinical Trials," "The MicroArray and Sequencing Quality Control Project," "Understanding 'Silent' Mutations," and many other topics. These sections also cover "The Story of Herceptin," which is described as "the first genetically-guided therapy for the treatment of HER 2 positive metastatic breast cancers," and FDA's "Sentinel Initiative," which the Agency launched in 2008 "to create a national, integrated, electronic system...for monitoring the safety of FDA-regulated medical products."¹⁸

Conclusion

The final chapter of FDA's report declares that "[f]rom FDA's vantage point, the era of personalized medicine has clearly arrived."¹⁹ Nonetheless, FDA acknowledges that "significant challenges" remain in the development and implementation of personalized medical products. These include the currently-limited comprehension of "the intrinsic biology of disease;" the fact that many common conditions involve numerous genes and biomarkers; reluctance among clinicians to use new technologies; investment disincentives due to the possibility of lower returns from the development of drugs that target smaller populations; and an "outdated disease classification system" in which diseases are defined by a set of symptoms rather than biological causes.²⁰

The report pledges FDA's commitment to collaborate with "all key stakeholders" to facilitate the further development of personalized medicine,²¹ adding that FDA will continue to identify opportunities "to streamline regulatory processes" and will issue additional guidance to "help shepherd new products through regulatory review."²² Interested parties should continue to closely monitor FDA's actions and be prepared to offer input as the Agency's efforts continue to evolve in response to, and in support of, this "new era of medical product development."

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Endnotes

- 1 Food & Drug Admin., *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, at 2 (Oct. 2013), available at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf>.
- 2 *Id.* at 4.
- 3 *Id.* at 57.
- 4 *Id.* at 6.
- 5 *Id.*
- 6 *Id.* at 10.
- 7 *Id.* at 13.
- 8 *Id.* at 16.
- 9 *Id.* at 23.
- 10 *Id.* at 21.
- 11 *Id.* at 20.
- 12 *Id.* at 21.
- 13 *Id.* at 40.
- 14 *Id.* at 38.
- 15 *Id.*
- 16 *Id.* at 40.
- 17 *Id.*
- 18 *Id.* at 14, 40.
- 19 *Id.* at 54.
- 20 *Id.* at 4.
- 21 *Id.* at 56.
- 22 *Id.* at 57.