Chapter 10
The Critical Path to Successful Biomarker Development

Key Topics

- Challenges with Biomarker development
- Biomarker methods development and validation
- Biomarkers and surrogate markers
- Role of the Food and Drug Administration (FDA) in biomarker development
- The FDA’s Critical Path Initiative
- The FDA’s Drug Development Tools
- Evaluating clinical utility of biomarkers
- Biomarker adoption into clinical practice

Key Points

- The paucity of cancer biomarker products in the clinic is partly attributable to the inherent challenges in biomarker development. These challenges include tumor biologic variables, pre-analytical and analytical variables, study design issues, statistical and bioinformatics issues, and stakeholder factors. All these factors often lead to discovery of putative biomarkers that fail large-scale validation studies and hence unqualified for regulatory approval.
- To be clinically valuable, a biomarker should possess strong analytical method validation and meet the rigorous qualification standards for safety and effectiveness.
- Regulatory bodies, including the FDA, have developed programs to facilitate accelerated product development. These collaborative efforts among the FDA, industry, academia, stakeholders, and patient advocacy groups (continued)
10.1 Introduction

Cancer biomarkers are important integral part of cancer research and oncologic practice. First, they can serve as laboratory tools for making clinical decisions such as cancer risk predictions, diagnosis, prognosis, treatment predictions, and monitoring for therapy response and disease relapse. However, to be even of much value, a clinical biomarker should be applied to diseases that have treatment interventional agents. Alternatively, a useful biomarker should have biologic implications in disease pathogenesis such that, in the absence of a therapeutic agent, targets can be identified for new drug development. Second, biomarkers are useful in pharmaceutical drug development. Indeed, 30–50% of all biomarkers are coupled to drug development. Many drug development programs rely on model systems such as animal and cell lines, as well as clinical judgments. While these tools and metrics are useful in the drug development process, the adoption and use of biomarkers has resulted in cost reductions and accelerated development timelines. Specifically, prognostic, predictive, and pharmacodynamic biomarkers play unique roles that not only facilitate the development process but also can identify unique patient groups for targeted drug development. A prognostic biomarker may be used to select a group of patients who are more likely to have aggressive disease for a specific drug development program. In this situation, the ability to demonstrate safety and reductions in case fatalities among this cohort may enhance the drug approval process. A predictive biomarker may also be used to enrich for patients who are more likely to respond to a drug in a specific manner, to be included in a drug development program. Unique gene mutations, for instance, may confer sensitivity or resistance to a specific interventional agent. Finally, pharmacodynamic biomarkers are adept to early identification of drug toxicities prior to clinical evidence of such events. These pharmacodynamic biomarkers are therefore useful in phase II clinical trials to help establish safety and dose standards for phase III studies. Thus, the entire drug development process benefits from valid biomarkers.

To be useful, however, cancer biomarkers must be validated and qualified to meet safety and effectiveness standards within the context of use. Unfortunately there is a disconnection between the plethoric number of biomarkers discovered and those that end up as clinical products, or in use for drug development. This paucity of biomarker product development is partly due to the real challenges faced by the industry. Multiple factors impede the biomarker development process. Various issues including study design, pre-analytical and analytical issues (e.g., sample types and adopted technologies), as well as inherent issues with tumor biology, such as heterogeneous molecular cellular types in the primary cancer,
and clonal diversity due to selection pressures from the metastatic cascade and/or therapy. To enhance the chances for success therefore, biomarker development ought to be a collaborative process. Patients, their clinicians, biomarker scientists, biostatisticians and bioinformaticians, industry sponsors, stakeholders, and members from regulatory agencies should all be part of the biomarker development team from start to finish.

Biomedical devices and other products intended for public consumption must meet the claimed safety and effectiveness standards of the US Food and Drug Administration (FDA), because part of the mandate of the FDA is to ensure public safety. However, the organization is also tasked with improving public health, which includes accelerating the production and delivery of safe, healthy, and cost-effective products to the public. Hence, when the FDA recognized a decline in biomedical or biologic product submissions, and biologic license applications (BLAs), the organization performed a 10-year (1993–2003) retrospective review of biomedical research funding (from the NIH budget and pharmaceutical companies research and development investment) and new molecular entities submissions and BLAs. It uncovered that the increased research expenditure did not match product development. This observation prompted the FDA to establish the Critical Path Initiative (CPI) to help reverse this trend. Additionally, the FDA developed guidelines for drug development tools (DDTs) intended for drug development programs. These guidelines provide a forum for interactions between drug developers and the FDA’s Center for Drug Evaluation and Research (CDER), aimed at bridging the previous barrier between the FDA and product developers. This initiative serves to accelerate the process of regulatory clearance of products for safe clinical applications. Additionally, this collaborative effort ensures confidence in CDER reviewers that the developed DDT meets the specific context of use (COU) and hence has potential utility.

Another challenge in product success is efficient ethical marketing. Product acceptance by the public is dependent on a number of factors. Product quality (safety and effectiveness) and approval by the FDA ensures public trust and comforts insurance companies and healthcare providers. It behooves every product developer to therefore heed the call by the FDA in collaborative product development.

10.2 Biomarker Development Challenges

Established are the enormous challenges that biomarker developers encounter. These difficulties translate into the virtual lack of clinical translation of the numerous biomarkers being discovered. In addition to the concerns discussed in Sect. 3.3.4, biomarker development also faces other issues such as tumor heterogeneity, applicable biomarker clinical utility, logistics, regulatory oversight, commercialization process, and eventual adoption (Table 10.1). Thus, the development and approval of biomarkers for clinical applications encounters comparable hurdles to
those associated with the developmental process of a new drug. Here are some challenges and pertinent issues worthy of note in the biomarker development process:

- Biomarkers may be easy to develop if they give a positive measurable signal. Even then, very few such biomarkers demonstrate uniquely elevated levels in any particular cancer type. Unfortunately, many cancer-associated gene expression changes involve molecular pathways also used for normal cell functions, such as proliferation, growth, differentiation, apoptosis, survival, and immune functions. Except for a few biomarkers such as PCA3 and TMPSS2-ERG, finding a cancer-specific biomarker is almost impossible.

- Even when a biomarker appears to be associated with a particular cancer, it tends to be deregulated in several other different types of cancer, making its association with cancer from any specific tissue type unlikely. In many of these scenarios, the biomarkers often lack screening or diagnostic utility and are often reserved for other clinical uses following cancer diagnosis. These are issues faced by several traditional cancer biomarkers in clinical practice (e.g., CA125).

- Expressed transcripts do not necessarily correlate with protein levels, which are the preferred disease biomarkers. Posttranscriptional and posttranslational modifications account in part for this failure in correlation.

- A screening or diagnostic biomarker is considered relevant when therapy for the condition is already in place, and/or its role is established in the biologic process of the cancer. The functional role of the biomarker could then help with the
understanding of tumor biologic mechanisms with possible development of targeted therapies.

- Secreted or cell surface-bound biomarkers are more adept to clinical translation. Thus, biomarkers that are not released into body fluids or attached to cell surface may have limited applications and hence less attractive for developers.

- Genome-wide association studies (GWAS) have been very informative in uncovering risk alleles for diseases. However, the predictions of increased cancer risk based on such biomarkers are often not too relevant to the general population. SNPs in familial cancer syndromes such as VHL, TP53, and BRCA have proven very useful, but the associated cancers afflict only a small percentage of the population.

- Genomic alterations are emerging as useful players in cancer biology and hence of biomarker potential. However, even cancers of the same histology demonstrate heterogeneous genomic changes. For cancers whereby a single gene has been identified as relevant, very few show mutation “hotspots.” Mostly, these mutations are scattered across the gene, which necessitates the development of cost-effective technologies for mutation scanning. Moreover, no single gene is altered in all (100%) of any cancer type, suggesting the need to develop panel assays to cover the vast majority.

- To overcome the issues of overdiagnosis and overtreatment and hence reduce morbidity and healthcare costs, an effective screening biomarker should have prognostic predictions as well. Being able to differentiate at the very beginning between indolent and aggressive cancers will be the “Holy Grail” cancer biomarker. But, because of the intricate and adaptive pathways employed for malignant progression, it is almost an utopian endeavor finding such a biomarker. Tumor progression may also depend on cancer-cell interaction with the surrounding stroma, including immune cells. While heavily marketed, such issues are identified for the PSA test. A European randomized study of screening for prostate cancer, for instance, found that 48 PSA screened detection of men have to undergo surgery to save one man’s life 9 years later [1].

- The presence of cancer stem cells poses a unique challenge to biomarker development. Many biomarkers are developed for the bulk of the cancer tissue or cells. Any signal from the negligible cancer stem cell niche is overshadowed. Thus, biomarkers that miss the stem cell population, which are important for cancer metastasis, cannot therefore accurately predict disease course.

- Many tumors grow slowly such that it takes several years from initiation to metastasis. High-throughput sequencing data suggest it may take 15–20 years for pancreatic cancer to initiate and metastasize [2]. Moreover, at the time of metastasis, cancers tend to be large, and such high tumor burden is often associated with worse outcome. To reduce mortalities, cancer must be diagnosed early to enable curative interventions. Circulating biomarkers of early cancer are often diluted, such that sensitive and accurate technologies are needed for clinical application.

- The lack of high-grade reagents also hampers the development of some biomarker technologies. For example, some immunoassays, such as been adopted in
microfluidics and nanodetection technologies, require very pure, well-characterized, and highly specific monoclonal antibodies, which are often lacking.

- Nucleic acid detection technologies are becoming common. However, many such assays (e.g., PCA3, Oncotype DX) require special sample handling, which limits their use to a few specialized facilities. Transferring these technologies onto a lab-on-a chip platform for point-of-care utility will enhance their global presence.

- Developing a biomarker test for clinical translation requires high performance characteristics in assay accuracy and reproducibility, to satisfy the requirements for clinical laboratory improvement amendment (CLIA) regulatory approval. The stringency required by the FDA is even much higher. Companies need to demonstrate assay safety, effectiveness, and performance that affect clinical decision-making in the realm of evidence-based medicine. Obtaining these metrics require large multicenter randomized clinical trials. Designing, conducting, and funding such studies (which often fail to demonstrate the desired high accuracy) are a formidable and costly undertaking.

- A predictive biomarker may fail as a valid biomarker due to flawed clinically design. For example, evaluating the predictive performance of the biomarker in a setting of combined use of two agents from different manufacturers may fail to reveal the biomarker’s authentic ability to be predictive for one of the agents.

- Flawed biomarker discovery studies and prototype development affect subsequent validation efforts. The many possible factors in this situation include:
  - The use of inappropriate samples (e.g., using advanced tumor stage samples to discover early-stage biomarkers).
  - Not defining the clinical utility question prior to conducting studies.
  - Poor statistical power or analysis and often the use of nonstandard in-house proprietary algorithms that later fail simple statistical scrutiny.
  - Developing prognostic biomarkers with samples from patients who have already received some form of treatment.
  - Establishing prognostic biomarkers by comparing people with treatment failures or death to those without relapse years after therapy.

- Common confounding issues that need early consideration in biomarker development, but often neglected, are who is the intended target population? When should testing begin or be performed? How often should the test be performed? Does the test have the same performance metrics across different ethnicities and geographic areas? How should the test result be interpreted and used? How are the end users (clinicians and patients) going to be educated on the clinical utility of the test? Clinician education on the assay performance and meaning is important in ensuring accurate test interpretation. How is the test result to be communicated to patients, and how should patients subsequently be managed?

- Development of valid biomarkers requires teamwork. At the beginning, a multidisciplinary team needs to be assembled. At its minimum, this should comprise of patients, clinicians, epidemiologists, biomarker experts, engineers,
industry partners, possibly academia, and regulatory agencies such as members of the FDA biomarker qualification program.

10.3 Biomarker Method Development and Evaluation

Biomarkers are used in two broad applications: (1) as laboratory assays to help in clinical decision-making such as disease diagnosis and prognosis and (2) in drug co-development. The regulatory requirements for these two applications are identical but controlled by two bodies. The former utility falls under the requirements of the Clinical and Laboratory Standards Institute (CLSI) guidelines for CLIA certification. For use in co-development of a drug, the biomarker must meet the standards of the FDA. To help address the biomarker validation concerns, and the stringency required for safe applications in drug development, the American Association of Pharmaceutical Sciences (AAPS) and the Clinical Ligand Assay Society (CLAS) convened a joint meeting in 2003 to stratify and make recommendations for biomarker method validation. Additionally, the FDA developed guidelines for qualification process for drug development tools, as well as the biomarker qualification program, all aimed at helping sponsors, industry, academia, and other stakeholders to accelerate the pace of safe and effective drug development.

It should be noted that biomarker analytical method validation is different from biomarker qualification. The analytical method validation is the process of assessing the performance characteristics of a given biomarker assay. This requires stringent bioanalytical method development, taking into account all performance metrics. Clinical qualification of a biomarker is the evidence and statistical process that connect the biologic, pathologic, and clinical endpoints of the biomarker to drug effect.

10.3.1 Fit-for-Purpose Approach to Biomarker Method Validation

Biomarkers are integral part of the drug development process, from discovery, prototype, to product development for commercialization. Depending on the type of biomarker (prognostic, predictive, or pharmacodynamic), the intended or defined utility may be different. Biomarker utility may also change from the initial discovery phase to the more advanced validation and qualification stages. Thus, biomarkers may be applied early for selection of potential drug candidates for subsequent development. Such utility may be more economical than some model systems in regard to resources involved. Given the diverse uses of biomarkers in the drug development process, Lee et al. proposed the fit-for-purpose approach to biomarker methods development and validation, when used in co-development of
a drug [3]. This strategy of biomarker method validation relaxes the stringency at the initial exploratory phases of drug development and increases the rigor of method validation as the drug progresses to advanced stages and toward eventual approval. One advantage of this approach is economics, because it enables resource conservation at the exploratory stages of biomarker methods development. The intended use or purpose of the biomarker method validation data determines the stringency or rigor of the bioanalytical methods used for data generation, and this increases as critical decisions on drug development are being made.

The nature of the bioanalytical method of the assay used for validating the biomarker also needs consideration. Lee et al. recognized four categories of the assay methods, namely, definitive quantitative, relative quantitative, quasi-quantitative, and qualitative.

- **Definitive quantitative assay** provides absolute quantitative values using physicochemical or biochemical methods such as mass spectrometry.
- **Relative quantitative assay** relies on the use of response-concentration calibration function, such as in immunoassays (ELISA).
- **Quasi-quantitative assay** does not use calibration standards, but rather a continuous response, whereby assay results depend on a characteristic of the test sample. Examples are antibody titers and qRT-PCR.
- **In qualitative assay**, the data generated does not reflect on the mount in the analyte. Data output can be nominal (yes or no) or ordinal using discrete scoring system as in immunohistochemistry.

The fit-for purpose approach also identifies four interrelated levels of assay validation, namely, pre-analytical considerations, exploratory method validation, advanced method validation, and in-study validation with sample analysis acceptance criteria. Detailed recommendations are provided for consideration in the execution of each level of the biomarker methods development [3].

- **Pre-analytical considerations**: This is a planning stage whereby the study design in regard to the intended use of the biomarker must be considered. A study plan should be crafted to include defined objectives, intended target population, sample types (body fluids and tissues), sample collection, and bioanalytical methods to use for initial assay design.
- **Exploratory method validation**: This is the stage of initial quantitative method development and characterization of its basic performance in regard to a number of parameters including accuracy, precision, analytical sensitivity, biomarker normal levels (baseline range in healthy individuals), biomarker stability, assay dynamic range, as well as statistical consideration for advanced validation for its intended purpose.
- **Advanced method validation**: This level is an extension of the exploratory validation stage with increased levels of biomarker characterization. The analytical rigor is increased and tailored to decisions on intended purpose, while considering important issues of safety, efficacy, pharmacodynamics, and
surrogacy. The formal acceptance performance of the biomarker for its intended use in drug development is established.

- In-study validation with sample analysis acceptance criteria: While in use for its intended purpose in drug development, the biomarker should continue to perform optimally as established. This in-study validation therefore ensures continuous robust assay performance as expected or defined for each study run. These validation runs also help with the establishment of definite acceptance criteria for the assay throughout the drug development process.

10.4 Biomarkers and Surrogate Endpoints

In clinical trials, an outcome measure is needed for prediction of drug effect on the body in regard to safety and effectiveness. The clinical endpoint, which is a characteristic that reflects on how a patient feels and functions or how a disease progresses in terms of survival, death, or relapse, is the ideal measure of the effect of an intervention (e.g., drug treatment). However, relying on clinical endpoint such as death, disease relapse, or the appearance of a sign or symptom in a clinical trial may be unethical or less effective approach to the drug development process. Therefore a biomarker can be used as a substitute or stand-in for the expected clinical endpoint, and such biomarkers are referred to as surrogate endpoints or surrogate markers. Biomarkers used as surrogate endpoints undergo very stringent method validation and qualification processes and are usually well characterized and evaluated to possess the desired clinical relevance and as substitutes. Even then, such valid surrogate endpoints can be misleading or poor predictors of clinical outcomes and hence can adversely affect the drug development process. In view of these shortcomings, the FDA permits provisional approvals that are dependent on surrogate endpoint predictions of safety and effectiveness. However, this acceptance usually requires a follow-up phase IV study or data collection to show a correlation between the actual clinical and surrogate endpoints.

10.5 FDA and Biomarker Development

The FDA is a federal agency with a number of mandates including:

- To promote and protect public health. This mission includes ensuring the delivery of safe, secure, and effective treatments to the public.
- To be responsible for enhancing public health. This is achieved through leadership in ensuring the rapid development of innovations to accelerate the process of making medicines safe, effective, and affordable to the public.
- To help provide information on accurate and scientifically sound evidence on available medications to the public.
Over the past couple of decades, the FDA recognized a problematic trend concerning the development of prototypes, devices, and biologics and thus provides solutions to mitigate them. Analysis of a decade trend (1993–2003) revealed that while the spending on biomedical research has been on the rise, submissions of drugs and biologic products to the FDA had been on the decline. In 2004, the Critical Path Initiative (CPI) report was issued to address this eminent crisis, which not only could stall innovation but also could contribute to increase healthcare cost. The report centers on three important issues needed to accelerate basic science discoveries to market:

- It aimed at identifying the problem in terms of what contributed to this observed pattern, so as to offer actionable solutions.
- Provides some efforts made by the FDA to improve the critical path and offers opportunities for future progress in product development for approval.
- Importantly, it calls for collaborative efforts among academia, industry, and the agency (FDA) to scope out the problems and hence offer effective solution in terms of how to create the needed path forward for success.

10.6 The Problem with Successful Biomarker Development

The considerable funding of basic science research, including the expansive biomedical discoveries after sequencing of the human genome, has resulted in several discoveries of biologics (biomarkers) that putatively should translate into better disease prevention, early diagnosis, treatments, and possible cures for many serious afflictions, including cancer. The progress from “bench-to-bedside” has unfortunately been lagging behind this rapid discovery phase. Translating the biomedical discoveries into effective safe and affordable medical products for public use has been dismal. Continuing on this trajectory without actions will lead eventually to stagnation or decline in biomedical innovations with associated increases in healthcare cost. Compounding this problem will be the proclamation by many companies of having developed valid biomarkers for translation without any outside oversight. Overseeing all these issues will further burden the efforts of the FDA.

The FDA recognized the disconnection between basic science discoveries and the applied sciences needed for medical product development. The focus of research has heavily been on developing cutting-edge technologies for discovery research. Thus, the accelerating technologies for discoveries outpaced those required for product development.

A major issue with biomarker or device development is performance, which is a measure of product safety and effectiveness. Thus, to accelerate biomedical product development for commercialization, the FDA recognized the need for new tools to cost-effectively demonstrate product safety and effectiveness. The challenging issues with biomarker validation at the clinical trial phases are obvious. Many
prototype and biologics fail to reach the desired effectiveness of safety standards for public use. The FDA has therefore identified the need to develop “new product development toolkits,” with the aim of accelerating efficient development of safe and effective medical products. The critical path to new medical product is a result of this effort.

10.7 The Critical Path Initiative

Considering all the identified issues, and the eminent catastrophe with inaction, the FDA developed the CPI to help product developers accelerate the process of getting safe and effective drugs, devices, and medical biologics to market. As soon as developers have identified prototype or discovery product, they are encouraged to consider entering into the program. Once they enter into the critical path, FDA experts, developers, and other stakeholders ensure a rigorous evaluation process toward product approval.

The disconnection between basic science discovery and commercialization has been recognized globally by a number of organizations as well, and efforts have been made to help bridge this gap. These endeavors aim at accelerating the clinical translation of biomarkers, including the NIH roadmap, the NCI SPORE program, the EORTC, the NIST biomarker program, and the National Translational Cancer Research Network from the British government.

However, by definition, translational research extends from prototype, device, or discovery stage through preclinical to clinical development. The gap from this stage to regulatory approval becomes murky at this stage. How these products pass the stringent approval process of safety and effectiveness is not addressed. To this end, the FDA recognized the need for “bridged” research efforts, which is referred to as critical path research (Fig. 10.1). This targeted or focused research is aimed at providing the critically needed path from translational research to successfully approved product development. A challenge for the critical research mandate is the high failure rate of getting discovery research through product development. It is recognized that a newly discovered medical biologic entering phase I studies has just 8% chance of success, partly because of the failure in identifying candidate medicinal compounds or biologics likely to succeed. That is, from the discovery phase, being able to identify which biomarker, compound, or device has the highest probability of success is critical to downstream efforts at further development. In view of these difficulties, the goal of critical path research is to develop tools to guide efficient product development. These tools include standards, assays, biomarkers, clinical trial endpoints, and computer-modeling techniques aimed at identifying promising agents early in the development process, so as not to pursue products that are likely to fail. Obviously this approach should save thousands of dollars in pharmaceutical development processes.

The CPI report identifies three not mutually exclusive dimensions in development of biologics, drugs, and devices. These are product safety establishment,
demonstrating medical utility, and the industrialization process. These three critical dimensions must meet desired quality at all stages of product development.

- Is the product safe enough for human testing and eventual clinical distribution?
- Will the product be beneficial to the public? This requires demonstrating clinical effectiveness.
- How do we get the product from bench to market? This process involves developing a high-quality product for mass commercial production. This process may involve product characterization and specification, physical designs, manufacturing scale-up, and quality control for patient safety.

There are specific tools for each of these dimensions. These are tools for assessing safety, demonstrating medical utility and characterization and manufacturing.

### 10.7.1 Product Development Tools

In order to accelerate development of products, tools are needed to ensure product safety, effectiveness, characterization, and manufacturing throughout the process. While the FDA is providing leadership in this direction, opportunities exist for industry, academia, and other interested parties to help identify and develop some of these tools.

#### 10.7.1.1 Safety Assessment Tools

Medical product safety for public use is a major mandate of the FDA. Therefore, part of the CPR is devoted to developing tools for safety product assessment. To reduce cost to industry, safety concerns should be identified and addressed early in the development of a biologic. The paucity of safety assessment methods can result
in advancing products to late stages before recognition of how unsafe they may be to the public or even result in product withdrawal after commercialization. Such issues have occurred in regard to a number of drugs. Methods for early detection of significant safety issues should be a major focus of product developers.

While any product may have safety concerns, much attention in this area has been on drug development. In regard to biomarkers for clinical applications, safety issues will relate mainly to product performance accuracy, such that the harms to consumers are minimized. Tools that can be developed to help achieve this will include developing standard operating procedures with efficient protocols for biomarker qualification programs.

The FDA’s identified areas for safety assessment method development include product testing for possible contamination, toxicology testing, and human exposure. Animal models have commonly been used for drug toxicity testing; however, they can be labor intensive, costly, and yet unreliable. More reliable methods are therefore needed, and the FDA’s leadership in this area is commendable and noteworthy:

- One example of successful safety too development is the recommendations by the FDA for the use of in vitro human cell lines to characterize drug metabolism. This leadership has helped with reductions in the issues of drug safety after development due to drug-drug interactions.
- Another success story from the FDA is the development and standardization of methods for documenting the clearance of retrovirus-like particles from tissue culture media. This feat has accelerated the development of safe monoclonal antibodies, some of which are currently been advanced rapidly as targeted therapies.

The FDA has identified several opportunities for the expansion of the safety toolkit, which needs to be reviewed by industry, academia, and other researchers for development.

10.7.1.2 Medical Utility Tools

To be of benefit to patients and the healthcare system, medical products must be effective at what they claim to accomplish. This area of method development has been challenging partly because of the lack of predictive value of animal models, and yet sources of variations during human trials are unpredictable. Hence, the FDA has earmarked a number of opportune areas to be explored. Additionally, the FDA has made some efforts at enhancing the ability for drug developers to demonstrate medical utility in a timely fashion. For example:

- Adopting CD4+ T-cell counts and measurement of viral loads as surrogate biomarkers of the effectiveness of anti-HIV drugs accelerated the drug development and approval process.
- Adopting the eradication of *H. pylori* as surrogate for effective treatment for duodenal ulcer disease enhanced drug development.
• Finally, by accepting the use of validated surrogates as evidence for vaccine effectiveness in establishing desired immunity has enhanced the vaccine approval process.

10.7.1.3 Characterization and Manufacturing Tools

Another issue with product development is the apparent dissociation of discovery efforts from the product manufacturing process. New technologies are surging for discovery research and possible prototype developments. These techniques tend to focus very much on analytical sensitivities, which are of importance in early disease biomarker discovery. The obvious issue is the often little attention given to the transition of such technologies to market. Thus, product failures may occur because of problems with the transition to industrialized production. The product development process can be expedited if technical standards are developed, especially when new technologies are used for initial research and development. Additionally, developers should consider what is needed for physical design, characterization, manufacturing, and scale-up in order to successfully bring products to market.

10.8 Biomarkers in the Drug Development Process

Biomarkers fall into two utility categories: (1) for clinical applications such as screening and (2) for drug development. These are not mutually exclusive applications of any specific biomarker. The very tenet that biomarkers are entities or factors that are objectively measured and, which modulate in physiologic states, with disease features or processes as well as treatment responses pivots their utility in the drug development process. For drug development purposes, biomarkers are classified simplistically as diagnostic, prognostic, predictive, and pharmacodynamic biomarkers.

• Diagnostic biomarkers are used to stratify people into diseased and healthy categories in regard to the physiologic or pathophysiologic characteristics of the disease.
• Prognostic biomarkers predict the natural course of a disease prior to any treatment interventions. They identify an individual’s risk level of disease progression.
• Predictive biomarkers forecast treatment outcomes in relation to the likelihood of response to a specific therapeutic agent.
• Pharmacodynamic biomarkers measure therapeutic effects. They change to indicate that a biologic response to an agent being received by a patient has occurred.

These definitions do not mutually exclude any specific biomarker. A single biomarker may possess any combinations of the four designated utilities.
10.8.1 Utility of Biomarkers in Drug Development Programs

On the thesis of the above classification, biomarkers can be applied in a number of ways in the drug development process.

- Pharmacodynamic biomarkers may be used to monitor for early detection of drug toxicity before clinical evidence of a disease state. They are also useful in treatment regimen and dose establishment, usually in a phase II trial to plan for phase III studies.
- Biomarkers may be used for patient selection during a clinical trial enrolment. Predictive biomarkers may identify a group of patients likely to respond to a drug in a predictable manner. Such treatment outcome predictions can be very important in successful drug development. For example, the EGFR inhibitor, gefitinib (Iressa), failed as a lung cancer-targeted therapy in unselected lung cancer patients. However, by targeting only the ~5% of adenocarcinoma subtype of NSCLC with EGFR mutations, the dramatic effectiveness of the drug was proven.
- Biomarkers may be used for patient stratification for randomized clinical trials. For example, a prognostic biomarker may identify a group of patients more likely to develop progressive metastatic disease for a specific drug development program. Being able to demonstrate a reduction in metastatic events can be evidentiary of drug effectiveness.
- Biomarkers can serve as surrogate endpoints in the drug development process. A stringent qualification is mandatory for such biomarkers to prevent failures to demonstrate desired benefits or outcomes at large clinical trials.
- Some biomarkers can identify a subgroup of patients with specific diseases for which there currently is no effective therapy available. These patients can be enrolled for new drug development programs.

10.8.2 Regulatory Requirements for Biomarker Use in Drug Development

Drug developers may use an existing qualified biomarker for drug development. Under such circumstances, there are two possible regulatory choices or paths of methods or assays to employ:

- Developers can use within their investigational new drug application (IND), new drug application (NDA), or biologic license application (BLA) the assays or methods that were reviewed and used for biomarker qualification. If within their IND/NDA/BLA, the proposed methodology to be used in the drug development program is the same as was used for biomarker qualification, it can be used without any further regulatory submissions.
• An alternate method or assay may also be used. Should this path be opted for, a submission of information to support equivalency of the new methods or assays to the one used for biomarker qualification has to be made to the review division via submission to the particular IND/NDA/BLA. A performance comparison of appropriate samples using the new assay can be carried out with the assay used for qualification of the biomarker. If successful, further required regulatory evidence on the new assay/methods will not be required.

An imaging biomarker may be chosen for drug development. This understandably may require the injection of an imaging drug. In this situation, the marketing regulatory requirements for the use of the imaging drug and its use as an imaging biomarker are distinct. An IND for the imaging drug may be required prior to use. However, if the FDA has already approved the imaging drug, and the biomarker utility falls within this approval, it can be used without the need for an IND.

### 10.8.3 Use of Diagnostic Devices for Qualified Biomarkers

Biomarkers used in drug development may already be cleared for clinical practice. The vast majority of biomarkers require measurements using diagnostic devices. Thus, the review or evaluation of data submissions for the drug under development also considers the analytical performances of the device used for biomarker measurement. Fortunately, many of these devices, especially those used in the clinics, will have been reviewed and cleared for marketing by the CDRH/CBER branch of the FDA. The qualification program for drug development is however not dependent on any specific diagnostic device. Thus, if many different devices were used to measure the biomarker, they should yield the same results. This should provide a level of comfort in terms of rigor in biomarker performance.

From a regulatory standpoint, the drug development qualification program is separate from the device review and market approval program. Therefore, an FDA-cleared device does not necessarily imply that what it has been used to measure constitutes its qualification for use in the drug development program. Conversely, the eventual qualification of a drug development tool does not imply that the device used is cleared for commercial use. It is imperative that the use of an FDA-cleared device has some advantages; however, the use of multiple devices to measure the biomarker, at least initially, may offer much comfort.
10.9 Biomarkers and Qualification Process for Drug Development Tools

The FDA defines drug development tools (DDT) as “methods, materials, or measures that aid drug development.” The defined or identified DDTs by the FDA are not the only paths or elements needed for valid drug development, but are useful recommendations for any developer. Thus, the DDT qualification program is not required by a drug developer, but is useful and obviously accelerates the approval process because it is a collaborative effort that meets the requirements of both parties. It is a process that instills comfort in DDT developers as they get to understand the process by which submitted data will be reviewed by the FDA-CDER for specific context of use (COU).

10.9.1 Qualification

Qualification is when the DDT can be relied on to provide specific interpretation and application in drug development and regulatory review as stated in the COU. Thus, the COU guides the utility and purpose of the DDT and fully provides the circumstances under which the DDT is qualified. This path ensures that when the DDT is qualified for a specific COU in drug development, it will guide the production of analytically valid measurements reliable to have specific use and meaning. This is a critical path useful for drug development because in the specific qualified context, the DDT can be used for IND, NDA, and BLA submissions. The review of such submissions is relatively easy on the CDER reviewers because of their participation and hence prior knowledge of the DDT. Here are some advantages of DT qualification program:

- Ease of IND, NDA, and BLA review, thus accelerating the drug development process. This benefits the developer, patients, and the healthcare system.
- The qualified DDT can be used for additional studies to generate new data for new DDT submission to support expanding the original qualified COU. The new DDT can hence be used in IND programs for new COU.
- The presence of qualified DDT also helps the FDA. For example, an unqualified DDT can be used by multiple sponsors/developers, or a particular DDT can be used by one sponsor/developer in multiple different clinical settings. In these scenarios for the utility of such a DDT, the FDA-CDER staff need to review each DDT separately to justify its use on a case-by-case basis. However, with qualified DDT, review of data has to be conducted only once.

The FDA qualification programs are based on three types of DDTs: biomarkers, clinical outcome assessments, and animal models.
10.9.1.1 Biomarkers

Biomarkers are important in the qualification process of DDTs. Because of the objectivity in their measurements, they can accurately identify changes in people in an unbiased fashion. Valid biomarkers of a disease process that are measurable prior to treatment interventions may serve as useful tools for patient selection for a clinical trial. Biomarkers for treatment monitoring modulate with or change following treatment. These changes may be indicative of pharmacologic response or raise an alarm in regard to possible toxicity. The directions or levels of biomarker change may be useful in assessing pharmacokinetics and pharmacodynamics of the drug and help in establishing efficacious dose without unwanted effects.

Because of tumor heterogeneity, valid biomarkers for DDTs utility may not be a single, but multiple entities. Multimarker or panel biomarkers (referred to by the FDA as “composite biomarkers”) are usually combined using some form of statistical algorithm to make a defined call.

10.9.1.2 Clinical Outcome Assessment

Clinical outcome assessment (COA) is an important component of the DDT qualification process. It is the measure of patient outcome in regard to symptoms, mental status, or effect of ill health on how the individual functions. This evaluation predicts drug performance in terms of benefits or harms.

Because COA needs to be an objective measure, and yet is a complex process, they are reported as a scoring system in conjunction with methods and instructions used in administering and assessing response. COA of treatment outcome may be from direct or indirect evidence. In the case of the latter, the evidence has to address how adequately the COA corresponds to how patients feel or function. The reported clinical outcome can be from three possible sources: directly by the patients, or indirectly by a physician, or another third-party observer. The patient-reported outcome (PRO) is a direct report on patients symptoms or functioning without any interference such as interpretations or otherwise by a clinician or anybody. The clinician-reported outcome (ClinRO) is an assessment (e.g., motor, sensory, or cognitive performance) based on clinical observations and interpretations by a qualified clinician. An observer-reported outcome (OBsRO) is an assessment made by non-clinician observer.

10.9.1.3 Animal Models

Animal models continue to be an integral part of biomarker research and development. For the purposes of DDTs, an animal model is considered by the FDA as the combination of the appropriate animal species, the agent used to establish disease in the animal (the challenge agent, referred to as etiologic agent in humans), and the
route of exposure to recapitulate the human disease process or pathology in the animal.

The animal model qualification (AMQ) program by the FDA refers to appropriate model animals used in efficacy studies to provide ample evidence of effectiveness for the drug. The developer can establish different animal models and use each for efficacy testing of multiple investigational drugs for the same-targeted disease. To be accepted in the qualification process, animal models must meet three important requirements to provide comfort that the efficacy or otherwise outcomes in the animal model closely represent expectations in humans. These three FDA requirements are:

- The animal model disease process or condition should correspond in multiple important aspects to the disease or condition in humans.
- The pathologic or toxic mechanisms should be similar in the model animals and humans.
- The challenge agent and etiologic agent should be the same.

These requirements ensure that the disease etiology, mechanisms, and processes in the animal model faithfully recapitulate the human condition.

10.9.2 The Qualification Process

The FDA has defined a streamlined process for the DDT program. The DDT qualification process is split into three stages: (1) initiation, (2) consultation and advice, and (3) full qualification package review. The center for drug evaluation and research (CDER) staff is supportive and works proactively to help DDT submitters through the development process.

Stage I or the initiation stage begins the DDT qualification process. After a developer has identified and defined a sound DDT concept, a request is made to the FDA-CDER for a DDT tracking number. This request initiates the generation of a tracking number, which is provided to the developer and also entered into the electronic database of the FDA. The next step is the writing and submission of a letter of intent (LOI) to the FDA. This letter should include consultation request with the FDA-CDER to discuss potential value of the DDT, a description of the DDT, the proposed context of use (COU), and planned activities to be conducted to support qualification of the DDT. Once received, the FDA-CDER reviews the LOI and decides whether or not to proceed with the request. This decision is based primarily on the proposed scientific merit of the DDT and its COU, as well as availability of resources to undertake the review and the process. Should the request be unacceptable, the developer may be required to provide additional information or otherwise explanations as to why the request was declined is provided, together with advice on other paths for the DDT development process.

Stage II or consultation and advice stage is entered into when the review of an LOI is successful. At this stage the developer agrees to have the qualified DDT
made public on the FDA’s guidance web page under drug development tools. The primary purpose of stage II is coordinated expert advice to the developer to help with the acquisition of the relevant data for submission of a full qualification package (FQP) for internal review.

A team of experts including CDER staff, relevant centers, and disciplines form a qualifications review team (QRT). This team then requests the developer to submit an initial briefing package (IBP) to be reviewed at their initial meeting. The IBP includes biomarker qualification, clinical outcome assessment (COA) qualification, proposed plans for COA qualification, summaries of completed or planned studies, conduct of study to ensure data quality and integrity, limitations of the qualification, and any questions or clarifications from the FDA-CDER.

A meeting is held to review the IBP in detail such that appropriate advice can be provided to the DDT developer on needed evidence for the qualification. The developer then works to generate and gather any additional data required, in consultation with the QRT. Periodic meetings between both teams are conducted to review data, identify gaps, alignment of studies and DDT with COU, and any expert advice necessary to generate data for the qualification DDT review submission.

Stage III or review stage is entered when both teams are satisfied with the qualification data accumulated. The developer now prepares and submits a full qualifications package (FQP) to the QRT for internal review. In addition to detailed descriptions of studies and analysis, primary data from studies conducted may be included. With the agreement by the developer, summary information from the package is posted on the FDA-DDT qualification web page.

Internal meetings by the QRT ensue to review the FQP so as to make eventual recommendations. During this process, the QRT interacts with the developer should any clarifications or request for more information becomes necessary. Although the developer may make a specific COU for the qualified DDT, the final decision of COU is made by the QRT based on submitted supporting data. Should a successful recommendation be made to qualify the DDT, the FDA will post summary of the recommendation on its web page. The qualified DDT may also be expanded or withdrawn in the future as additional data become available.

### 10.10 Evaluation of Biomarker Clinical Utility

Biomarkers for clinical utility or drug development must go through rigorous evaluation process to be considered valid for clinical applications. To be useful in the clinical setting, appropriate use of biomarkers is mandated. The clinical utility of a new biomarker can be evaluated by adopting the tumor marker utility grading system (TMUGS) proposed by Hayes DF and colleagues [4]. TMUGS helps clinicians and developers determine the efficiency of biomarker clinical utility. The rubrics of the TMUGS consist of two parts: (1) definitions and specifications
and (2) clinical utility of tumor markers. The TUMGS rubrics are summarized herein:

- Biomarker needs to be clearly identified in regard to its molecular form or otherwise: genes, transcripts, proteins, metabolites, cells, vesicles, or even a process.
- The specific alterations being detected or measured ought to be clearly noted, e.g., gene amplification, mutations, and protein levels.
- The assay used to detect and/or measure the changes should be identified, e.g., RT-PCR, ELISA, and massively parallel sequencing.
- Identify and use specified reagents. Standardize reagent conditions and keep note of possible lot-to-lot variations.
- Specify how the signal is detected and biomarker quantified. Should there be a cutoff value for the biomarker, specify how this was established. The robustness of the statistics used to arrive at the concluded biomarker cutoff value should be clarified.
- Specify specimen type and source used for biomarker evaluation, as well as pre-analytical handling in regard to methods of collection, preparation, storage, and transportation, e.g., serum, EDTA, 4 °C, transported on ice. Any temporal delays, storage times, and freeze-thaw cycles should also be noted.
- Specify the disease for which the tumor marker is being evaluated for, e.g., colorectal cancer.

The clinical utility evaluation is very important as well. Determine the biomarker development process and the level of evidence for claims being made.

- Clinical applications of biomarkers should be determined, e.g., screening, prognostic, etc. Note that a single biomarker may have more than one utility – a prognostic biomarker may be predictive as well.
- The biologic relevance of the biomarker should be noted. A biomarker linked to a biologic process or pathway may have treatment reagents present that patients can benefit from. Alternatively, a biomarker with clear biologic attributes can inform discovery and development of therapeutic reagents targeting pathway components.
- To be useful, a biomarker clinical utility should help with favorable patient outcome in terms of survival benefits, reduced morbidity (increase quality of life), and decreased overall healthcare costs.

### 10.11 Biomarker Adoption into Clinical Practice

Another challenge often faced by biomarker developers is ensuring successful adoption of the new biomarker into routine clinical practice. A number of issues affect how slowly or quickly a particular biomarker gets accepted for making clinical decisions:
A valid biomarker is more likely to be adopted than one that makes unsubstantiated marketing claims on performance. There is a need to establish uniform standards for demonstrating biomarker validity before commercialization. To achieve this requires oversight from authorities such as the FDA, NIH, Centers for Medicare and Medicaid Services (CMS), and NIST. Collaborative development between these authorities, industry, and academia, as being offered by the FDA CPI, the biomarker qualification program as well as the qualification process for drug development tools, should enhance the development of biomarkers with clear clinical impact. There should be facile clinical adoption of such biomarkers.

To be successful, there ought to be reimbursements for the new biomarker. Healthcare payers demand evidence of biomarker value in regard to cost and clinical effectiveness in order to make reimbursement decisions. Because all such information may be lacking for a new biomarker (e.g., being able to provide cost-effectiveness data without marketing), slow adoption may require lower or appropriate pricing. Stakeholders and expert panels can determine these coverage and pricing issues. Controlled coverage may have to be adopted, with limited use in specified circumstances until such time that sufficient data has been accrued to demonstrate a value proposition for the biomarker.

An adopted test may not necessarily be able to sustain its initial claims once on the market. Post-market assessment is needed for the accuracy, quality, clinical and cost-effectiveness of the test, or biologic. Preferably, an independent unconflicted body should conduct this assessment.

10.12 Summary

- Many challenges are encountered during cancer biomarker development. These challenges include the inherent tumor biologic variables, pre-analytical and analytical variables, statistical and bioinformatics considerations, and stakeholder factors, all of which often lead to the generation of putative biomarkers that fail large validation studies and hence unqualified for regulatory approval.
- In view of these challenges, many discovered cancer biomarkers never proceed to product development.
- The post-human genome project era has been filled with excitement about novel genetic and genomic product developments for clinical oncology.
- On the contrary, the FDA recognized a rather decline in biologic submissions for review, despite increasing biomedical research funding.
- To help avert this trend, various organizations and institutions including the NIH and the FDA put into place actions and mechanisms to accelerate the development and commercialization of safe and effective biomedical products.
- One solution to the problem is rigorous biomarker analytical method development and validation.
- The FDA also produced guidance documents to help with collaborative efforts in this regard. The Critical Path Initiative, the biomarker qualification program, and
the qualification process for drug development tools are all aimed at assembling stakeholders and FDA scientists/staff to collaborate in accelerating product development.

References


Further Reading
