FDA and ICH Quality Initiatives on Risk-Based Approaches: Opportunity and Challenges in the Plasma Fractionation Industry

Plasma Product Biotechnology 2007
Fifth International Meeting

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Senior Director
Outline

- FDA and ICH New Science and Risk-Based Quality Assessment System
  - Big picture (desired state)
  - How to get there
- Opportunity and Challenges in the Plasma Fractionation Industry
  - State of the Industry
  - Gap Analysis
  - Can Risk-Based Quality System Help to fill the Gaps?
Biography

Education
- B.Sc., Pharmaceutical Chemistry, CPU
- Ph.D., Biochemistry, SUNY
- Post Doctor, Immunology, NIH

Professional Experience
- Senior Director, Pharmanet consulting (7/2006 – present)

Professional Experience (Cont.)
- Served more than 11 years at the FDA
  - Special Assistant to the Director, DH/OBRR/CBER (7/2000 – 11/2002)

FDA Expert Committee Member
- FDA Deputy Topic Leader for ICH Q5E and current discussion on drug substance
- CMC Coordinating Committee
- Manufacturing Science and Continuous Improvement
- Follow-on Biologics
The Desired State - A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight

J. Woodcoak (2005)
Characteristic of Desired State

- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
- Manufacturers control process through quality system over life cycle and strive for continuous improvement
- FDA role: Initial verification, subsequent audit
- No manufacturing supplements needed (may need for formulation)

J. Woodcock (2007)
How to Get There?

- FDA - Council on Pharmaceutical Quality (J. Woodcock, Chair)
  - Process Analytical Technology (PAT)
  - Risk Management
  - Manufacturing Science and Continuous Improvement
- GMP Regulation
- Quality Systems
- Others

- Develop Concepts of New Quality Management
  - Quality by Design
  - Design Space
  - PAT
  - New Thinking Of “Old” Concepts
    - Quality System
    - Process Validation
    - Comparability Protocol

- ICH
  - Q8, Q9 and Q10
  - QOS (Module 2 vs. Module 3)

- FDA Implementation
  - CMC Pilot Program – CDER
  - Question Based Review – Generics
  - CMC Changes
    - Debate on revision of 21CFR314.70 for NDA
    - Revise guidance for Biologics
What IS “Quality by Design”?

■ **Quality**
  - “Good pharmaceutical quality represents an acceptable low risk of failing to achieve the desired clinical attributes.”

■ **Quality by Design (QbD)**
  - “Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.”

  J. Woodcock (2004)
ICH Q8

“Quality can not be tested into products; it has to be built in by design” (QbD)

- Product quality and performance achieved and assured by design of effective and efficient manufacturing process
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance

- In doing so, can provides a framework for continuous “real time” assurance of quality and continuous improvement
Process Analytical Technology (PAT)

- A system for designing, analyzing, and controlling manufacturing through
  - timely measurements (i.e., during processing)
  - of critical quality and performance attributes of raw and in-process materials and processes
  - with the goal of ensuring final product quality.
FDA Quality System Guidance and ICH Q10

The Goals:
- For industry to be able to carry out continuous improvements without prior regulatory approval
- Allow regulators to delegate the responsibility for change management to companies with approved quality systems

Objectives:
- Harmonize the quality system approach to continuous improvement and change management
- Provide a structured approach to process and product monitoring and improvement
- Encourage a climate for continuous improvement
- Facilitate and encourage the introduction of new technologies, e.g., PAT
- Stimulate the move from a “corrective action” culture to a “preventive action” culture
- To be confident that the regulated industry is managing quality, continue improvement, and changes effectively based on product and process knowledge and risk assessment
FDA Public Meeting – February 7, 2007
Supplements and Other Changes to an Approved Application

Scope

21 CFR 314.70 (NDA/ANDA Drugs)

Purpose:

Solicit comments from the public on issues that FDA should consider when developing revisions to its regulations regarding CMC supplements and other changes to approved marketing application for human drugs

FDA’s Vision for Change

Allow for some manufacturing changes to be made without prior FDA approval based on:

- Process and product understanding which leads to risk-based approaches to change
- Use the firms’ internal change control system

Reduce number of post marketing supplements

Manufactures would still be responsible for ensuring product quality
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## Plasma-Derived Products Licensed in USA

<table>
<thead>
<tr>
<th>Category</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihemophilic factor (AHF)</td>
<td>Immune globulin: intravenous and intramuscular</td>
</tr>
<tr>
<td>AHF/von Willebrand factor complex</td>
<td>Cytomegalovirus immune globulin</td>
</tr>
<tr>
<td>Anti-inhibitor coagulant complex</td>
<td>Hepatitis B immune globulin</td>
</tr>
<tr>
<td>Coagulation factor IX</td>
<td>Rabies immune globulin</td>
</tr>
<tr>
<td>Factor IX complex</td>
<td>Rho(D) immune globulin</td>
</tr>
<tr>
<td>Fibrin sealant</td>
<td>Tetanus immune globulin</td>
</tr>
<tr>
<td>Thrombin</td>
<td>Vaccinia immune globulin</td>
</tr>
<tr>
<td>Protein C</td>
<td>Varicella-zoster immune globulin</td>
</tr>
<tr>
<td>Albumin</td>
<td>Botulism immune globulin</td>
</tr>
<tr>
<td>Plasma protein fraction</td>
<td></td>
</tr>
<tr>
<td>Alpha 1 proteinase inhibitor</td>
<td></td>
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<tr>
<td>Anti-thrombin III</td>
<td></td>
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</tbody>
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Plasma-Derived Products (Cont.)

- Products in the Pipe Line
  - CT Products
    - Specialized Immune Globulin
    - Antitoxin, e.g., anthrax
    - Hemostatic Bandage
  - New Products
    - Plasmin
    - Estarase Inhibitor
  - New Indications
    - AHF/VWF Complex
    - IGIV
- Alternate manufacturing processes to increase yield and quality
- New Market
  - e.g., China, India, South America, and Africa
Recombinant Blood Analogues

**FDA Licensed Products**
- Coagulation Factor VIIa
  - NovoSeven (1999)
- Factor VIII Products
  - Recombinate (1992)
  - Bioclate (1993)
  - ReFacto (2000)
- Factor IX
  - Benefix (1997)

**Products in the Pipe Line**
- Next Generation of the Licensed Recombinant Products
- New Products
  - rThrombin
  - Porcine rFVIII
  - Recombinant Polyclonal Antibodies
  - rFXIII
  - rVWF
  - rATIII
  - rAlbumin
  - Alpha Fetoprotein
  - Apolipoprotein A
  - rAPI (Alpha-1-Proteinase Inhibitor)
- Gene Therapy Products
Gap Analysis - Concerns Related to Plasma-Derived Protein Therapeutics

- Poorly defined starting material
  - Source plasma vs. recovered plasma
  - Different pool size
  - Demographical and racial differences
- Lack of robustness of manufacturing process
  - “Minor” changes with “major” impact
  - Low yield
- Low purity
- “Impurities” may be active, may affect activity, immunogenicity, or absorption
- Often highly complex and heterogeneous proteins
- History of viral transmission
Current Paradigm

Variability

Raw Material → Manufacturing Process → Product

Locked Process Variables
Consequences of State

- Inability to predict effects after manufacturing changes
- Usually takes years to bring up a new production site
- Inability to understand reasons for manufacturing failures
- High cost and low efficiency of manufacturing
- Drug shortage due to inability to manufacturing
- Slowed development/access for investigational drugs
- Need for intensive regulatory oversight
Can Risk-Based Quality System Help to fill the Gaps?

- **QbD**
  - Control starting source material based on its intend use
  - Specification – If no likely impact on S and E don’t include as a specification (no rejection limit)
  - Platform strategies

- **PAT**
  - Enhance process and product knowledge
  - Assist in defining “Design Space”
  - Elevate manufacturing efficiency and yield
  - Control product variants and impurities

- **Design Space**
  - Reduce supplement

- **Quality System**
  - Stimulate continuous improvement and change management
Dynamic System

Raw Material → Manufacturing Process → Product Attributes

Input Response → Measurement Dependant Process Variables → Endpoint Response
Target Critical Quality Attributes

Range

Range of Raw Material and Facility Attributes

Process Designed to Limit Product Variability

CQA
Thank You

Questions?

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