By Alexander J. Varond

As decades of experience have shown, drugs can work very differently in different individuals. Advances in genetic sequencing and genomics made early in the last decade sparked the hope that identifying certain genetic characteristics or biomarkers would yield significant advances in healthcare and give rise to a new era of personalized medicine or, as it is often defined, the practice of administering “the right drug, at the right time, at the right dose, for the right person.”

Many, both at the US Food and Drug Administration (FDA) and in industry, felt this renaissance was just around the corner. Years later, however, personalized medicine is still in its infancy, and the majority of drugs approved with companion diagnostics—tests for biomarkers that are used to support specific treatment decisions—have been limited to cancer, infectious diseases or monogenic hereditary conditions.

This article surveys recent trends and developments in personalized medicine, FDA's current stance and new challenges facing industry.

FDA Has Grown More Familiar With Personalized Medicine

In a speech earlier this year, Janet Woodcock, MD, director of FDA’s Center for Drug Evaluation and Research (CDER), announced that the era of personalized medicine had arrived. This was a significant pronouncement since the promise of personalized medicine has remained on the horizon for so long. In her speech, Woodcock encouraged industry to shift its focus from merely pushing for acceptance of personalized medicine to answering the field’s more difficult questions, such as: how to deal with rare genotypes; tackle diseases that were, in the past, grouped as one but are now being subdivided into many different groups; and reconcile the traditional way of thinking about cancers by organ with recent studies that show that different cancers share genetic traits.
Woodcock’s statement is supported by the number of breakthrough therapy designations FDA has granted to drug therapies that include companion diagnostics. In fact, approximately two-thirds of breakthrough therapy designations granted since the program’s inception include a companion diagnostic. As a reminder, these designations are reserved for therapies intended for serious or life-threatening diseases and with preliminary evidence that the therapy may be a substantial improvement over existing products. Moreover, of the 39 new molecular entities approved in 2012, one-third had genomic biomarker information in their original submissions.

This added experience has given Woodcock and other FDA officials greater confidence in personalized medicine generally, and has encouraged industry to develop strategies for targets beyond cancer, infectious diseases and monogenic hereditary conditions. Such strategies, according to Woodcock, should also include “other diseases where the biomarkers are more fuzzy.”

Uncertainty With Co-development Remains

In vitro companion diagnostics (IVDs) are critical to personalized medicine. In a 2011 draft guidance, FDA stated: “in most circumstances, if use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, the IVD companion diagnostic device and therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling.” Generally, this means FDA aims to have same-day approval of separate new drug applications (NDAs) and device applications, which typically are premarket approval applications (PMAs) but can be 510(k)s, depending upon the seriousness of the risks associated with the tests. Recent examples of such approvals include Boehringer Ingelheim’s Gilotrif (afatinib dimaleate), approved with QIAGEN’s therascreen EGFR RSQ PCR Kit (NSCLC) in 2013; and GlaxoSmithKline’s Mekinist (trametinib dimethyl sulfoxide) and Tafinlar (dabrafenib mesylate), approved with bioMérieux’s THxID-BRAF Assay Kit (melanoma) in 2013.

Importantly, however, FDA has yet to finalize its companion diagnostics policy. Thus, the agency’s rationale behind requiring simultaneous approval of companion diagnostics and directions on how to conduct studies for these tests are not always clear. Industry has been eagerly awaiting the release of two relevant guidance documents. The first guidance document addresses IVD companion diagnostics in general. Elizabeth Mansfield, PhD, director of FDA’s Personalized Medicine Staff, recently indicated the guidance was nearly complete and emphasized that it would contain few changes from the draft guidance issued in 2011. On the other hand, FDA stated it has no imminent plans to release a draft guidance document on how to prospectively co-develop a drug therapy and companion diagnostic. Agency officials explained that questions continue to arise and complicate the drafting of the guidance document.

Industry Confusion Persists Over “Laboratory-developed Test” Regulation

Some companies believe it is possible to use laboratory-developed tests (LDTs) as a shortcut around traditional companion diagnostic requirements, including quality system and facility qualification requirements. FDA, however, has repeatedly stated that LDTs used as companion diagnostics are subject to the same requirements as companion diagnostic kits. FDA’s Mansfield and agency guidance make it clear that LDTs are subject to these rules. On 10 November 2011, for example, Mansfield stated in a webcast hosted by IVD Technology that a companion diagnostic must comply with FDA’s device regulations, “even if the test that’s brought forward is a laboratory-developed test.”

In addition, on 2 June 2013, FDA Commissioner Margaret Hamburg, MD, explained that the increasing complexity and importance of LDTs have led FDA to consider expanding its regulatory oversight to all LDTs, not just companion diagnostics. FDA believes it has this regulatory authority and explained that it previously chose not to enforce these requirements. Whether FDA steps up enforcement of LDTs, as Hamburg indicated, has yet to be seen.
Novel Diagnostics May Replace Companion Diagnostics

A number of companies have been advancing next-generation sequencing (NGS), which is, in essence, a higher-throughput, more efficient means of genetic sequencing than the methods used to decode the human genome. A consequence of NGS development could be the obsolescence of companion diagnostics. Instead of ordering tests specifically developed to evaluate a patient prior to the use of a drug, genetic screens performed using NGS could be done up front, at the time of diagnosis, to identify a vast number of biomarkers. NGS could be used for a number of conditions, including cancer. For example, upon identification of a tumor, an oncologist could order a screening of the tumor’s genetic makeup, thus revealing a large number of biomarkers, including those that would have been tested by a companion diagnostic.

The idea of screening patients for a variety of biomarkers at the time of diagnosis is not a new concept. Kalydeco, a drug for cystic fibrosis that is only effective in the approximately 5% of cystic fibrosis patients with a G551D mutation, was approved without a companion diagnostic, in part, because 95% of cystic fibrosis patients are screened at the time of their diagnoses. In fact, no companion diagnostic test was specified for enrolling patients in Kalydeco’s pivotal trials.

FDA's Mansfield stated that the agency is “excited” by NGS’s potential. She also remarked that FDA is “ahead of the curve,” and that the Center for Devices and Radiological Health (CDRH) has a plan to work with the National Institute of Standards and Technology (NIST) to develop standards that can be used to assess these NGS tests. NGS, however, presents a new regulatory challenge and some unique regulatory issues, and FDA likely will clear or approve these tests on a diagnostic-by-diagnostic basis rather than approve the entire platform at one time.

New Regulatory Pathways Needed To Keep Pace With Breakthroughs

To date, there have been more than 90 requests for breakthrough therapy designations, and about a third of these have been granted. Because breakthrough therapy designation, in theory, expedites the review of the designated therapy, concern has begun to grow at FDA and in industry over whether the pace of approvals for companion diagnostics can keep up with the speed of breakthrough therapy approvals. Efforts are under way to expedite the regulatory pathway for companion diagnostics for breakthrough therapies.

During a meeting in September 2013, CDRH Director Jeffrey Shuren, MD, JD, stated that the center “already assigns companion diagnostics priority designation, ‘which means they move to the top of the queue for PMAs’ [and CDRH has tested] an ‘innovation pathway’ that provides extensive collaboration and involvement of senior management for breakthrough medical devices.” At the same meeting, Shuren voiced concern regarding CDRH’s ability to continue dedicating the extensive resources needed to keep pace with the breakthrough designation program. Thus, FDA, the National Institutes of Health (NIH) and industry are exploring ways to ensure device review can keep pace with CDER’s breakthrough therapy program, such as creating a similar breakthrough therapy designation for companion diagnostics themselves. This is an area of great interest for industry because of the time currently required for Quality System Regulation-related activities and preapproval inspections by FDA.

The “Therapeutic-First” Approach Dominates Co-development

One of the recurring issues in personalized medicine, especially in industry, is the “therapeutic-first” approach. Taking a therapeutic-first approach means pharmaceutical companies, instead of diagnostic test makers, drive the development of a targeted therapy and companion diagnostic. This strategy can be problematic because pharmaceutical companies often underestimate the time and effort required for clearance or approval of companion diagnostics. In addition, pharmaceutical companies may not fully appreciate the procedural and philosophical differences between the drug and device centers at FDA, or between drug and device companies. This lack of understanding can create delays and hold up development and approval of targeted therapies. Therefore, pharmaceutical and diagnostic companies should work as partners to coordinate the parallel tracking of
their products through CDER and CDRH approval pathways. In addition, pharmaceutical and diagnostic companies should attend at least some FDA meetings together and coordinate their interactions with both FDA centers.

**Clearer Strategies to Deal With Marker-negative Patients**

Marker-negative patients pose a major challenge in personalized medicine. By enrolling only marker-positive patients, sponsors may show greater treatment effects, enroll fewer subjects in trials and overcome concerns related to safety. However, marker-negative patients may lose out on the potential benefit of new therapies. Thus, industry has proposed an approach with two arms. The first arm would apply to tests that differentiate patients on a binary basis (e.g., have or do not have a genetic mutation). The second arm would apply to tests that measure a continuous biomarker (e.g., levels of gene expression). Table 1 summarizes the suggestions offered by industry.

### Table 1. Proposed decision matrix for studying marker-negative patients

<table>
<thead>
<tr>
<th></th>
<th>Binary biomarker</th>
<th>Continuous biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative risk-benefit in marker-negative</strong></td>
<td>None</td>
<td>Some assessment near threshold levels of biomarker</td>
</tr>
<tr>
<td><strong>No clinically meaningful benefit in marker-negative</strong></td>
<td>None or minimal</td>
<td>If the relationship between the marker and outcome is unclear, full assessment</td>
</tr>
<tr>
<td><strong>Positive risk-benefit in marker-negative (but less than in marker-positive)</strong></td>
<td>Full assessment</td>
<td>Full assessment</td>
</tr>
</tbody>
</table>

Marker-positive-only trials have certain disadvantages: they do not generate information on marker-negative patients; it is difficult to assess the diagnostic’s value; and, without good mechanistic data, trial results may be misleading.

**Payers Have Emerged As Gatekeepers To Personalized Medicine**

If personalized medicine is to reach its full potential, payers must be convinced of the necessity of such therapies and their companion diagnostics. Thus, a trend toward including government and commercial payers in the design of trials has emerged. One way payers are helping speed the adoption of personalized medicine is by working with sponsors to define meaningful endpoints. Whereas clinicians may view improvement in quality of life as an adequate endpoint, payers find such metrics relatively unhelpful. However, if trials are designed to show a reduction in lost workdays or the need to administer other therapies, payers can more easily justify reimbursement for such personalized medicines.

**New Trial Designs for Personalized Medicine**

Some have argued that the adoption of personalized medicine has been slowed by trial designs that are inefficient tests of biomarkers and targeted therapies. In response, several trials are being developed to test multiple therapies matched to different target biomarkers within the same disease, such as the I-SPY 2 trial in metastatic breast cancer and the master protocol proposed by FDA and NIH for non-small-cell lung cancer. By studying multiple therapies at the same time, these trials may prove more efficient than traditional designs because they can share a common placebo arm and permit head-to-head comparisons between therapies. Despite its many challenges, such a master protocol design may be a great step forward in accelerating the evaluation of targeted therapies for diseases or conditions with high degrees of unmet medical need; testing drug pipelines with many candidates against a variety of biomarkers; and fostering cooperation between drug companies, device companies, research institutions and FDA.
Conclusion

As with any major advance in basic science, healthcare or regulatory science, the development path for personalized medicine is uncertain; however, the last several years have shown that the path is becoming clearer and the science is beginning to yield important new therapies for patients. It is hoped that by raising these issues, regulators and sponsors will be able to identify and work through the obstacles that delay development of targeted therapies and their companion diagnostics more quickly.

References
7. Op cit. 3.
15. Op cit. 3.
16. Mansfield E. Address at the Conference on Drug/Diagnostic Co-Development for Breakthrough Therapies. 6 September 2013.
18. Twachtman G. “With Personalized Medicine, Payers Want A Role In Early Development. The Pink Sheet. 3 June 2013.

About the Author
Alexander J. Varond is an associate in the Washington, DC law firm of Hyman, Phelps & McNamara. He holds a BS in Biomedical Engineering and Management Science from University of California, San Diego, and a JD from The George Washington University Law School. Prior to law school, he worked as an engineer and operations manager in the medical device industry. Varond can be reached at averond@hpm.com.


© 2013 by the Regulatory Affairs Professionals Society. All rights reserved. Reprinted with the permission of RAPS.