ENGELBERG CENTER for Health Care Reform at BROOKINGS

Achieving the Promise of Personalized Cancer Therapy: The role of public-private collaboration

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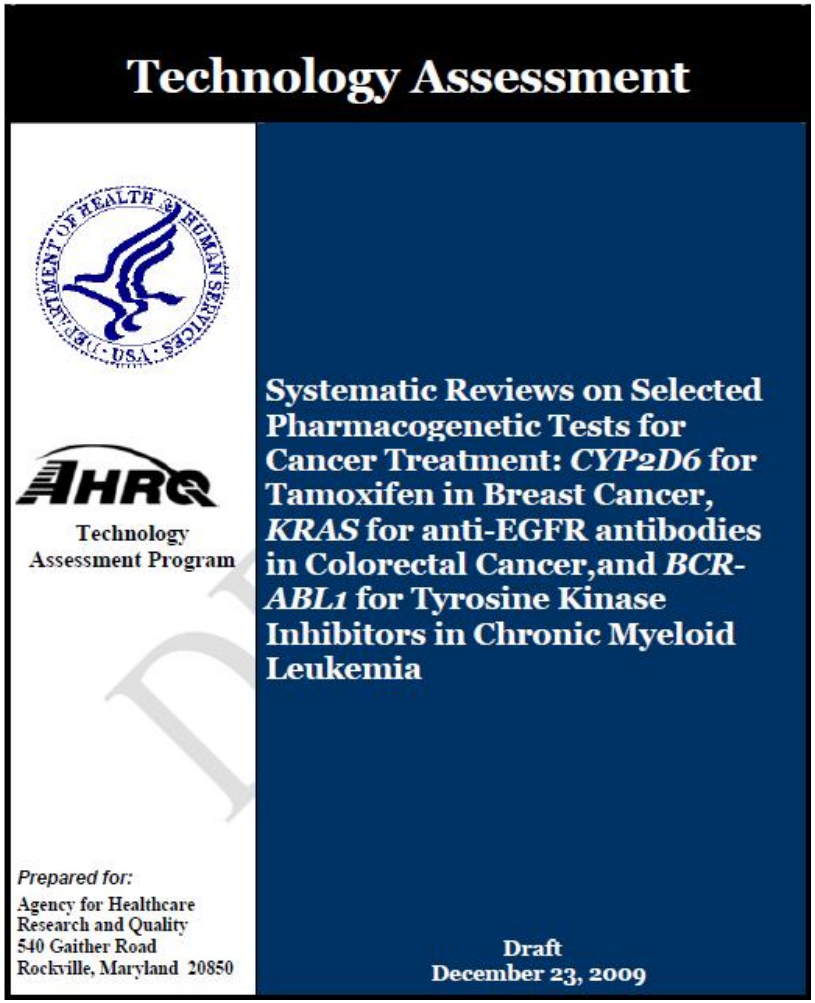
Uncertainty Limits Development

- Absence of validated disease models complicates trial design, clarity on expected duration and costs
- Absence of validated markers makes trials longer and less predictable
- Challenges in validating predictive tests, and limits in their predictive power, complicates development of targeted therapies
- Uncertainty about reimbursement pricing pressure regardless of value may favor development of treatments that can be widely used over more effective targeted therapies

Uncertainty about the impact of genetically-targeted cancer strategies was recently highlighted



- What patient- and disease-related factors affect results, their interpretation, or their predictive response to therapy?
- How does gene testing impact the therapeutic choice?
- What are the benefits and adverse effects for patients managed with gene testing?
- *These questions can't be answered with the existing data* **à** *we need better evidence.*

Pre-competitive collaboration has potential to reduce uncertainty in development science

- More data
  - Validation of disease models
  - Validation of markers
- Consensus building
  - Broader range of viewpoints, broader perspectives on field
  - Path to more confident foundation of regulatory science
- Economies of scale and scope
  - Less duplicative work
  - More and faster value creation for participating organizations
- Greater ability to engage FDA and public
  - Powerful way to highlight outstanding issues and suggested solutions
  - Leads to more confidence in value of products

Pre-competitive collaboration has costs…

- Dealing with inconsistent or otherwise non-comparable data requires standards and infrastructure
- Management and coordination costs for collaboration may be significant, and developing consensus for action may be difficult
- "Lowest common denominator" focus may slow progress on key innovative issues
- Potential opportunity cost of diverting attention of collaborators away from other priorities and more innovative approaches
- Tradeoff: smaller share of reward with higher probability of success vs. larger share of reward with lower probability of success

… How to maximize benefits and minimize costs?

Precompetitive collaborations have the potential to increase availability of targeted therapies

- Defined space
  - Must be within legal boundaries of anti-trust laws
  - All partners should benefit
  - Deliverables must create opportunities for partners to compete more effectively to develop new and better therapies

- Area with significant potential payoff (there are many)
  - Basic Science
    - Preclinical models
    - Biomarkers for targeted therapy
    - Biomarkers for drug safety
    - Natural history models
  - Clinical Development
    - Endpoints
    - Data collection standards
    - Methodology (adaptive/Bayesian designs)
  - Regulatory Science
    - Evidentiary standards for markers, tests, and therapies
    - Guidance for trial designs and endpoints
    - Co-development

Streamlining data collection will improve the overall quality of data submitted in sNDAs/sBLAs

ISSUE BRIEF

Conference on Clinical Cancer Research

September 2009

PANEL 1

Data Submission Standards and Evidence Requirements

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Importance of streamlining data collection

The goal of FDA guidance documents is to provide insight into the data necessary for FDA reviewers to reliably assess the risk-benefit ratio of an investigational agent for a particular clinical indication. The current U.S. Food and Drug Administration (FDA) registration guidance for cancer therapy trials does not completely describe the level of detail necessary for informative data capture to support claims of safety and efficacy for supplemental indications of new cancer treatments[1]. The guidance, as currently set out, does not distinguish between drugs with substantive safety information and definite benefit to patients from drugs with limited safety data which may carry safety risks that have not yet been recognized. Data collection requirements, thus, become essentially the same whether for a primary indication or a supplemental application. This can result in collection of excessive and sometimes unnecessary data by investigators, particularly for trials designed to explore additional indications where substantial toxicity data about an agent already exist. Further, since there is no established standard for collection of data in support of supplemental applications, sponsors interpret the requirements variably resulting in inconsistent quality and quantity of data. Frequently the data collected do not result in modifications to FDA labeling or inform medical practice yet the data collection requirements add complexity and cost to conducting the study. Therefore, optimized standards for data collection should be developed for well-studied cancer therapies to improve the efficiency of safety evaluations without sacrificing the scientific integrity and validity of study results.

Streamlining data collection will help ensure better patient safety by improving the overall quality of data submitted in supplemental applications. Collecting essential data that will help inform patient safety such as toxicities leading to death or dose discontinuations is more important than collecting large amounts of data such as cataloguing all mild adverse events that ultimately adds little information to the existing safety profile of the drug. Collection of unused data may actually distract from gleaning crucial information. When faced with large amounts of safety data, it becomes difficult to prioritize safety events; distracting sites from focusing on the collection of important information such as understanding what makes physicians or patients modify or stop treatment. Thus, large amounts of data can sometimes obfuscate knowledge of new and relevant safety data. Furthermore, streamlining data collection will greatly reduce the administrative burden on the clinical trial system and will focus finite resources on collecting key data elements. Reducing burdensome and unnecessary data collection will improve physician participation in clinical trials. Surveys to understand why patients do not participate in clinical trials reveal that doctors often do not recommend clinical trials to their patients. Among various other reasons, doctors cite that they are weary of the high administrative workload and liability associated with conducting clinical trials. In an effort to understand the burden of excessive data collection on trial administrators, the working group solicited input from several cooperative group and industry sites. Of 110 responses received to the poll, over

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An effective strategy for developing combination therapies will improve the availability of new targeted therapies

ISSUE BRIEF

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PANEL 4

Development of Rational Drug Combinations with Investigational Targeted Agents

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Introduction and Background

Recent research advancements have identified molecular mechanisms underlying cancerous transformation and growth, leading to a new generation of therapies. Key signaling intermediates and genetic mutations associated with oncogenic cell-cycle regulation have been identified as specific targets for the development of new therapies that would be less toxic and more effective than currently available interventions. Progress has also been made in the understanding of how extracellular factors; such as hormones and growth factors; can influence the progression of tumor growth. For example, targeted agents against HER2 (trastuzumab) and Abl (imatinib) have altered the natural history of the diseases in populations for which they were initially developed. However, in the case of other cellular targets, such as Epidermal Growth Factor Receptor (EGFR) in colorectal cancer and mammalian target of rapamycin (mTOR) in renal cell cancer, clinical results have been more modest.

The challenge facing the development of safer and more effective therapies can lie both with the specificity of new targeted agents and the complexity of disease biology, which usually involves multiple redundancies and pathway crosstalk. By selectively and specifically inhibiting one aspect of tumor cell growth or survival, the therapeutic effect may be lessened by concomitant up-regulation of another aspect of the same pathway or by the development of acquired resistance through activation of a compensatory pathway. For example, clinical data suggest that Met pathway activation can compensate in lung tumors when EGFR signaling is inhibited[1], while inhibition of mTOR with rapamycin analogues results in an increase in AKT signaling[2] that may reduce the overall therapeutic effect. Given the limited number of approved targeted agents most rational combinations will require dosing of two or more (as yet) unapproved new molecular entities (NMEs). The strong scientific rationale for such combinations warrants a re-examination of our current developmental model and suggests that a new developmental model may; in select circumstances; facilitate evaluation of two investigational agents in combination.

The existing combination rule (21CFR300.50) provides one mechanism for approval of the combination of two investigational agents, typically by the demonstration in a Phase III trial of the contribution of each agent to the claimed effects of the combination, compared to standard of care therapy. However, there may be circumstances in which there is sufficient evidence to consider alternatives to the standard Phase III factorial trial design or to consider alternative criteria for the regulatory burden of proof necessary for approval of the combination of two investigational targeted therapies. The objective of this panel is to explore specific examples and criteria in which an

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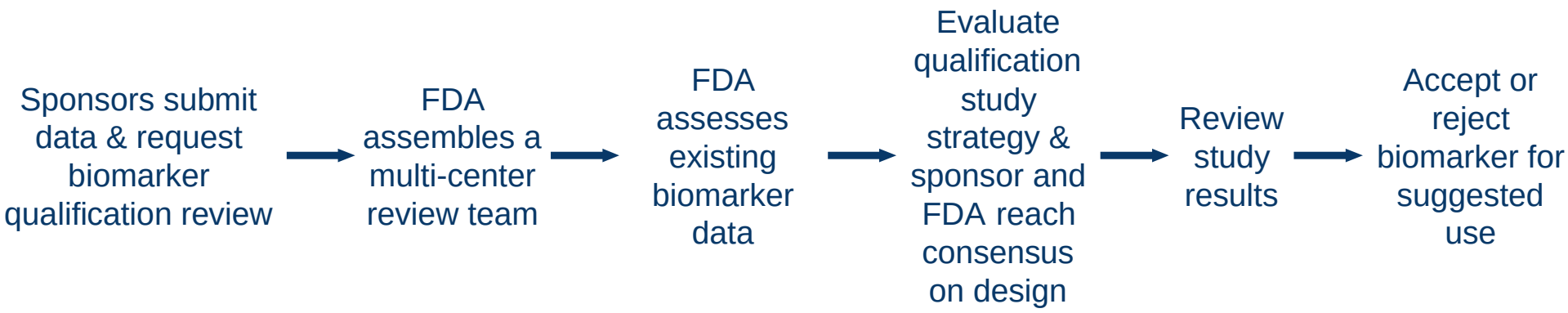
Collaborations can help advance regulatory science: FDA's pilot process for biomarker qualification



Flow chart adapted from Goodsaid F, Frueh F. Biomarker Qualification Pilot Process at the US Food and Drug Administration. *AAPS Journal*. 2007; 9(1): E105-E108

Reagan-Udall Foundation: source of support for collaborations in development and regulatory science

- Purpose: Advance FDA's mission to modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety.

- Duties:
  - Identify unmet needs
  - Establish goals and priorities
  - Identify relevant Federal intramural and extramural R&D programs (in collaboration with the Secretary)
  - Collaborate or contract with stakeholders (e.g., FDA, university consortia, public-private partnerships, academia, non-profits, industry) to efficiently and effectively advance the goals and priorities
  - Convene meetings
  - Release and publish information
  - Manage IP
  - Provide objective clinical and scientific information to FDA
  - Conduct an annual review

Some key elements of a successful collaboration

- Neutral convener
  - Needs to bring all relevant stakeholder perspectives
  - Legal safe harbor for collaboration
  - For cancer: FDA and global regulators, NCI, developers, manufacturers, clinical researchers, basic science community, patient and consumer advocates
- Effective management
  - Efficient operation requires experienced, full-time management
  - Governance structure that allows collaborators to drive strategy
  - Promote economic and intellectual sustainability
- Sufficient incentives
  - Must overcome existing incentives to compete with new incentives to collaborate in academia and private sector
  - Develop policies that reward development of shared data repositories and infrastructure for effective collaboration

Considerations for Incentives

- Support for process: direct payments for infrastructure, payments for participation or reporting
- Support for results: payments for achievement of (well-defined) outcomes
- Infrastructure for data exchange and meaningful analysis vs. use of the network for results

More efficient development and availability of effective targeted cancer therapies requires…

- Identification and prioritization of "bottleneck" knowledge gaps, and which can likely be addressed more effectively through precompetitive collaboration
- Incentives to develop information "utilities":
  - Data standards
  - Data infrastructure
- More head-to-head evaluations of collaboration models to identify key features and best practices
- Full participation of the cancer community in research collaborations, *especially FDA and patients*
- Less regulatory uncertainty—a "critical path" for drug-diagnostic pairs in cancer
- Effective incentives for collaborative research, especially on disease models and biomarker qualification