

Regulatory Considerations for Validation & Qualification of Multimarker Panels

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Why We Need New Safety Biomarkers

- n Improve predictability of drug development**
- n Increase value of therapeutics and preventatives by improving benefit/risk**
- n Improve outcomes in clinical practice**

Already Seeing Examples

- n **Dose adjustment for drugs based on drug metabolizing enzyme results**
- n **Avoidance of treatment**
 - Abacavir
 - Carbamazepine
 - ? Lumiracoxib
- n **? Monitoring**

Definitions: Validation

- § Analytical validation = demonstrate how well test detects/quantifies analyte under various conditions**
Generate performance characteristics of the assay

Definition: Qualification

- n Fitness-for-use**
- n Context-specific**
- n Amount of evidence needed proportional to consequences of using result**
- n Variety of ways to generate evidence – also indication-specific**

Analytical Validation is Always Necessary, often Not Sufficient

- **Stable platform required**
- **Often neglected in academic research**
- **Inability to link results across laboratories**
- **Need inter-user variability, lab-to-lab variability, etc**
- **Need to understand interference (drugs, conditions)**

Route to the Market for in vitro diagnostic

- n As medical device: 510(k) or PMA**
 - Requires submission to FDA
 - 510(k) is “substantially equivalent” to predicate device
 - PMA for more novel diagnostics
 - “de novo” classification possible
- n As laboratory-developed test:**
 - Oversight by CLIA program
 - Not submitted to FDA
 - Most genetic tests

Standard of Evidence for IVD's

- n Analytical validity**
- n Clinical utility**
 - Could be demonstration of adequate detection of analyte if clinical link well established in literature (e.g., DMEs)
 - Could be established through other means, for example analysis of stored specimens
 - Burden of proof proportional to risk, e.g, prognostic claims don't have a high burden
- n Diagnostic directed drug therapy: specific evidentiary standards**

In vitro diagnostic indexed multiplex assays (IVDMIAs)

- n Uses results from multiple analytes to create an “index”, “score” or other result from testing**
- n Method of deriving score often algorithmic; not clinically transparent**
- n Typical of certain new technologies— proteomics or genomics**
- n In contrast to many genetic tests, results frequently empirical based on studies of an association with a clinical outcome**
- n Studies often retrospective**

IVDMIA_s

- n FDA has proposed a regulatory framework for these assays, involving submission and review**
- n This has created significant controversy**
- n Balance between benefits of impartial third party review of evidence vs. rapid innovation**

Safety Markers: Range of uses in drug development

- n Preclinical screening**
- n Sponsor go/no go decisions**
- n De-select patients for trial/treatment**
- n Monitor for development of toxicity**
- n Forecast worse events with wider exposure (liver toxicity)**
- n Understand mechanism**

Preclinical Screening

n Predictions from:

- Structure activity relationships
- Gene expression studies in vitro
- Cell system studies

n Animal studies

- Genomics, proteomics, etc.
- Safety for first human use
- Relevance of animal findings to humans

n Connection with clinical trial and postmarket data

Clinical Safety Screening

- n Pharmacogenomic risk factors: de-selecting for trials**
- n Drug toxicity monitoring**
 - Soluble markers
 - Proteomics, metabolomics etc.
- n Imaging studies**

Marketing Standards for Drug-Diagnostic Pair

- n Standards don't really differ if diagnostic is a single assay, a set of assays, or a IVDMIA type of panel**
- n Technical issues are more significant for IVDMIA type assay**
 - Which analytes to include and how/whether to weigh them**
 - Development of cutoff values**
 - How to handle change control**
 - Quality control**

Regulatory Issues with Marketing Drug-Diagnostic Combination

- n Generally, clinical utility of diagnostic will be shown in trial(s) of drug-dx pair**
- n Major issue is to what extent do you demonstrate predictive value of negative test (i.e., what is test worth?)**
- n Assay may already be on the market with another indication, or may need to be co-developed with the drug**
- n FDA would like applications for these assays, and is willing to work with sponsors**

Clinical Issues with Marketing Drug-Diagnostic Pair

- n Example: Warfarin pharmacogenomics**
 - **Marketed drug and assays**
 - **Standard of care method of dealing with initial dosing (coagulation clinic)**
 - **NHLBI proposing randomized trial to see if incorporation of algorithm with PG testing is as good or superior**
 - **Alternative would be to do enriched trial randomizing those whose dose would be altered up front after testing**

Example: Abacavir

- n Significant incidence (8%) of adverse event limited drug use**
- n Randomized controlled trial demonstrated risk reduction with use of marker**
- n Diagnostic testing well established (use in tissue typing etc)**
- n Recommendations in label**

Carbamazepine and SJS

- Small association studies demonstrated significant increased risk in Asians of certain ethnic background**
- Small supportive studies in other populations**
- Very rare AE with probable significant increase in risk for those with allele**
- Recommendation for testing added to label**

New Drugs and Safety Markers

- n Ethical considerations dictate ascertainment of value of test as early as possible in drug development**
- n Explicit design for answering safety question, i.e. at what point do you stop enrolling test positive patients or discontinue treatment in those with a rise in the biomarker?**
- n Need to consider both getting a definitive answer on safety and keeping people in the trial as safe as possible**

New Drugs and Other Multiplexed Assays

- n Uses include:**
- n Issues for markers intended to enhance effectiveness slightly different than safety**
- n Need definitive hypothesis testing of intended population for efficacy**
- n Several trial designs have been proposed in the literature for doing this**
- n NCI: randomized trial of treatment or non-treatment of early stage cancer based on gene expression panel**
- n Note: none of these biomarkers are “surrogate endpoints”**

Summary

- n Urgent need for new biomarkers to enhance drug safety and effectiveness; new technologies provide opportunities**
- n Much more explicit look at new markers on the part of drug regulators; new types of regulatory evaluations are being developed**
- n Controversy over path to market for more novel technologies (IVDMIAAs)**
- n FDA thinks markers used in directing drug therapy should undergo agency evaluation**
- n Technical issues with multiplex assays probably less difficult than the trial design and interpretation problems**