THEME: GENERAL

REVIEW

Integration and use of biomarkers in drug development, regulation and clinical practice: a US regulatory perspective

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The US FDA encourages the integration of biomarkers in drug development and their appropriate use in clinical practice. It is believed that this approach will help alleviate stagnation and foster innovation in the development of new medical products, and, ultimately, lead to more personalized medicine. To facilitate the use of biomarkers in drug development and clinical practice, the FDA organized workshops, issued guidances, established a voluntary submission process, developed online educational tools and, most importantly, strives to ensure the integration of this information into drug labels, for example, via the update of existing labels, or the inclusion of appropriate language in new drug labels. A pilot process has been set up to qualify novel biomarkers that are not associated with specific drug products, but are of more common use (e.g., biomarkers for drug safety). In addition, the FDA has initiated the creation of various consortia that are working towards the identification and characterization of exploratory biomarkers in order to qualify them for a specific use.

New drug approvals have declined and remain low; in 2007 only 24 new molecular entities (18 from the Center for Drug Evaluation and Research and six from the Center for Biologics Evaluation and Research) were approved [101–103]. The US FDA, recognizing the continued divergence of increasing resources going into drug development and the decrease in output (i.e., productivity), issued a white paper entitled "Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products" in March 2004 [104]. The document details why the agency believes drug development is stagnating and proposes a series of opportunities to increase productivity. A key prospect described in detail in the Critical Path document, and illustrated with a series of concrete proposals in the list of opportunities [105,106], is the use of biomarkers in drug development. Effective integration of biomarkers into clinical development programs (e.g., to enrich a responder population or identify patients at risk for an adverse event) may facilitate new medical product development and promote personalized medicine [1–5]. This commentary provides our perspective on current efforts and successes in integrating biomarkers in applications found in drug development, regulatory review and clinical practice.

The last decade created a wealth of information about established and novel biomarkers, including genetic or genomic markers, which have had, and can have, great impact and utility over the next few years. To provide guidance about their use and clarify regulatory consequences of using these genomic markers, the FDA issued a "Guidance for Industry: Pharmacogenomic Data Submissions" in 2005 [107]. This guidance explains when and how to submit pharmacogenomic data to the FDA, and introduces a novel, voluntary submission path for early, exploratory research data. The purpose of this novel submission path is to create an environment in which regulators and stakeholders can interact without making a regulatory decision, i.e., it is recognized that the data discussed are exploratory and not yet ready for use in regulatory decision-making. This approach has greatly facilitated an early interaction between the two parties and allowed several biomarker-driven drug development programs to move forward effectively. **Box 1** details the therapeutic areas and interests covered in the approximately 40 voluntary data submissions the agency has received between 2004 and 2007. A list of valid genomic biomarkers identified in the context of approved drug labels can be found on the FDA website [108].

Application of biomarkers in different phases of drug development

Biomarkers have been used in drug development and treatment monitoring for a long time. However, development of new, predictive safety and efficacy biomarkers is expected to reduce the time and cost of drug development [6].

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Box 1. Voluntary genomic data submitted to the US FDA between 2004 and 2007 (40 submissions).

Submission types

- '-omics'
- Pharmacogenomics
- Proteomics
- Metabolomics

Therapeutic areas

- Alzheimer's disease
- Cancer
- Cardiovascular diseases
- Depression
- Diabetes
- Obesity
- Rheumatoid arthritis
- Sepsis

Technologies

- Genotyping devices
- Microarrays
- 2D Gels
- Mass spectrometry
- NMR

Issues discussed

- Clinical/analytical
  – Clinical trial design/statistical issues
  – Genetic association to adverse events
  – Genetics and variations in response to drugs
  – Use of biomarkers in stratification
  – Impact on labels
- Preclinical
  – Toxicology markers
  – Renal toxicity
  – Vascular toxicity
  – Hepatotoxicity

Updated from [25].

Preclinical development

In preclinical/animal toxicology studies, the goal of using novel qualified predictive safety biomarkers is to assist in selecting drug candidates that are more likely to be tolerated in humans, thereby reducing cost and time required for preclinical safety evaluation. The qualification of novel biomarkers requires a concerted effort of a team of experts, with expertise in areas including pharmacology/toxicology, clinical pharmacology, clinical medicine, biostatistics and other relevant disciplines. Qualifying preclinical (and also clinical) safety biomarkers for regulatory purposes is likely to be more feasible in collaborative approach that includes representation from industry, academia and government. An example of such collaboration is the Predictive Safety Testing Consortium (PSTC), which includes 16 different pharmaceutical companies and is led by the C-Path Institute [109]. The initial focus of PSTC is on preclinical biomarkers [7]. A first set of new nephrotoxicity biomarkers is currently being evaluated based on studies performed in rats using known nephrotoxicants such as gentamycin and cisplantin (**Box 2**). These biomarkers reflect toxicity in different anatomical regions of the kidney and are intended to provide earlier warning signs of drug-induced toxicity. Observable changes in traditional nephrotoxic biomarkers, such as serum creatinine or glomerular filtration rate, occur only after marked toxicity has already occurred. The ultimate goal is to transition these preclinical markers into drug development and possibly into clinical evaluation. Another example of public and private biomedical research consortia is the Biomarkers Consortium managed by the Foundation of National Institutes of Health (FNIH). This consortium was launched to identify and qualify new biomarkers to accelerate disease detection, diagnosis and treatment. Assessment of the utility of fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in non-small cell lung cancer and lymphoma is slated to be their first project [8].

Clinical development

Biomarkers can be used in early or late drug development for enrichment of patient populations to increase the odds of detecting a phenotypic or clinical efficacy signal. For example, data from early clinical trials that enroll patients with poor metabolizer (PM) genotypes in early phases of clinical trials to evaluate dose–concentration–response relationships in patients with different genotypes can inform the study design of later-phase clinical studies. In later stages of development, stratification approaches might be employed for looking at response in subgroups of patients.

Besides metabolism biomarkers, other markers, such as CCR5 in the context of maraviroc [9], and KRAS in the context of panitumumab [10], assist in identifying the subset of patients most likely to respond favorably to targeted drug treatment. Maraviroc was recently approved by the US FDA for the treatment of AIDS and the drug's efficacy is mediated through blocking of the CCR5 receptor. Thus, the entry of CCR5-tropic viruses, but not of CXCR4-tropic viruses, into human cells is blocked by maraviroc, making the drug effective only in patients infected by CCR5-tropic HIV. Panitumumab is a human

monoclonal antibody to EGFR, approved for the treatment of patients with metastatic colorectal cancer that express EGFR and experience disease progression. The efficacy of panitumumab treatment was observed in patients with wild-type *KRAS* genes, but not in patients with variant *KRAS* genes.

Another example is that of *ApoE4* in the treatment of Alzheimer's disease with rosiglitazone. No clinical improvement was observed in all comers (patients with and without the marker) upon treatment. However, when the data was analyzed for response in *ApoE4*-positive subset and in *ApoE4*-negative subset of patients, significant clinical improvement was observed in the *ApoE4*-negative population, but not in the *ApoE4*-positive population [11]. Further prospective evaluation may provide information on the utility of *ApoE4* genetic test for this specific use.

Postmarketing
The usefulness of a biomarker may also be discovered in studies carried out as Phase IV commitments (or long after the drug approval) as in the finding of strong association of *HLA-B*5701* to abacavir-induced hypersensitivity reaction in HIV-infected patients. This discovery has been successfully applied in clinical practice and a pre-screening for *HLA-B*5701* before treatment with abacavir has shown a reduction in the occurrence of abacavir-associated hypersensitivity reactions [12,13].

Serious and rare adverse effects of drugs are often observed only after marketing of the drug, since premarketing clinical trials are limited in the number of patients being studied. For example, ximelagatran was withdrawn from clinical development due to rare, idiosyncratic adverse events involving elevations in alanine aminotransferase (ALAT) levels. A retrospective genome-wide association study demonstrated a

strong association between *HLA-DRB1*07* and elevation in ALAT levels. These results suggest that the drug may be used safely in *HLA-DRB1*07*-negative individuals pending further evaluation in a prospectively designed clinical study [14].

Ideally, biomarkers that predict adverse events would be available to screen patients before prescribing the drug. An example of such an application is carbamazepine, an anticonvulsant and mood stabilizer: a small proportion of patients from Taiwan treated with carbamazepine developed Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), a rare but serious adverse event. Genetic studies illustrate a strong association between carbamazepine-induced SJS and the presence of the *HLA-B*1502* allele; rendering the *HLA-B*1502* allele in this population a risk factor (i.e., a predictive biomarker) for carbamazepine-induced SJS [15]. Genetic testing may help prevent this adverse outcome. Accordingly, the US label for carbamazepine (Tegretol®) was recently updated to include this information [110]. This case also illustrates the need to have access to biomarker data in ethnically diverse populations.

Another example is that of warfarin. A significant proportion of variation in the pharmacokinetics and pharmacodyanmics between patients influences the anticoagulation response (INR) from a fixed dose. Variability has been linked to the genetic variants of *CYP2C9* and *VKORC1*. Knowledge of the polymorphisms in these genes in addition to other clinical and patient considerations such as age and BMI, can help in selecting the optimal initial dose of warfarin to be prescribed, achieving a target INR more efficiently and lowering the risk of bleeding adverse events. The US label of warfarin (Coumadin®) [111] was updated with this information [16].

Pilot projects in biomarker qualification at CDER

Existing and new biomarkers must be qualified for a specified purpose prior to their use in drug development and regulation. A biomarker qualification pilot process has been set up at the CDER to take an exploratory biomarker through a series of scientific review processes and conclude with a decision on qualification of this marker for a specific purpose [17,18]. An alternative approach of biomarker qualification has been proposed to eliminate the subjectivity of case-by-case qualifications [19,20]. This cost-effectiveness approach is based on the principle that

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Box 2. Proposed preclinical nephrotoxicity biomarkers.

- Predictive Safety Testing Consortium: Proposed preclinical biomarkers for nephrotoxicity
  – Albumin
  – Clusterin
  – β2-microglobulin
  – Cystatin C
  – Kim-1
  – Trefoil factor 3
  – Total urinary protein

Data from [114].

"the value and frequency of a true result must exceed the cost and frequency of a false result". A framework for developing evidentiary standards for biomarker qualification was discussed in a workshop in July 2007 conducted with experts from industry, academia and regulatory authorities. Although some of the participants found the quantitative cost–risk–benefit analyses attractive, the information needed was found to be difficult to obtain [21]. It is noted that only through close collaborations among the stakeholders, as to their perspective on benefit and risk, and considerations of standardized approaches to scientific evidence, will the translation of biomarkers to patient practice occur [22].

Genetic & genomic tests

There are numerous 'metabolism biomarker' tests that are on the market as FDA-approved or laboratory-developed tests. For example, AmpliChip® (Roche Diagnostics) analyzes a patient's DNA for the presence of genetic variations in two drug-metabolizing enzymes, cytochrome P-450 *(CYP)2C19* and *CYP2D6*. The test results are indicative of whether the patient is an ultrarapid, extensive, intermediate or poor metabolizer of a drug that is a substrate for *CYP2C19* or *CYP2D6*. This type of genotyping knowledge may assist the treating clinician in selecting the right dose for a given patient to achieve target systemic drug exposures. Another example is the utility of *UGT1A1* genotype information in the treatment use of irinotecan [23,112].

In addition to genetic (i.e., genetic variation) tests, new genomic (i.e., gene expression) tests are becoming rapidly available. For example, Oncotype DX predicts the risk of women with node-negative, estrogen receptor-positive (ER⁺) breast cancer of experiencing cancer recurrence 10 years following diagnosis and also predicts the extent of benefit with chemotherapy. A gene expression signature is derived from a panel of 21 genes and used to generate a patient's recurrence score; the higher the score, the greater the risk of recurrence, and, therefore, the better the chances for successful treatment.

MammaPrint®, a similar test to OncotypeDx, was recently approved by the FDA. This assay relies on the gene-expression profiles of 70 genes, the results of which are converted to scores using an algorithm and used to determine whether the patients are at low or high risk for metastasis. Thorough, long-term clinical testing will be needed to fully establish the clinical utility of these tests and clinical trials (e.g., TAILORx [113]) are underway addressing these questions.

It is important to note that the development of these tests was made possible by the availability of appropriately consented specimens that could be analyzed in a prospective and/or retrospective manner. Therefore, sample collection and sophisticated methods of analysis are key tools to develop many of these new diagnostic tests, while their full clinical utility can often only be evaluated during longer-term clinical trials.

In cases for which the mechanisms of action of drugs are understood, however, long-term outcome studies may not always be required. An example of genetic tests recently approved by the FDA are tests for the polymorphisms in two enzymes, *CYP2C9* and *VKORC1*, for determining an optimal starting dose for warfarin therapy [111].

Table 1. Comparative sensitivity and specificity data of various widely used biomarkers.				
Test	Sensitivity*	Specificity*	Therapeutic, prognostic & diagnostic use of biomarker	Ref.
CYP2C9*1/*2/*3	46%	69%	Prediction of bleeding events associated with warfarin (dose selection)	[26]
Serum PSA level (4 ng/ml as the upper limit of normal)	21%	94%	Prostate cancer: diagnosis and monitoring	[27]
Serum AFP 30ng/ml	65%	89%	Liver cancer: diagnosis	[28]
Serum AFP + VEGF+ AFU	100.%	95%	Liver cancer: diagnosis	[29]
HER2–FISH	96–98%	100%	Breast cancer: patient selction: use of trastuzumab	[30,31]
HER2–IHC (Hercep) 2+, 3+	66%	98%	Breast cancer: patient selection: use of trastuzumab	[32]

*The sensitivity and specifcity values in the table represent the association of the biomarker to relevant clinical events and may vary depending on factors such as clinical phenotype and cutoff values.

AFP: α-fetoprotein; AFU: α-fucosidase; FISH: Fluorescence in situ hybridization; HER2: Human epidermal growth factor receptor-2; IHC: Immunohistochemistry; PSA: Prostate-specific antigen; UGT: UDP-glucuronosyltransferase; VEGF: Vascular EGF.

It is reasonable to expect that as our knowledge of drug metabolism (pharmacokinetics) as well as drug action (pharmacodynamics) increases, many more such tests will be available to patients. Ultimately, we believe that testing for these biomarkers will greatly enhance drug therapy, making drug products safer to use, while at the same time making efficacious outcomes more predictable.

Analytical and clinical validity of clinical biomarker tests is important to characterize. **Table 1** shows examples of widely used laboratory tests, comparing their sensitivities and specificities. Notably, many of the older tests (e.g., prostate-specific antigen [PSA], α-fetoprotein [AFP]) have never been formally validated or tested in prospective trials. However, these tests have been very useful in cancer detection, although they have not been shown to reduce the mortality of cancer, such as PSA for prostate cancer and AFP for hepatocellular carcinoma. The addition of vascular-EGF (VEGF) and α-fucosidase (AFU) can further increase the specificity and sensitivity of cancer detection. These data, when taken together, demonstrate the usefulness of a panel of biomarkers in increasing the overall sensitivity and specificity of cancer detection.

Future opportunities & challenges of biomarker identification, qualification & clinical utility

The emergence of new technologies has opened doors for biomarker research and resulted in a huge increase in exploratory studies to delineate their clinical usefulness. In a variety of therapeutic areas, exploratory biomarkers have been identified, as illustrated by recent literature and from the FDA's experience with voluntary submissions. However, other important factors need to be considered when moving exploratory biomarkers into the realm of drug development and regulation:

- Resource and data leveraging: biomarker qualification is a complex process that requires significant time and resources, and is more feasible in a collaborative format. Genomic sample or data sharing is imperative to achieve results efficiently and cost-effectively;

- Timing: efficacy and safety biomarkers need to be identified as early in drug development as possible (e.g., in Phase II or earlier) in order to incorporate their proper use in the late-phase trials for clinical validation and clinical qualification;

Executive summary

Application of biomarkers in different phases of drug development, regulation & clinical practice

- To facilitate the use of such biomarkers in drug development and clinical practice, the FDA has established a voluntary submission process, developed online educational tools and strives to ensure the integration of genetic/genomic biomarker information into drug labels.

Preclinical development

- Recent collaborative efforts have resulted in a set of preclinical safety (nephrotoxicity) biomarkers that will be evaluated further for clinical use.

Clinical development

- Besides metabolism biomarkers, other biomarkers are being used in patient selection and stratification (e.g., CCR5 receptor).

Postmarketing

- Information obtained postmarketing has resulted in recent labeling changes (e.g., warfarin, carbamazepine).

Biomarker qualification

- A process is being developed to facilitate the qualification of biomarkers to be used in drug development, regulation and clinical practice.

Future opportunities

- Important factors (e.g., resource and data sharing, education) must be considered in order to integrate and use biomarkers efficiently in drug development, regulation and clinical practice.

- Study design: many initial studies with limited number of subjects may generate positive correlation results; the data need to be looked at carefully and in many cases would be hypothesis-generating and require confirmatory trials, unless there are strong mechanistic bases for the correlation; each case, however, must be looked at individually to determine what is necessary for qualification;

- Performance of the tests: the analytical and clinical validity of biomarkers must be demonstrated using relevant clinical samples to assure performance in drug development and clinical practice;

- Education: FDA reviewers and medical professionals should be educated on the benefits and limitations of genomic information. Physicians, pharmacists and other healthcare professionals have to be trained in the use and interpretation of genetic/genomic and other novel biomarkers/tests [24].

While, a few years ago, debates over whether or not new biomarkers would be successfully developed were common, translation of many markers into clinical practice are now occurring at an increasing rate. A greater understanding of disease biology and drug pharmacology has helped immensely. This must be a pragmatic, well studied process to understand how to qualify biomarkers efficiently and cost-effectively. Hype and overpromising the utility of these new markers without adequate evidence will counteract our intention to better the use of drugs and clinical therapy. There is little doubt that if evidence is obtained appropriately, new markers will continue to be developed and have the potential to profoundly change drug development, regulation and therapy.

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