

Regulatory Issues in Genetic Testing and Targeted Drug Development



Janet Woodcock, M.D.

Deputy Commissioner for Operations

Food and Drug Administration

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Genetic and Genomic Tests are Types of Biomarkers

- Biomarker: a measurable characteristic that reflects physiologic or pathologic processes or states, or responses to pharmacologic interventions
- Genetic or genomic biomarkers: characteristics of an individual's genes or gene expression



Biomarker Measurement is the Foundation of Medicine

- Early biomarkers were physical signs and symptoms that could be measured by observation
- Later biomarkers (e.g., cholesterol) could provide rough prognostic information for the individual or diagnose serious organ malfunction (e.g., ECG, serum creatinine)
- A new generation of biomarkers that can transform diagnosis is under development: these include genetic-based assays but the universe is much broader

Challenges in Biomarker Development



- Many candidate biomarkers are discovered
- Few are evaluated rigorously for their clinical implications—i.e., what they really mean in terms of human health
- A number enter clinical use but fewer receive regulatory acceptance (e.g., for use in drug development) and reimbursement is uneven



Reasons for Lagging Development of Clinical Biomarkers

- Lack of good business models for diagnostics
- Difficulty in establishing clinical correlation: what is needed?
- Clinical community focus on intervention vs diagnosis—e.g., reimbursement practices
- Until recently: not so many good candidates



FDA's Critical Path Initiative

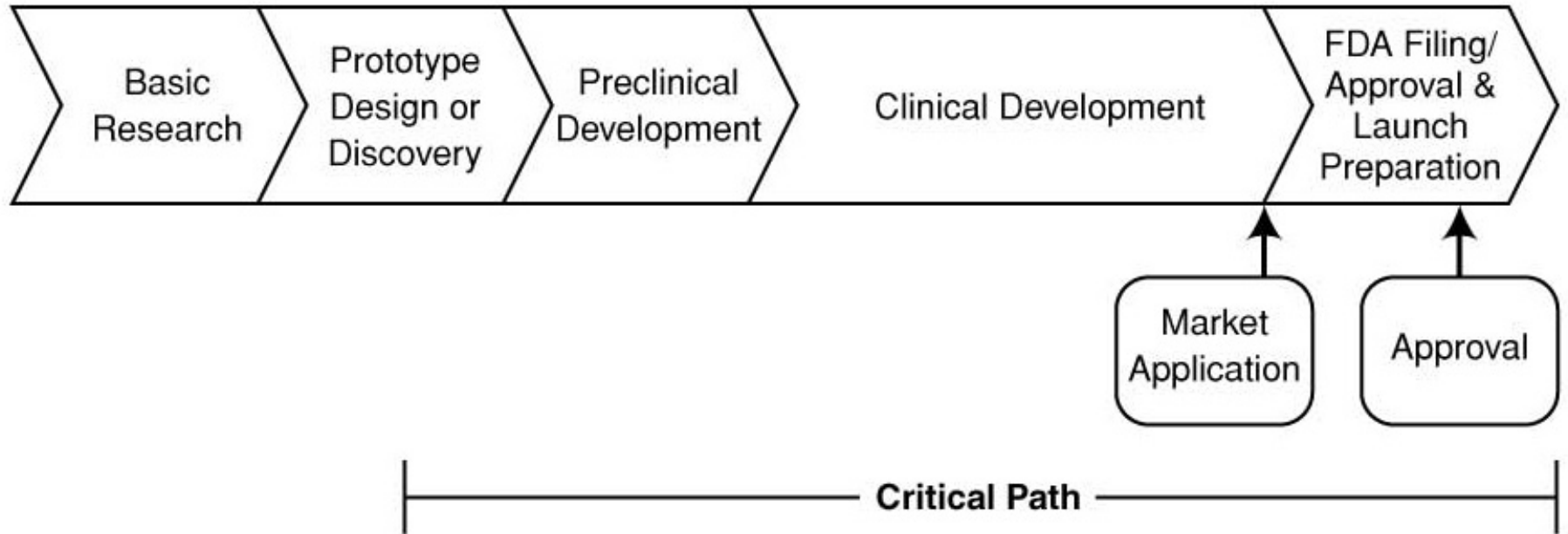
A serious attempt to bring attention and focus to the need for targeted scientific efforts to modernize the processes and methods used to evaluate the safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture.



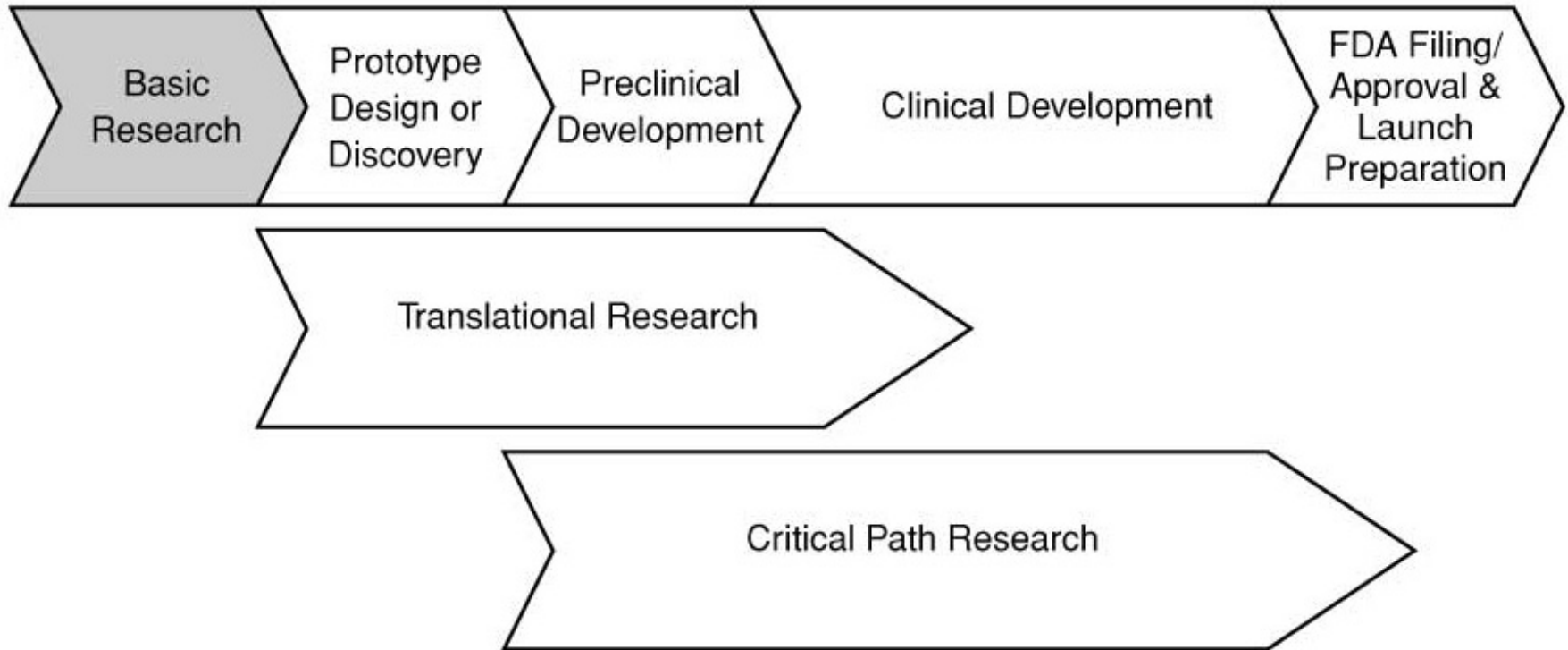
What is the “Critical Path”?

- There is a “critical path” stretching from candidate identification to commercial product
- Involves serial evaluation of product performance through preclinical testing and clinical evaluation
- The science underlying the critical path has lagged behind the progress of other biomedical science
- FDA’s Critical Path Initiative focuses on improving the science used for these evaluations

The Critical Path for Medical Product Development Is Now the Bottleneck



Evaluative Science Underlying The Critical Path



Science to predict and evaluate safety & efficacy performance of new products, and enable manufacture, is different from basic discovery science



"Critical Path" Dimensions

Evaluative science to address 3 key product performance dimensions:

- Assessment of Safety – how to predict and assess the risks of a potential product?
- Proof of Efficacy -- how to predict and demonstrate that a potential product will have medical benefit?
- Industrialization – how to manufacture a product at commercial scale with consistently high quality?



Steps to Date

- Published Initial Report: “Innovation or Stagnation”, 5/04
- Opened Docket; numerous public discussions about drug, device and biologic development challenges
- Initiating multiple public-private partnership consortia with non-profit conveners
- Published “Critical Path Opportunities Report and List” 3/06



Major Opportunities for Modernization per Critical Path Opportunities List

- Biomarker Qualification
 - In-vitro diagnostics
 - Imaging
 - Preclinical toxicogenomics

- Clinical Trial Modernization
- Bioinformatics
- Modernizing Manufacturing
- Pediatric Treatments
- Public Health Emergencies



Genetic Tests and FDA's Critical Path Initiative

- Major opportunity: Utilize new biomarkers to modernize product development
- Genetic/genomic markers prominent
- Proposal: “Qualify” biomarkers for regulatory use via public-private partnership consortia to overcome the identified obstacles

Progress in Biomarker Qualification



- Predictive Safety Consortium: Sponsored by C-Path Institute, Tucson, AZ. Developing safety biomarkers for organ toxicity using animal models—hope to move into human evaluations after animal qualification
- C-Path also evaluating pharmacogenetic-directed dosing of warfarin
- Oncology Biomarker Qualification Initiative (FDA/NCI/CMS): Qualifying imaging, genetic, genomic and other biomarkers for use in cancer treatment



“The Biomarker Consortium”

- Announced last week
- Convened by FNIH: NIH/FDA/CMS; PhRMA/BIO; Nonprofit patient groups
- Goal: Development and Qualification of new human biomarkers
- Announced projects include imaging; serum protein and genetic biomarkers



Genetic Biomarkers and the FDA: Current Issues

- FDA regulation of genetic and genomic tests
- Use of genetic and genomic testing in therapeutic product development

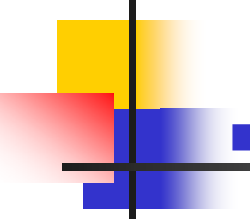


FDA Regulation of Genetic and Genomic Tests

New FDA Guidances:

- Testing of “leftover specimens”
- Regulation of “home brew” and ASRs
- New draft guidance on “IVDMIA”s

New FDA Guidance Documents

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- Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable

<http://www.fda.gov/cdrh/oivd/guidance/1588.pdf>

- Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions (Draft)

<http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>

- In Vitro Diagnostic Multivariate Index Assays (Draft)



Leftover Specimens

- FDA law and regulations make patient samples subject to human subject protections and requirement for informed consent
- Differs from NIH Common Rule
- Means unidentified left-over discard samples and specimens cannot be used for development or research on new tests for FDA submissions



Leftover Specimens

- FDA intends to exercise enforcement discretion, under certain circumstances, with respect to requiring informed consent when human specimens are used in FDA-regulated IVD Device investigations
- Guidance is first step – regulation to follow



Leftover Specimens: Enforcement Discretion

- Investigation meets the IDE exemption criteria at 21 CFR 812.2 (c)(3)
- The study uses leftover specimens
- Specimens may be coded but not individually identifiable
- Specimen may be accompanied by clinical information if source not identifiable
- Individuals caring for patients are different from those conducting the study
- Supplier of specimen has established policies and procedures to prevent release of identifiable information
- Study protocol must be reviewed by an IRB



ASR Draft Guidance

- Intended to address confusion in the marketplace and to clarify the regulations regarding commercially distributed ASRs and the role and responsibilities of ASR manufacturers
- Guidance was adapted from a document submitted to FDA by AdvaMed



ASR Guidance

- Intended to clarify the definition of an ASR
- Intended to communicate limitations on marketing of ASRs
- Not intended to eliminate legitimate home brew testing
- 90 day comment period



ASR Guidance

Examples of ASRs:

- a single antibody
 - e.g., an anti-troponin I antibody
- a single nucleotide primer
 - e.g., a forward primer for amplification of the $\Delta F508$ locus of the CFTR gene
- a single purified protein or peptide
 - e.g., purified estrogen receptor protein



Multivariate Draft Guidance

Identifies a class of laboratory developed devices subject to FDA regulation –
In Vitro Diagnostic Multivariate Index Assays:

IVDMIA_s



Multivariate Guidance

IVDMIAs:

- Use clinical data (from one or more IVDs assays and sometimes demographic data) to empirically identify an algorithm
- Employ the algorithm to integrate these different data points in order to calculate a patient-specific result (e.g., a “classification,” “score,” or “index”)
- The result cannot be interpreted by clinicians using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness



Multivariate Guidance

- IVDMIAs are a narrow niche of laboratory developed devices that are not subject to enforcement discretion
- Guidance indicates regulation will be risk-based by intended use (same as all other medical devices)
- 90 day comment period: draft has generated some confusion



Genetic Tests and Therapeutic Product Development

- Voluntary Genomic Data Submission
- Use in targeted therapy
- Drug-Diagnostic Co-development Guidance



Voluntary Genomic Data Submission Process

- FDA procedure to evaluate emerging genetic or genomic data relevant to investigational products outside the regulatory arena
- Enthusiastic participation by industry—multiple types of genetic data shared (e.g., prognostic, patient stratification, adverse events etc)
- FDA able to develop expertise to evaluate proposals for standard drug development
- FDA also working on microarray standards via MAQC consortium (FDA's NCTR)



Use of Genomic Markers to Target Therapy

- Pharmacogenomic markers
 - Proper dosing: Drug metabolism polymorphisms: avoiding serious side effects—first tests have been approved
 - Improving efficacy: Predictors of drug response or nonresponse (to target treated population)
 - Improving safety: Genetic basis of adverse events—avoid treating those at risk—prevention is preferable to warnings



The Current Clinical Development Model

- The randomized controlled clinical trial represented a scientific triumph over anecdotal medicine in the 1960s
- Used to control for bias and the impact of “random” (unexplainable) variability—but this variability is at the heart of personalization
- Basis for many of the advances of modern medicine



Limitations of Controlled Trials

- Theoretically can answer any and all questions via controlled experiments
- Can answer one or a few questions per trial
- There are an unlimited number of questions about the appropriate use of medical products and the outcomes of such use, and these questions evolve over time
- There is a decidedly limited universe of funding, patients, investigators, time and resources to conduct trials to answer these questions



Limitations of Controlled Trials

- Fact: at the end of most drug development programs, after huge expenditures of time and resources, we don't know a great deal about the drug
- We're quite confident it has a measurable beneficial effect in a described population-but the overall treatment effect is often small. Did few people respond a lot or did a lot of people respond a bit?
- Often many of the people who take the drug do not benefit



Limitations of Controlled Trials as Currently Conducted

- Binary outcome—success or failure-- determined by p value—limits information gain and often results in misinterpretation of data (e.g., estrogen trials)
- Large time expenditure—and may find out at the end that the wrong question was being asked
- Little flexibility



Healthcare Consequences of Current Development

- Health care cost controversy: Debates about value of products: we can't quantify
- Health care policy community believes that increased technology=greater expense, and usually lower productivity
- Safety controversies: Products are "Safe" or "Unsafe"
- Health care quality: Confusing results and conflicting reports lead to anecdotal approach to care



More Informative Clinical Trial Designs

- Pair diagnostic(s) with therapeutic in development to identify responsive subgroup(s), or prevent toxicity
- Adaptive designs to answer series of questions—i.e, what dose is correct for which group



Critical Path Payoff for Development Process

- More predictable process; higher success rate, lower development costs
- More information about product performance
- Continuous improvement of development science and processes



Critical Path: Payoff for Patients: More Personalized Treatment

- Much larger treatment effects via more targeted therapy
- Stopping ineffective therapy faster
- Avoidance of side effects and injury through prevention
- Better/earlier product availability
- Higher quality healthcare



Drug-Diagnostic Co-Development Guidance

- Need clear regulatory pathway for developing a investigational genetic or genomic test along with an investigational therapy
- Issues of sequencing, trial design, and statistical analysis important
- Also must clarify claims that would be allowed under various scenarios
- Much progress made although guidance not out yet



Summary

- FDA regulation of genetic tests remains a somewhat controversial area
- New draft guidances to provide greater clarity
- FDA is intensifying involvement in development of genetic/genomic markers
- Standardization of platforms for analysis is a key issue that is currently being addressed
- Critical Path Initiative brings intense focus on genetic/genomic biomarkers that may be used in drug development