Minireview

Regulatory landscapes for biomarkers and diagnostic tests: Qualification, approval, and role in clinical practice

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Impact statement

This work summarizes very recent developments in the US FDA's biomarker qualification program. Furthermore, it contrasts biomarker qualification with companion diagnostic evaluation. As such, it will be highly informative for researches considering taking a biomarker discovery farther along the road to validation.

Abstract

While the term 'biomarker' is relatively new, the concept is millennia old. However, with the introduction of new technologies to discover potential biomarkers comes the need to assess their utility and veracity for any given use. This is particularly true for the use of biomarkers to support regulatory decisions in medical product development. Hence the US Food and Drug Administration has developed processes for the qualification of biomarkers and other medical product development tools, processes that are underscored by recent legislation (i.e. the 21st Century Cures Act). In addition to these qualification processes, diagnostic tests that measure a biomarker may follow a process for regulatory decision through the processes that evaluate companion diagnostics. This mini-review provides an overview of these processes and their role in pharmaceutical development and clinical use.

Keywords: Biomarkers, diagnostic, drugs, Food and Drug Administration, qualification, validation

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> *The difference between the almost right word and the right word is really a large matter – 'tis the difference between the lightning-bug and the lightning.* – Mark Twain[1]

Biomarker. In the 40 years since the term was used to describe serum ribonuclease levels[2] it has risen in implications from the equivalent of the lightning bug to that of lightning itself. Not even concepts such as polymerase chain reaction or DNA sequencing have caught the attention of the regulatory, medical product, and legislative community so as to merit inclusion in two public laws.[3,4] The word 'biomarker' itself has had different meanings in different contexts, and as such has merited a committee of scientists to develop a definition of it and related terms[5]; even here the discussion is sufficiently animated that this resource is viewed as subject to ongoing refinement. Biomarkers have an importance that is not going away anytime soon.

Of course, it has long been noted that while the word is relatively new, 'biomarkers' are not.[6] The Edwin Smith Papyrus describes Egyptian medical practice ca. 1500 BCE wherein the degree of injury is assessed by monitoring the pulse.[7] In 1732, Stephen Hales recorded blood pressure using a probe introduced into the aorta of a horse,[8] presaging the critical use of blood pressure measurements today. And the analysis of blood and its components began in the mid-18th century,[9] evolving to the point where multiple 'biomarkers' are routinely measured in standard clinical chemistry, facilitating diagnosis, for example, of liver damage.[10] So, biomarkers have long been an integral part of medical practice in diagnosing disease and injury, guiding and monitoring treatment and intervention, and providing prognosis for a patient's future condition.

However, with the explosion of molecular tools over the last 40 years the number of molecules and/or measurements claimed as 'biomarkers' has also exploded. The question then becomes as to the process to go from the biomarker 'claim' (i.e. discovery) to a level of confidence that the biomarker measurement can reliably serve a purpose, i.e. support a decision. When the decision is one impacting human health, either in clinical diagnosis and treatment decisions, or in evaluating the risk of

environmental chemicals, or in supporting the use of a novel treatment as 'safe and effective,' this process must be seriously considered. Hence the concepts of 'validation' and/or 'qualification' have been discussed extensively – to date over 2400 review publications – and are associated with the terms 'biomarker' and 'validation,' dating back to Schulte's proposals in 1989[11]; several books cover this topic as well.[12–14]

A particularly contentious application of biomarkers, though, is their use to support regulatory decisions in pharmaceutical product development, and especially in clinical trials. With the economic challenges of the current drug development process[15] the hope has been that biomarkers may be used to improve the success rate of clinical trials and/or shorten the time frame of such trials. The latter application, i.e. the use of 'surrogate endpoints' (for a thorough definition the reader should consult the BEST resource[5]) is particularly contentious, for along with their clear conceptual benefit, there are several cautionary notes as to their use.[16–20] Nonetheless, the importance of defining a validation/qualification process was such that it was the top of the Food and Drug Administration (FDA)'s Critical Path Opportunities List published in 2006.[21] This document explicitly stated 'The process and criteria for qualifying biomarkers for use in product development should be mapped' and led to subsequent discussions as to the nature of such a process.[22,23]

The first approach to define such a process was a joint effort of the FDA, European Medicines Agency (EMA), and the Critical Path Institute, a non-profit organization that coordinated a consortium of industry and academic scientists. That consortium, the Predictive Safety Testing Consortium, had assembled a large dataset on the performance of seven novel biomarkers of drug-induced kidney injury, and in discussions with the FDA and EMA created both a model submission and a review process.[24] This process led to a decision by both FDA and EMA as to the suitability, i.e. qualification, of these biomarkers for use in submissions to these agencies.[25–27] Other biomarker qualifications followed.[28–30] However, it should be noted that the data presented allowed qualification for only nonclinical use, and key questions as to the evidence needed (evidentiary standards) for qualifying biomarker for a clinical use remained unanswered.

In the seven years since that first 'biomarker qualification' the process has evolved and, it should be emphasized, continues to evolve. In addition to addressing biomarkers, the process has been expanded to cover additional types of 'Drug Development Tools' (DDTs) and has been described in publications[30,31] and in a Guidance for Industry[32] from the FDA Center for Drug Evaluation and Research (CDER). A parallel process for qualifying 'Medical Device Development Tools' (MDDTs) is described in a Guidance[33] from the FDA Center for Devices and Radiological Health (CDRH). What is clear and concordant in these documents is the definition of 'qualification': a conclusion (CDER) or expectation (CDRH) that within the specified context of use (COU), the tool (CDER) or results of an assessment that uses the tool (CDRH) can be relied upon to support drug (CDER) or medical device (CDRH) development and regulatory review (CDER) or decision-making (CDRH). Further underscoring the importance of biomarker qualification is its mention in the '21st Century Cures Act.'[3] Section 3011 explicitly echoes and expands upon concepts in the FDA documents. In doing so, it puts in public discourse the issues and challenges of this process.

Key to any qualification is a careful description of 'context of use.' This COU 'is a complete and precise statement that describes the appropriate use of the DDT and how the qualified DDT is applied in drug development and regulatory review.'[32] A similar emphasis and description is echoed in the CDRH Guidance document.[33] The 21st Century Cures Act[3] describes COU as 'the circumstances under which the drug development tool is to be used in drug development and regulatory review.' COU also drives the concept of 'fit for purpose' for both a biomarker and the analytical technology used to measure it.[34] Importantly, the COU defines what standards of evidence would be required for qualification of the tool and validation of the analytical method. It goes without saying that the greater the risk to human health of an incorrect decision based on the use of a biomarker, the greater the level of evidence required for qualifying it for that COU.

Both the CDER and CDRH qualification programs recognize three types of tools: biomarkers/biomarker tests, clinical outcome assessments (COAs), and animal/nonclinical models. Both programs draw the distinction between an 'objective' biomarker (measurement) and the COA which has human input into its measurement. COAs include patient-reported outcome measures and issues with these are discussed in a separate Guidance.[35] It is of note that for the last tool type, the CDRH program currently encompasses *in vitro* models as well as materials to evaluate imaging devices.

It is worth noting that per their respective documents these two programs have procedural differences, reflective of their Center's different missions. The CDER qualification process consists of three stages: (1) an initiation stage, (2) a consultation and advice stage, and (3) a review stage for the qualification determination. These stages are marked, respectively, by three submitting sponsor documents: a Letter of Intent (LOI), an Initial Briefing Package, and a Final Qualification Package. These three stages are echoed in the 21st Century Cures Act, albeit described as (1) a LOI, (2) a qualification plan, and (3) a qualification package for review.[3] Per the CDER document the middle stage involves multiple interactions between the submitter and the agency. The CDRH qualification process consists of four phases: (1) a proposal phase, (2) an optional 'incubator' phase, (3) an optional prequalification phase, and (4) a qualification phase. The second and third phases may be viewed as analogous to the second stages of the CDER process, but the descriptions of these phases or stages differ somewhat in the two documents. Both processes note that proposals may be prioritized. Both Guidance documents outline the components of packages to be submitted. On the other hand, in addition to emphasizing the importance of the COU, the CDRH Guidance proposes that the package explicitly address 'the strength of available evidence

supporting the MDDT (including tool validity and plausibility); and an assessment of the advantages and disadvantages of relying on assessments using the MDDT within the specified context of use.' Both the CDER Guidance and the 21st Century Cures Act note the importance of evidence sufficient to support a COU, without explicitly requiring such a section in the submission. Finally, the CDRH process notes that the composition of a Qualification Review Team 'may include FDA as well as external expertise, where appropriate,' a concept ('Engagement of External Experts') also applicable to DDT qualification as described in the 21st Century Cures Act.

All that being said, it is also important to note that the objective of the CDER DDT Qualification Process described above is to 'establish the biomarker for use in multiple development programs'[30] and this point, and the range of qualified DDT use is reiterated in the 21st Century Cures Act.[3] On the other hand, a biomarker may be used in a single drug development program without going through this process. Rather, the sponsor communicates directly with the review division responsible for its program and through this dialog establishes the data required to support the use of the biomarker in that program. The information on that biomarker and its use would then be documented in the product label.

Similarly, the CDRH document 'does not discuss the review of tools that are submitted in individual premarket regulatory submissions for use with a particular medical device.' It also notes that some of the Medical Device Drug Development Tools 'may meet the definition of a device in section 201(h) of the FD&C [Food, Drug, and Cosmetic] Act' and further discusses regulatory considerations for use of an MDDT in clinical trials.

Finally, a cautionary note must be emphasized – that these concepts and process are still evolving and the reader is encouraged to visit the appropriate FDA internet sites for DDT Qualification and MDDT Qualification.

Regulatory paths in companion diagnostic evaluation and approval

'An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.'[36] Regulatory pathways for companion diagnostics have developed in close association with the identification through genetic testing of enrichment biomarkers for selection of specific patient subpopulations. The biomarkers in this case are mostly enrichment biomarkers, and their tests are approved concurrently with therapies developed for the specific patient subpopulations selected by the enrichment biomarkers. The Center for Drugs at the FDA issued in 2012 an enrichment guidance[37] which covers the application of enrichment biomarkers in drug development.

This enrichment guidance is essential to understand the pathway to companion diagnostic approval. A rationale for a biomarker which could be used as a companion diagnostic is possible if the biomarker is a candidate as an effective tool for patient selection to receive targeted therapies. The confirmation of this patient selection marker is obtained in the pivotal study for the therapy. The value of a patient selection marker, therefore, is closely linked to the efficacy of the therapy for which it is used for patient selection.

A major regulatory question which was addressed by the final Companion Diagnostic Guidance[36] was whether an independent clinical utility claim could be made – and should be proven in a pivotal study for a therapy – for a companion diagnostic. Analytical and clinical validity are expected for companion diagnostics, but the question remains as to whether their clinical utility claims can be defined independently from those of the therapy for which they were used as patient selection criteria.

Initial drafts for the Companion Diagnostic Guidance were jointly written by CDER and CDRH around 2005–2006. Proposals at the time[38] were being discussed regarding companion diagnostics with relatively modest development and regulatory review burdens by diagnostic companies and regulatory reviewers at CDRH. If only analytical and clinical validity need to be shown for a companion diagnostic, its development costs are independent of those for targeted therapies, and its regulatory reviews only require assessment of how accurate the measurement is for a marker which has an independent compelling biological value.

Guidance documents in the development of companion diagnostics

In vitro diagnostics are regulated by the FDA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and will soon also have a formal regulatory framework in Europe.[39] When novel targeted therapies are approved by the FDA, EMA, and PMDA, the companion diagnostic test required to select patients who will receive the therapy is considered for approval concurrently with the therapy. Guidance documents for the submission and review of companion diagnostic products have been developed over the past decade.

The FDA Pharmacogenomics Guidance[40] suggested in 2005 the need for a second document which would cover companion diagnostics. Regulatory documents drafted in this area cover not only the regulatory review process for these companion diagnostic products, but also a continuous expansion of the regulatory space claimed by the FDA CDRH. These are the key guidance documents in the development of companion diagnostics:

2007: FDA Pharmacogenetic Tests and Genetic Tests for Heritable Markers[41]

Initial, high-level guidance summarizing information needed for regulatory review and approval of pharmacogenetic and genetic tests for heritable markers.

2007: FDA In Vitro Diagnostic Multivariate Index Assays[42]

This was a draft guidance which was never issued in final text. In Vitro Diagnostic Multivariate Index Assays (IVDMIAs) are tests such as those which require microarrays where an algorithm translates the results from multiple variables into a clinically actionable outcome.

In oncology, an example of an IVDMIA is the OncotypeDx® test from Genomic Health. This guidance requested the regulation by the FDA (in addition to Clinical Laboratory Improvement Amendments (CLIA)) of tests which made use of these algorithms. This guidance was the initial attempt for regulation by the FDA of Laboratory Developed Tests (LDTs).

2011 (draft) 2013 (final): FDA Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only[43]

Frequently Asked Questions (FAQs) in this guidance discuss limits to the use of Research Use Only or Investigational Use Only diagnostic tests in providing clinically actionable data. FAQs B5 and B8 in this guidance specifically addressed the interest of the FDA to regulate these products. This Guidance on the regulation of LDTs[44] was issued in 2014. No final version of this Guidance is anticipated in the near future. A Discussion Paper was published in 2017[45] updating the approach for LDTs at CDRH, and the issue of LDT regulation remains an open – and contentious[46] – issue for the application of companion diagnostics.

2011 (draft) – 2014 (final): FDA In Vitro Companion Diagnostic Devices[36]

The Companion Diagnostic Guidance suggested by the Pharmacogenomics Guidance in 2005 was finally issued as a draft in 2011. Answers to three key product development questions are covered by this guidance:

- Whose burden is it to show the clinical utility of a companion diagnostics? What determines the clinical utility of a companion diagnostic? *Answer:* the developer of the therapeutic product with data from pivotal studies for therapeutic products requiring a companion diagnostic.
- What determines that a companion diagnostic will require a premarket approval application versus A 510(k)? *Answer:* this is a case-by-case decision for CDRH, closely linked to the risk level for each test.
- What will be the goal of a Phase 3 trial for a therapeutic product which requires a companion diagnostic? *Answer:* to prove that both the therapeutic product as well as the companion diagnostic independently show clinical utility.

Over the course of the past decade, an independent clinical utility concept was developed by CDRH for an independent companion diagnostic clinical utility to be shown in the pivotal study for the targeted therapy. This independent clinical utility claim shifts the financial burden for companion diagnostic development primarily to companies testing the therapeutic product, as major investments are made by these companies in the clinical development of companion diagnostics. It has also crippled the development of follow-on companion diagnostics, since regulatory approval for these requires not only analytical and clinical validity, but also a study with clinical samples (ideally from the original pivotal study) to confirm clinical utility.

The outcome of these strategies has led to ambiguity for the regulatory status of day-to-day testing of companion diagnostics. Companion diagnostic products are initially approved by CDRH concurrently with their targeted therapies approved by CDER. However, clinical (CLIA) laboratories around the US have for the most part forgone the FDA-approved tests and instead run LDT companion diagnostic tests. CLIA labs prefer the development of LDTs for structural, financial, and other reasons,[47] beyond the scope of this review. From one perspective, this approach with a goal of greater availability, lower costs, and market competition for diagnostic tests is desirable for patients, physicians, and care-givers. However, the lack of an effective internal and/or external reference framework – regulatory or not – to assess the accuracy and reproducibility of LDT tests is a major challenge for the development of accurate and reproducible clinical testing in the US and warrants a discussion among all stakeholders. In the meantime, FDA-approved companion diagnostic tests will continue to be required for targeted drug approvals, while the practice of medicine for targeted drug patient selection will not require them.

There are also some unexpected consequences for the current regulatory pathways for companion diagnostics. While the FDA has not yet developed a guidance for targeted cancer therapeutic patient selection with next-generation sequencing (onco-NGS) panels, the FDA white paper and workshop of February 2016[48] laid out the expected label claims for a targeted onco-NGS panels. These include a section on the follow-on companion diagnostics (and corresponding clinical utility claims) and a section on all variants with their analytical and clinical validity claims. The white paper's section on follow-on companion diagnostics still leaves open issues that other companion diagnostic tests have: after the launch of the therapeutic product, most testing for the companion diagnostic will not be carried out with FDA-approved tests. It is possible that this may be avoided for sufficiently complex NGS companion diagnostic tests, such as those which require variant signatures across multiple genes. Thus, FDA-approved onco-NGS panels may still succeed in the marketplace for tests whose complexity cannot justify their internal development in individual CLIA labs.

Summary

The regulatory framework for companion diagnostics has been developed at the FDA over the past decade. It has accomplished the successful development of precision medicine in the US with accurate and reproducible tests at product launch. It is challenged, however, by lack of a reference framework for CLIA lab testing which could support market selection of accurate and reproducible tests to identify patients for targeted therapies. This problem may or may not require additional regulation, but it will certainly require a reference framework for third-party payors to assess the accuracy and reproducibility of these tests.

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