The Role of Regulatory Science for Development of Innovative Drugs

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*Please note that some of the views presented do not necessarily reflect those of the Food and Drug Administration.*

Problems Facing the Biopharmaceutical Industry

- Struggling to meet increasing demands on R&D investments
- Declining levels of productivity/innovation
- Loss of revenue due to patent expirations
- Three dozen drugs lost patent protection from 2007-2010

Problems Facing the Biopharmaceutical Industry - Driving Towards Stratified Medicine

- Deficiencies in the economics of the blockbuster business model
  - 70% of approved drugs do not meet or match their R and D cost
  - Lower efficacy levels (40%-60% for most blockbuster drugs)

- Successes in stratified medicine
  - Genetech’s Herceptin
  - Novartis’ Gleevac


15-Year NME Applications

<table>
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<tr>
<th>Calendar Year</th>
<th>Applications Filed</th>
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<tr>
<td>1996</td>
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<td>2010</td>
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NME applications to CDER are not increasing. If the number of applications does not increase, CDER does not expect to see much of a year-to-year increase in approvals.

Source: FDA data on NME applications to CDER. NME applications include New Drug Applications (NDAs) and Original Biologic License Applications (BLAs). NME applications do not include therapeutic biologics.

By Vicki Seyfert-Margolis
Vemurafenib (Metastatic Melanoma)

- New Metastatic melanoma drug
  - Vemurafenib, with brand name Zelboraf,
    - to treat patients with metastatic melanoma who has a certain genetic mutation called BRAF V600E
    - drug inhibits the cancer-spreading action of that particular gene, which is held in about 50% of people who have metastatic melanoma
  - FDA approved this drug under expedited review process two months early than expected.

![Image showing how a new anti-cancer drug prevents a mutated enzyme from promoting the growth of tumors. The new drug, vemurafenib, is the green honeycomb structure at middle left. Four dotted red lines show where it attaches to a target area in the enzyme, disabling it.](Image courtesy Plexxikon Inc.)
What is regulatory science?

• The application of basic science to the development and utilization of new tools, standards, and approaches for the assessment of medical product efficacy, safety, and quality

• The critical bridge between basic scientific research discoveries and new marketed, medical products

Why do we need regulatory science?

• Major investments and advances in basic sciences are not fully translating into products to benefit patients

• Product development is increasingly costly, success rates remain low, many uncertainties exist

• Development/evaluation tools and approaches have neither kept pace with nor incorporated emerging technologies

• Economic health of innovative biotech and medical product industry at risk
Regulatory Science, Innovation and Critical Path Updates

- FDA Science Strategic Plan
  - Final draft completed, released -- presentation and discussion later today
- Regulatory Science targeted RFA’s issued-- awards to be made in upcoming days
  - Advancing Regulatory Science through Novel Biomarker Research and Science Based Technologies
  - Innovation in Development and Qualification of Alternative Testing Methods for Reproductive Toxicology
    - Workshop planned on validation of new approaches
Advancing Regulatory Science at FDA: Strategic Plan

Released August 19, 2011

VISION STATEMENT

“FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get safe and effective products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to promote and promote the health of our nation and the global community”
Purpose

• Identify priority opportunity areas of regulatory science essential to the success of medical product innovation and FDA’s public health mission
• Develop/use the 21st century regulatory science tools and approaches needed for development and evaluation of 21st century products
• Promote innovation through targeted and collaborative approaches to regulatory science that enable new technologies and product development
• Build FDA’s scientific capacity, infrastructure, culture and collaborations, including through scientific and professional development of FDA’s scientists

Eight (8) Priority Areas

• Modernize Toxicology to Enhance Safety
• **Stimulate Innovation in** Clinical Evaluation & Personalized Medicine
• Support new Approaches to Improve Product Manufacturing and Quality
• Ensure FDA Readiness to Evaluate Emerging Technologies
• Harness Diverse Data through Information Sciences to Improve Health Outcomes
• Enable a Prevention Focused Food Safety System
• Facilitate Development of Medical Countermeasures to Protect US and Global Health and Security
• Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions
1. Modernize Toxicology to Enhance Product Safety

- Develop better models of human adverse response
- Identify and evaluate biomarkers and endpoints that can be used in non-clinical and clinical evaluations
- Use and develop computational methods and in silico modeling

2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes

- Develop and refine clinical trial designs, endpoints and analysis methods
- Leverage existing and future clinical trial data
- Identify and qualify biomarkers and study endpoints
- Increase the accuracy and consistency, and reduce inter-platform variability of analytical methods to measure biomarkers
- Develop a virtual physiologic patient
3. Support New Approaches to Improve Product Manufacturing and Quality

- Enable development and evaluation of novel and improved manufacturing methods
- Develop new analytical methods
- Reduce risk of microbial contamination of products

Collaboration in Manufacturing

Quality by Design (QbD)

- Systematic quality control of development and manufacturing that builds safety into the process
- QbD Pilot with EMA
  - Launched 3/16/2011
  - FDA / EMA “parallel assessment” of Quality by Design applications
  - Both agencies assess QbD components of new drug applications
What is Quality by Design (QbD)?

- Systematic approach to development
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

*from ICH Q8(R2)*

Quality Related Guidance and Initiatives

- Critical Path Initiative
- 21st Century Initiative Final Report
- ONDQA CMC Pilot Program
- OGD QbR Announced
- ICH IWG formed
- OBP Pilot Program

- PAT Guidance
- ICH Q8 Finalized
- ICH Q9 Finalized
- Quality Systems Guidance Finalized
- ICH Q11 Finalized
- ICH Q11 Concept Paper
- ICH Q8(R1) Finalized
- Process Validation Guidance Revision (Draft)
- ICH IWG Q&A's
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies

- Stimulate development of innovative medical products while concurrently developing novel assessment tools and methodologies
- Develop assessment tools for novel therapies
- Assure safe and effective medical innovation
- Coordinate regulatory science for emerging technology product areas

5. Harness Diverse Data through Information Sciences to Improve Health Outcomes

- Enhance information technology infrastructure development and data mining
- Develop and apply simulation models for product life cycles, risk assessment, and other regulatory science uses
- Analyze large scale clinical and preclinical data sets
- Incorporate knowledge from FDA regulatory files into a database integrating a broad array of data types
- Develop new data sources and innovative analytical methods and approaches
The Vision- FDA Science Enclave

- FDA has been working towards an electronic approach to acquire, receive, and analyze study data
  - FDA is working with CDISC standards to support our current regulatory and research activities. What we learn from this will help to inform our long term information database model.
  - FDA will working with Standards Organizations and other Government Agencies to define and design the next generation information database model, set of standards and scientific enclave to enhance our regulatory and research activities.

- Electronic capture of study data is vital to integrate pre-marketing study data and post-marketing safety data

- FDA is working towards development of a scientific computing environment to support research and a development for our data

Science Enclave and Data Repository: Central to the Vision

- An enterprise initiative to improve FDA’s management of scientific data about regulated products and improve regulatory decision-making

- Establish data architecture and science enclave to facilitate integration of scientific data – across studies, within studies, combine with outside data, enable collaborations

- Create structured scientific data repositories that support the acquisition, validation, integration, and extraction of data from the increasingly large and complex datasets received by the Agency

- Make use of enhanced analytical tools and techniques that enable scientists, and ultimately reviewers to search, model, and analyze data to enable personalized medicine and to conduct better safety and efficacy analyses
Scientific Computing Goals

- Institute a regulated product information data warehouse for exploration
  - Electronically acquire, validate, integrate, and extract standardized, structured scientific data
  - Synthesize information across product applications, across trials, with biomarker data, across classes of products, and across product lifecycle
    - For example, new nephrotoxicity biomarker approved in one area could be used to inform a different product area
    - Ingredient found unsafe or component found defective may be found in other product areas (e.g., combination products, kits, inactive ingredients)
- Transform the regulatory review and decision process
  - Transition to interactive, electronic reviews
    - Support quantitative decision-making to assess safety and effectiveness throughout a product’s life cycle (e.g., data mining to detect possible safety signal)
    - Leverage analysis tools across product areas improving consistency and efficiency
  - Provide springboard to environment of the future that enables
    - Enriched scientific interpretations that integrate latest domain knowledge
    - Advanced analytics (e.g., virtual clinical trials, disease models)

6. Implement a New Prevention-Focused Food Safety System to Protect Public Health

- Establish and implement centralized planning and performance measurement processes
- Improve information sharing internally and externally
- Maintain mission critical science capabilities
- Cultivate expert institutional knowledge
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security

- Develop, characterize, and qualify animal models for MCM development
- Modernize tools to evaluate MCM product safety, efficacy, and quality
- Develop and qualify biomarkers of diseases or conditions
- Enhance emergency communication

8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

- Know the audience
- Reach the audience
- Ensure audience understanding
- Evaluate the effectiveness of communication about regulated products
Key Implementation Components: Collaboration, Professional Development

• Goals: leverage expertise, resources, enhance culture of collaboration, promote scientific and career development

• Partnerships with Government Agencies
• Staff Scientific Training and Professional Development and exchanges
• Direct Funding Mechanisms
• Public-Private Partnerships

New Initiative: Centers of Excellence

• RFA issued by OCS, and applications now under review, for new National Capitol Region Center for Excellence in Regulatory Science and Innovation (CERSI)
  - “to advance the field of regulatory science (including laboratory, population, behavioral, and manufacturing sciences) and the Critical Path Initiative toward more effective and efficient product development and evaluation. CERSI efforts will focus on promoting innovation in support of the development and evaluation of safe and effective products through training, applied collaborative science, professional development and scientific exchanges.”
  - Three components planned for FDA support (up to $1 million) to academic institution(s)
    • Regulatory science collaborative research, focused on FDA Priority areas
    • Training and scientific exchanges (bi-directional)
    • Core dedicated infrastructure to support the above
Centers of Excellence: cont.

- MOU with State of Arkansas for Center of Excellence in Regulatory Science
  - Signed this August: Opportunity to builds on longstanding relationships with state and its educational institutions
  - Includes commitment to collaboration in science and training
  - Commitment to focus on the safety assessment of FDA regulated products that contain nanomaterials.
  - Collaborative development of a degree and certificate program in Regulatory Science in the School of Public Health, University of Arkansas

Summing Up

- We intend this plan as a foundation that is both realistic and aspirational
- Multi-sectoral and global engagement and collaboration is essential and a given
- We seek and see present and future outcomes that include:
  - New knowledge
  - New scientific tools, pathways, approaches and guidance to improve and speed product development, evaluation, manufacturing, quality and monitoring
  - FDA scientific staff engaged in cutting edge technologies and innovators with better tools for and understanding of product evaluation
  - Needed products to people faster, safer, and more efficiently, including in emergencies
  - Product use tailored to maximize benefit and minimize risk to every person
  - Improved health, safety and security
- We welcome discussion and continuing engagement
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FDA Organizational Components & Working Groups

- SISCA (Center Directors)
- Foods Program Science and Research Steering Committee
- Office of the Chief Scientist
- Office of External Affairs
- Office of Minority Health
- Office of Women’s Health
- Science and Innovation
  - Senior Advisory Council
  - Senior Science Council
  - Scientific Computing Board

Questions?

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