THE LEGAL GENOME

INTEL AND INSIGHTS INTO THE LAW AND REGULATION OF PRECISION MEDICINE
Setting the Stage - A Brief History of FDA Regulation of Precision Medicine, and a Glimpse to its Possible Future

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Precision Medicine occupies a complex space - driven by science, dependent upon third parties for financial support, and bounded by vague and emerging laws and regulations that may have outsized influence over its clinical and commercial success. The Journal of Precision Medicine provides valuable in-depth educational content and actionable business intelligence to stakeholders in this rapidly growing field, but to date there has been only ad hoc coverage of one of the most significant elements impacting Precision Medicine - namely, governmental regulation and policies and their impact (good and bad) on the players and products of this emerging medical revolution. To further round out the coverage of the Journal I have been invited to contribute a regular column covering the legal, regulatory and public policy issues affecting Precision Medicine.

In upcoming issues of the Journal I will explore in depth myriad legal and regulatory issues impacting stakeholders in Precision Medicine, including recent FDA regulatory developments, expectations for significant new policies and regulations, and specific issues impacting various segments of the Precision Medicine industry (test developers, drug manufacturers, hospitals, clinics, healthcare practitioners, and patients). I will also, with the help of my Life Sciences Industry Sector colleagues in the Precision Medicine Working Group at DLA Piper LLP, periodically explore other significant legal issues affecting the business of Precision Medicine, including intellectual property issues, competitive strategies in an increasingly crowded and fast-paced industry, patient-oriented issues such as genetic privacy and expanded access to experimental technology, as well as corporate finance and transactional issues and strategies for companies and financiers operating in this space.

For this introductory column, however, it will be useful to set the stage by providing an historical background and perspectives on the regulatory activities surrounding Precision Medicine – or as it was commonly called in the past, pharmacogenomics –
in the now-20 years since the first “rough draft” of the map of the human genome was published by the Human Genome Project. Readers will see tremendous progress reflected in the historical narrative, but also signs of significant continuing ambiguity and uncertainty as to where we will ultimately end up in terms of governmental involvement in and control of Precision Medicine in all its manifestations.

1990

Human Genome Project launched.

Late 1990s

Setting the Regulatory Stage for Precision Medicine.

As the Human Genome Project was progressing and the potential future benefits of Precision Medicine started to come into focus, FDA issued several Guidances that discuss, in very broad strokes, the role of identifying and evaluating genetic variations in the drug development process, including the following bits of rather rudimentary advice:

- “[i]dentifying metabolic differences in patient groups based on genetic polymorphism, or on other readily identifiable factors, such as age, race, and gender, can aid in interpreting results;” and “performance of phenotype or genotype determinations to identify genetically determined metabolic polymorphisms is often important in evaluating effects on enzymes with polymorphisms, notably CYP2D6 and CYP2C19.” FDA Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling (Nov. 1999)
- “[S]uch characteristics as clearance by an enzyme showing genetic polymorphism and a steep dose–response curve will make ethnic differences more likely. Conversely, a lack of metabolism or active excretion, a wide therapeutic dose range, and a flat dose response curve will make ethnic differences less likely.” ICH, Ethnic Factors In The Acceptability Of Foreign Clinical Data E5(Ri) (Feb. 1998).


Around this same period, other regulatory activity was taking place that would set the stage for further advancements in Precision Medicine, including work by the National Center for Toxicological Research into genetic polymorphisms that influence drug and carcinogen metabolism, individual cancer susceptibility, and therapeutic drug efficacy, and research by the Office of Science and Technology in FDA’s Center for Devices and Radiological Health (CDRH) into genetic polymorphisms that could be related to latex allergies, among other workstreams.

In addition, the late 1990s saw the creation of and early work from several advisory committees seeking to understand and predict the pathway for the evolving use of genetics in drug development and healthcare more generally. For example, the Department of Health and Human Services (HHS) established the Secretary’s Advisory Committee on Genetic Testing (SACGT) which was charged with advising HHS “on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests.” One of the SACGT’s early reports suggested “more genetics training and education of healthcare providers who prescribe genetic tests and use the results for clinical decision making.” 64 Fed. Reg. 67,274 (Dec. 1, 1999).

The focus of, and advice from, these early advisory committees and Guidances seem quaintly simplistic and generalized under the light of the current state of technology, but serve as a vivid and encouraging reminder of just how far the science of Precision Medicine has come in less than two decades.

June 2000

The first “rough draft” map of the human genome is announced.

April 2003

The Human Genome Project was declared complete, but in fact the Project only focused on euchromatic regions of the genome and did not attempt to sequence heterochromatic regions.

2005–2007

FDA Dips its Toes in the Water.

Recognizing the emerging potential for significant advances in Precision Medicine in light of the mapping of the human genome — although using the terms pharmacogenomics, pharmacogenetics, and personalized medicine — FDA issued two Guidances, Pharmacogenomic Data Submissions (2005), and Pharmacogenomic Data Submissions — Companion Guidance (2007). These Guidances represent the beginning of what would become an ongoing dialog between FDA and stakeholders in Precision Medicine. The 2005 Guidance, while recognizing that “the field of pharmacogenomics is currently in early developmental stages and [that its] promise has not yet been realized,” represented the first practical regulatory step toward the real-world use of Precision Medicine research and technology in the drug development and approval process.

The 2005 Guidance laid out scenarios in which the voluntary submission of pharmacogenomic
FDA approves Herceptin.

NCTR establishes the Center of Excellence for Bioinformatics, Functional Genomics, and Structural Genomics.

CDRH creates the Office of in Vitro Diagnostic Device Evaluation and Safety (OIVD).

CDER launches the Voluntary Genomic Data Submission (VGDS) Program.

NCTR reorganizes its staff, forming three new branches within the Division of Systems Biology: 1) Biomarkers and Alternative Models; 2) Innovative Safety and Technologies; and 3) Personalized Medicine.
data may be appropriate in support of an Investigational New Drug application (IND), a New Drug Application (NDA), or a Biologics License application (BLA), as well as circumstances in which submission of such data may be required. Voluntary submissions could be made for "[e]xploratory genomic data... from, for example, microarray expression profiling experiments, genotyping or single-nucleotide polymorphism (SNP) profiling experiments, or from other studies using evolving methodologies that are intended to facilitate global analysis of gene functions, but not specific claims pertaining to drug dosing, safety assessments, or effectiveness evaluations." Mandatory submission would apply primarily where the sponsor sought product labeling related to the genetic information at issue, specifically, either "informational" labeling, or use-specific labeling.

The Guidance described general informational labeling to include pharmacogenomic data “used to describe the potential for dose adjustment by drug metabolism genotype (e.g., CYP2D6*5) or to mention the possibility of a side effect of greater severity or frequency in individuals of a certain genotype or gene expression profile,” but where a specific test is not approved or is not widely available. Use-specific data included data “intended to be included in the drug labeling to choose a dose and dose schedule, to identify patients at risk, or to identify patient responders.”

The 2005 Guidance also laid some of the first regulatory groundwork for the agency’s evaluation of proposed Precision Medicine biomarkers, defining “probable valid biomarkers” and “known valid biomarkers.” Probable valid biomarkers were defined in relevant part as those “for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results,” but which is not yet accepted as “known valid” for one or more reasons, including that the data were generated by a single company, are not available for public scrutiny, or otherwise are not independently verified or conclusive. “Known valid biomarkers” were defined as those “for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results.”

The 2007 Companion Guidance provided a number of more-specific recommendations based on the agency’s experience to that date with sponsors and submissions operating under the 2005 Guidance.

**2008–2014**

**Infrastructure Building Boom for the Future Regulation of Precision Medicine.**

For a roughly 6-year period FDA and other entities of government engaged in what might be described as a frenzied effort to create a regulatory infrastructure to address the expected growth in Precision Medicine. This included the creation, or re-organization, of multiple offices, working groups, staffs, teams, and “collaboratives” within FDA, as illustrated by the following figure 1, previous page.

In addition to the efforts toward an “organizational transformation” during this time frame, FDA also issued a series of Guidelines on various topics, each of which, according to FDA, touched on, to greater or lesser degrees, issues in Precision Medicine. These Guidelines include, among others:

- ICH E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories (2008);
- Qualification Process for Drug Development Tools (2010);
- In Vitro Companion Diagnostic Devices (2011) (defining IVD companion diagnostic devices and providing information on possible premarket regulatory pathways for Precision Medicine-based therapies);
- ICH E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions (2011);
- Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling (2013) (providing recommendations on when and how genomic information can be used during drug development and regulatory review, including recommendations on general principles of study design, data collection, and data analysis in early-phase trials, and recommendations for product labeling).

In October 2014, FDA published a detailed report, Paving the Way for Personalized Medicine – FDA’s Role in a New Era of Medical Product Development, which provides a comprehensive overview of Precision Medicine from the scientific, clinical practice, and regulatory perspectives. A key section of the report, titled “FDA’s Unique Role and Responsibilities in Personalized Medicine,” serves as a line in the sand to define and preemptively defend FDA’s authority to regulate the tools and products of Precision Medicine. As described below, subsequent FDA Guidances attempt to operationalize the agency’s desire to assert specific and restrictive authority in this emerging field.

A year later, in October 2014, FDA issued the first of a series of major Guidances that have the potential to significantly transform the regulatory posture of the FDA vis a vis the major players in Precision Medicine. In the Draft Guidance, Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) (Oct. 3, 2014), FDA announced its plan to rescind its longstanding policy of exercising enforcement discretion – i.e., declining to directly regulate – with respect to LDTs, and to begin actively regulating them as in vitro diagnostic devices (IVDs). Under the FDA’s
enforcement discretion approach, LDTs were not subject to prior FDA clearance or approval before commercialization, nor were they subject to the plethora of other FDA regulatory requirements applicable to IVDs and other medical “devices” under the federal Food, Drug, and Cosmetic Act (FDCA). Rather, LDTs were only subject to oversight by the Centers for Medicare and Medicaid Services (CMS) pursuant to the Clinical Laboratories Improvement Act (CLIA). The LDT Draft Guidance generated vigorous opposition from some members of the LDT industry, and also prompted critical inquiries from members of Congress. In November 2016, the FDA announced that it would (at least temporarily) suspend efforts to issue a final version of the LDT Guidance, in consideration of comments and objections to the proposed approach.

2015–2016

The PMI and the Creep Toward a “Public Utility” Model for Precision Medicine.

In January 2015 President Obama announced the Precision Medicine Initiative (PMI) during his State of the Union Address. Declaring that “[p]recision medicine ... gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen,” the President outlined a broad series of action items, and over $200 million in funding, to facilitate the development of new Precision Medicine technologies and treatments. Under the PMI, the federal government, through NIH, FDA, the Department of Defense, and the Department of Veterans Affairs, (DVA) is systematically taking an increasingly dominant role in the basic scientific research that underpins much of Precision Medicine.

Specifically, a key element of the PMI is the National Institutes of Health’s (NIH) development of the PMI Cohort Program, which aims to collect genetic data from one million or more U.S. volunteers. The Cohort is intended to serve as a data base for multiple research projects, especially in common diseases such as diabetes, heart disease, Alzheimer’s, obesity, and mental illnesses, including depression, bipolar disorder, and schizophrenia, for which actionable genetic associations are currently limited or unavailable.

Similarly, or perhaps somewhat duplicatively, the DVA is developing the Million Veteran Program (MVP), which it describes as “a national, voluntary research program...to study how genes affect health.” The MVP seeks to “build one of the world’s largest medical databases by safely collecting blood samples and health information from one million Veteran volunteers. Data collected from MVP will be stored anonymously for research on diseases like diabetes and cancer, and military-related illnesses, such as post-traumatic stress disorder.”

In addition to the PMI Cohort and the MVP, which seek to establish massive genetic data bases, FDA has established an initiative dubbed “precisionFDA” which focuses on developing open source methodologies to analyze and develop clinical uses for such data. The precisionFDA program is intended to advance the use of Next Generation Sequencing (NGS) by “drawing upon the latest computing and storage technologies to provide an open source cloud-based space where experts can share data, ideas, and methodologies.” More than 1,600 participants have used the precisionFDA platform, including researchers, test developers, industry, academics, statisticians, and clinicians.

Combined, the PMI Cohort, the MVP, and precisionFDA represent an unprecedented level of direct government involvement in, and potential control over, basic medical research that has traditionally been the domain of the private sector (including both companies and academic institutions). While NIH and other agencies have long been involved in both funding medical research and conducting such research directly, those efforts have traditionally been more narrowly focused than what is emerging under the PMI. There are both positive and potentially negative ramifications to this emerging role. While privately-developed genetic data bases and registry programs may be available for use in Precision Medicine research, access may be restricted in order to protect the commercial value of the data and any innovations arising from such data. In contrast, by making much of the raw data and even emerging methodologies part of the public domain, more and faster innovation may be possible, but serious questions may ultimately arise over intellectual property rights and the ability to recoup investments through product pricing flexibility.

These major elements of the PMI could soon eclipse other sources of researchable data and methodology development, potentially leading to new levels of regulatory control over what would otherwise be primarily private-sector innovation. This bears close watching for its potential downstream impacts on investments in product-specific development efforts, intellectual property rights, and the commercial viability of new innovations. Essentially, the PMI appears to be positioned to move toward a “public utility model” for Precision Medicine, analogous to government control over electricity, water and natural gas providers, telecommunications spectrums, railroads and municipal transportation services (and formerly the airlines and telephone companies). Healthcare in many countries already operates in a public utility mode, and calls for such an approach in the United States have been made by many academics and politicians. These issues are worthy of a much deeper discussion and may be the subject of a future Journal column.

Beyond the governmental data bases and the precisionFDA program, FDA has in the past two years issued additional Guidance that will significantly impact participants in the Precision Medicine space. In July 2016,
FDA issued a lengthy Guidance, Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product, which “is intended to be a practical guide to assist therapeutic product sponsors and IVD sponsors in developing a therapeutic product and an accompanying IVD companion diagnostic, a process referred to as codevelopment.” This Guidance applies to situations where a drug is being specifically developed for use in conjunction with an in vitro diagnostic (IVD) genetic test, typically where the drug labeling will require the use of a test to identify appropriate patients for treatment (such as with Herceptin, the first example of a co-developed Precision Medicine drug, approved by FDA in 1998). Under the Codevelopment Guidance, the correlation of the targeted biomarker to specific aspects of a drug’s safety and/ or efficacy must be identified, and both the drug and the corresponding test must undergo clinical testing and analysis, and ultimately FDA review and approval under an NDA or BLA for the drug, and under a PMA for the diagnostic test. FDA views the codevelopment of IVD companion diagnostics and therapeutic products to be “critical to the advancement of precision medicine,” and moreover, these types of Precision Medicine solutions are likely to be the most commercially viable manifestations of Precision Medicine. Specific regulatory and commercial strategies for co-developed products under this Guidance may be the subject of a future column for the Journal.

Also in July 2016 FDA issued two draft Guidance on the use of Next-Generation Sequencing, titled Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases, and Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics. As with the LDT Draft Guidance, and the Codevelopment Guidance, these NGS Guidances are premised in significant part on increasing the FDA’s control over the tools of Precision Medicine. For example, the Standards Guidance asserts that NGS tests are a “new type” of device, presumptively Class III, which therefore would require an approved Premarket Application (PMA) prior to non-experimental clinical use. In the Clinical Validity Guidance FDA purports to reserve solely to itself the authority to determine “whether a particular NGS test has a reasonable assurance of safety and effectiveness.” While these Guidelines are couched in terms of ensuring the quality and reliability of NGS tests when used in connection with the development of potential human treatments, they do not meaningfully acknowledge the costs, burdens, and lost opportunities for medical breakthroughs that come with overly burdensome government regulation. To the extent the Guidelines are part of an overall public utility model plan for Precision Medicine, however, they may be quite effective.

The tension between regulation and innovation has existed as long as FDA has, and will (or at least should) always be part of the public policy debate concerning the role of government and the private sector in the field of medical research and product development. Where will Precision Medicine end up on the regulatory spectrum? That remains to be seen, but its success and commercial viability will certainly be affected by the answer to that question.

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