Evolving FDA’s Approach to Pharmaceutical Quality

Lawrence X. Yu, Ph.D.

Director (acting)

Office of Pharmaceutical Science
Food and Drug Administration

IPAC-RS/University of Florida Orlando Inhalation Conference Approaches in International Regulation, March 18-20, 2014
Brief History: Quality Regulation is the Basis of Drug Regulation

- Initial impetus came from bad quality products being foisted on the American public
- Harvey Wiley and the “poison squad”
- The earliest drug regulators were chemists
- Focused on impurities and toxic substances
- Quality remains the foundation of assurance of drug performance
Brief History (cont.):

20th Century: Standards for Manufacturing & Testing

- GMP regulations first published in 1963
- Evolution of CMC filing requirements
- Beginning in 1990s, ICH sought standardization of requirements, including many CMC areas
  - common technical document for regulatory filings
  - quality guidances
- Ongoing reliance on USP and other pharmacopoeias for public standards
Brief History (cont.): “21st Century Initiative”

- Succeeded at many levels:
  - ‘Enabling’ of modern technology (e.g., PAT)
  - Updates to GMP regs; revised GMP guidance
  - Multiple ICH documents:
    - Pharmaceutical Development and QbD
    - Quality Risk Management;
    - Quality Systems
  - Formation of Pharmaceutical Inspectorate
  - Risk-based selection of facilities for inspection
Brief History (cont.):
Early 2000s: FDA Embarks upon Pharmaceutical Quality for 21st Century Initiative

Vision

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
We Aren’t There Yet….

Current State of Pharmaceutical Manufacturing

Drug Product Recall

Drug Shortages

Low Process Capability

Total Product Recall

Total Product Shortage

CMC Supplements

Post-Approval Supplements

Calendar Year

Calendar Year

NDAs ANDAs

Calendar Year

2002 2003 2004 2005 2006 2007 2008 2009 2010 2011

0 1000 2000 3000 4000

NDAs ANDAs

2005 2006 2007 2008 2009 2010 2011

0 100 200 300 400

NDAs ANDAs
Current Challenges

• Generic application review backlog and large number of manufacturing supplements
  – Time required for regulatory approval holds back or blocks facilities improvements, e.g., site changes, major upgrades
  – Manufacturers with robust quality systems should be able to manage such changes without regulatory oversight

• Need for ongoing innovation in manufacturing
  – Regulatory oversight one factor in lack of industry adoption of modern manufacturing technology

• State of drug quality?
  – Lack useful quality indicators across-industry.
  – Can we predict these problems?
Where are we going?
CDER OPQ

Mission
The Office of Pharmaceutical Quality assures that quality medicines are available to the American public.

Vision
The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality.

One Quality Voice
CDER OPQ Structure

OPQ Immediate Office

➤ Office of Operations
➤ Office of New Drug Products
➤ Office of Lifecycle Drug Products
➤ Office of Process and Facilities
➤ Office of Surveillance
➤ Office of Testing & Research
➤ Office of Biotechnology Products
➤ Office of Policy
Current CDER Major Review Offices

- Office of New Drugs
- Office of Pharmaceutical Science
  - Office of New Drug Quality Assessment
  - Office of Biotechnology Products
  - Office of Generic Drugs
    - Generic Quality Assessment
    - Bioequivalence, clinical, and labeling programs
  - Office of Testing and Research
- Office of Surveillance and Epidemiology
- Office of Translational Sciences
- Office of Compliance
  - Office of Manufacturing and Product Quality
  - Office of Drug Security, Integrity, and Recalls
  - Office of Scientific Investigations
  - Office of Unapproved Drugs and Labeling Compliance
OPQ: Organizing Principles of Change

- Same quality standards for all drugs; lifecycle approach
  - Clinically relevant specifications
- Unified policy and standard development/analysis
- Establish clear standards for review and inspection
  - Clear enforcement policies
  - Surveillance using quantitative metrics
- Specialization and team review: Integration of review and inspection for a quality assessment
- Accountability: Overall QMS and evaluation system
Lifecycle and Team-based Approach

• Propose to organize review by dosage form
  – Same team to review generics to ensure efficiency and consistency

• Integrated team for product quality and facility assessment
  – also will assess need for inspection

• Surveillance activity for products and facilities manufacturing marketed products or API
Policy and Standards

- Proposed Office of Policy
- Much greater emphasis on developing and maintaining standards
- Develop standards and assess whether standards achieved the quality impact intended
- Support FDA Council on Pharmaceutical Quality
  - involving all FDA stakeholders: drugs, biologics, device, veterinary medicine, and inspection
Surveillance: Standards and Inspections

- Develop clear, written standards and inspectional procedures
  - Reinforcing industry QMS as the primary driver of quality
- Employ metrics to get product quality information
- Use of metrics in assessing facilities operating at risk or are operating in control based on a strong quality management system
- Evolve new approaches towards manufacturing supplement requirements
Program Alignment across FDA

- Transition to distinct commodity-based and vertically-integrated regulatory programs with:
  - Well-defined leads
  - Coherent compliance policy and enforcement strategy development
  - Well-designed and coordinated implementation
  - De-layered management structure
  - Investigators, compliance officers, import reviewers, laboratory personnel, and managers to become more specialized in a particular regulatory program
Pharmaceutical Quality Platform

Analyze & Decide

Risk-based Inspection and Review

Plan, Execute & Track

CDER

Work Flow Management

ORA

Master Data Repositories

Pre-market inspections

Post-market inspections

Field Alerts

Recalls

Drug Quality Reports

Inspection Results

External Risk Factors:
- Foreign Regulatory Agencies etc.

Facility/Site Selection

Pharmaceutical Quality Surveillance & Risk Evaluation

Pharmaceutical Quality Platform

Office of Pharmaceutical Quality (OPQ)
Risk-based Review

- FDA is planning to implement formal risk assessment for its drug product review functions
CMC Review System

- Question-based Review
- Lifecycle knowledge management
- Risk Assessment
- Regulatory commitment
We Are Moving to Performance-based Regulation

Stage of Production
- Planning
- Acting
- Output

Type of Regulation
- Management based
- Technology based
- Performance based
Draft BE Guidance on Fluticasone Propionate; Salmeterol Xinafoate

Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Fluticasone Propionate; Salmeterol Xinafoate

Form/Route: Powder/Inhalation

Recommended studies: In Vitro and In Vivo Studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing fluticasone propionate and salmeterol xinafoate.
## FDA-Funded Research for OIPs

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Title</th>
<th>Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Investigation of dose-response of exhaled nitric oxide after oral inhalation of fluticasone propionate</td>
<td>Dr. Rohit Katial (National Jewish Health)</td>
</tr>
<tr>
<td>2004</td>
<td>Stability of Asthma after High-Dose Corticosteroid: A study of the model for assessment of bioequivalence for inhaled corticosteroid products</td>
<td>Dr. Richard Ahrens (University of Iowa)</td>
</tr>
<tr>
<td>2008</td>
<td>Effects of Device and Formulation on In Vitro Performance of Dry Powder Inhalers</td>
<td>Dr. Anthony Hickey (Cirrus Pharmaceuticals)</td>
</tr>
<tr>
<td>Year</td>
<td>Study Title</td>
<td>Investigator(s)</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2010</td>
<td>Effects of Device and Formulation on In Vitro Performance of Dry Powder Inhalers</td>
<td>Drs. Robert Price and Jag Shur (University of Bath)</td>
</tr>
<tr>
<td>2010</td>
<td>Pharmacokinetic Comparison of Locally Acting Orally Inhaled Drug Products</td>
<td>Dr. Guenther Hochhaus (University of Florida)</td>
</tr>
<tr>
<td>2010</td>
<td>ASPD equivalence evaluation by Modified Chi-square Ratio</td>
<td>Drs. Benjamin Weber and Renishkumar Delvadia (ORISE fellows, FDA)</td>
</tr>
<tr>
<td>2011</td>
<td>Quality by Design for Orally Inhaled Drug Products: Chemistry, Manufacturing, and Controls</td>
<td>Drs. Robert Price and Jag Shur (University of Bath)</td>
</tr>
<tr>
<td>Year</td>
<td>Study Title</td>
<td>Investigator(s)</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2012</td>
<td>Predictive Lung Deposition Models for Safety and Efficacy of Orally Inhaled Drug Products</td>
<td>Drs. Worth Longest and Mike Hindle (VCU)</td>
</tr>
<tr>
<td>2013</td>
<td>Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active...</td>
<td>Dr. Guenther Hochhaus (University of Florida)</td>
</tr>
<tr>
<td>2013</td>
<td>Systematic evaluation of excipient effects on the efficacy of metered dose inhaler products</td>
<td>Drs. Jay Holt and Anthony Hickey (Cirrus Pharm.)</td>
</tr>
<tr>
<td>2013</td>
<td>Development of in vivo predictive dissolution method for orally inhaled drug products</td>
<td>Dr. Masahiro Sakagami (VCU), Drs. Robert Price and Jag Shur (UB), and Dr. Guenther Hochhaus (UF)</td>
</tr>
</tbody>
</table>
Summary

- FDA has made some progress in improving its overall approach to regulating pharmaceutical quality, but major challenges remain.
- Re-organization and re-alignment to achieve a “One Quality Voice” approach and performance-based quality assessment.
- We are making coordinated organizational, process, and policy changes that will move us more towards our articulated vision.
- FDA has published a draft BE guidance for an OIP and research continues.