An FDA Perspective on Drug Development and the Global Regulatory Landscape

AAPS Annual Meeting
Washington, DC
25 October 2010

Christine M. V. Moore, Ph.D.
Acting Director
ONDQA/CDER/FDA
Outline

• Trends in New Drug Applications
• Background on QbD and Product Understanding
• Examples of Product Understanding in Pharmaceutical Development
• Challenges for a Global Regulatory Environment
• Concluding Thoughts
Trends in New Drug Approvals
CDER New Molecular Entity Approvals (NDA & BLA*)

As of 10/24/11

* Does not include biologics in CBER
2010 New Drug Approvals (NDA & BLA*)

- 94 total approved applications (NME & non-NME)
  - 6 biologics
  - 20 combination products (more than one active ingredient)
- Dosage forms including:
  - Nasal spray - Ophthalmic solution
  - Auto injector - Tablets for oral suspension
  - Bowel prep kit - Powder for inhalation
  - Lotion - Intrathecal solution
  - Gel - Chewable tablets
  - Buccal Tablet - Transdermal
  - Sublingual film - Foam

* Does not include biologics in CBER
Summary of New Drug Trends

- New drug applications are becoming more complex
  - Wide variety of dosage forms
  - Combination drug and drug/device products
  - Complex molecules
  - Low solubility compounds

*Good science in development is needed to take turn these molecules into successful products*
Quality by Design (QbD) in Pharmaceutical Development
What is Quality by Design (QbD)?

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

*From ICH Q8(R2)*
Clarifying Some Misconceptions of QbD

• QbD doesn’t change/reduce regulatory requirements
  – Opportunities for flexible regulatory approaches
• QbD doesn’t equal Design Space and/or Design of Experiments (DOEs)
• QbD is important for all products including generics and biotech
• QbD doesn’t have to be expensive
  – Increased product and process understanding can reduce manufacturing and regulatory costs
Example QbD Approach - ICH Q8(R2)

- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement
QbD Approach

Understand the Product

- Product profile
- CQAs
- Risk assessment
- Design space

Understand the Process

- Control strategy
- Continual Improvement

Control the Process Over the Product Lifecycle
Understanding the Product
Understanding the Product

Product understanding questions include:

- What defines “good” quality drug substance?
- How do the formulation components interact during and after processing?
- How does the drug product interact with the container closure?
- How does the drug become available at the site of action?
- How might the patient incorrectly use or misuse the drug product?
Examples of Traditional Studies for Product Understanding

- Drug substance properties selection
  - Polymorph screening
  - Particle size evaluation
- Formulation selection
  - Excipient selection and compatibility
  - Container closure leachables and extractables
- Drug distribution within the body
  - Pharmokinetic/Pharmodynamic (PK/PD) studies
  - Bioequivalence studies to previous formulations
Challenges in Product Development

• Traditional approaches to product development often have been:
  – Focused on optimization and not robustness
  – Developed with little or no input from manufacturing
  – Performed without understanding the relevance to bioavailability
  – Not performed with the patient use in mind
Opportunities for Product Understanding

• Application of formal Quality Risk Assessment early in development
  – Involve of all stakeholders
  – Define potential failure modes
  – Include patient use factors
• Understand how variability of excipients and raw materials affects product performance
• Integrate biopharmaceutics into product development
• Use of advanced analytics for complex molecules or products
Examples of Product Understanding
Risk Assessment Example

Ishikawa Diagram for Tablet Compression

- **Machines**
  - Pre and Main Compression
  - Material Addition Method
  - Drop Height
  - Operators
  - Experience
  - Training

- **Methods**
  - Press Speed
  - Feeder Speed
  - Cam Size/Tooling
  - Machine set-up
  - Internal Temp
  - Humidity
  - External Temp

- **Measurements**
  - SOPs
  - Batch records
  - Weight
  - Thickness
  - Metal Check
  - Cylindrical fill height
  - Turret RPM
  - Manufacturing Suite
  - Drug Substance
    - Age
    - P.S. LOD
    - ID
    - Diluent
    - P.S. LOD
    - Batch Size
    - Other Excipients
    - Quantity
    - Properties

- **Personnel**
- **Environment**
- **Materials**

**Tablet Quality**
- Dissolution
- Hardness
- Appearance
Example of Understanding Excipient Variability: Artificial Neural Network Example

- **Problem:** Dissolution is highly dependent on polymer properties

- **Method:** ANN dissolution model developed from pilot and commercial batches

- **Results:** Dissolution properties successfully predicted based on excipient attributes
Product Understanding: Extractables and Leachable Studies

• Used to screen for and monitor presence of toxic materials from container closure system (CCS)
  – Usually related to plastic components of the CCS
• A risk-based approach can be used to:
  – Determine likelihood and identity of leachables
  – Based on prior knowledge and experimentation
  – Utilizing a team approach, including toxicologists
  – Consider risk to patient, based on route of administration
• Understanding can provide basis for effective and safe product design and CCS specifications
Extractables and Leachables

- Not all extractables are leachables
- Not all leachables are extractable
- When possible, develop a correlation between extractables and leachables
- Control and/or characterize the non-correlatable leachables
Approach for Product Understanding: Biopharmaceutics Studies

• The science and study of the ways in which drugs influence their pharmacodynamic and pharmacokinetic behavior
  – Typically uses plasma concentrations as biomarker for safety and efficacy
• Strives to relate in vivo performance of a drug to in vitro measurements
  – Enables development of clinically relevant specifications
  – Understand the impact of manufacturing process variables
• Supports control strategy development through setting clinically meaningful dissolution specifications to assure consistent therapeutic benefit
Example In vitro/In vivo Correlation (IVIVC) Approach

Formulation and Manufacturing Process

In Vivo Response
(Plasma Conc. Profile)

In Vitro Release
(Dissolution Profile)

In Vitro/In Vivo Correlation

Predictive Model

Reference: Medscape, 2002
In vivo/In vitro correlations (IVIVC)

• A predictive mathematical model describing the relationship between an *in vitro* property and a relevant *in vivo* response

• Links *in vitro* dissolution data to plasma drug concentration or amount of drug absorbed
  – May predict concentration-time profiles and/or exposure (depending on type of correlation)

• Assists formulation development and optimization

• Supports development and selection of release (e.g., dissolution) methods

• Can facilitate the use of *in vitro* dissolution data as a surrogate for human BE studies (e.g. biowaivers)
Example – Bioequivalence without IVIVC

- Multiple batches are produced with widely varied dissolution rates
- Clinical relevance is assured within established range
- Assures product robustness, and can achieve a wider dissolution specification

A, B, C, & clinical are BE

Std approach dissolution spec: Q= 80 at 30 min.

BE approach dissolution spec: Q= 80 at 45 min
Example Patient Use Factors: Alcohol Induced Dose Dumping

- Some modified release solid oral dosage forms can contain drugs or excipients that are highly soluble in ethanol (EtOH)
- Ingestion of alcohol could lead to dangerously high drug exposure
  - Either intentionally or unintentionally
- Dose dumping should be considered when designing modified release formulations
Alcohol Induced Dose Dumping

• QbD Approach:
  – Consider clinical impact during formulation development
  – Develop greater scientific knowledge and understanding of properties that induce dose dumping
    • Vulnerability of existing ER and MR products
    • Vulnerability of new ER and MR designs
  – Develop formulations and dosage designs not sensitive to dose dumping
  – Perform failure mode analyses (i.e., risk management) early in development – IND formulations
Characterizing Complex Products

• Characterization of complex/heterogeneous products can be difficult
  – Identity, purity
• Chemometrics allows extraction of information from analytical methods
  – Ability to handle multidimensional data
  – Can be used to simultaneously evaluate data from multiple analytical methods to make decisions
• May lead to discovery of “hidden/unexpected” patterns
  – “Fingerprint” approach
  – May be used to identify trace contaminants in products


Wednesday Poster: W5374
Newer Guidance Including Aspects of “Product Understanding”

• “Residual Drug in Transdermal and Related Drug Delivery Systems” – Final, Aug 2011
  – Recommendations for development and throughout lifecycle to minimize residual drug in transdermal, transmucosal and topical products

  – Recommendations on evaluation of tablet scores and data to provide in the application

• “Size of Beads in Drug Products Labeled for Sprinkle” – Draft, Jan 2011
  – Recommendations for size of particles for drug products to be administered via sprinkling
Global Regulatory Environment
Global Regulatory Environment

• Enhanced development approach should not be problematic for the global regulatory environment

• Opportunities for flexibility regulatory approaches might not be available in all regions, e.g.,
  – Acceptance of design space approach
  – Agreement on PAT and/or RTRT approaches
  – Establishing clinically relevant specifications

• Further collaboration, communication and education with non-ICH regions may be needed
ICH Quality Implementation Working Group (Q-IWG)

• Scope: Ensuring harmonized implementation of ICH Q8, Q9 and Q10

• Identified areas needing further clarification:
  – Knowledge Management
  – Design Space, Real Time Release, Control Strategy
  – Pharmaceutical Quality System

• Publication of Q&A

• Training issues

• Collaboration

(Adapted from: M. Nasr, J-L Robert, 2011 DIA Annual Meeting)
ICH Q-IWG Achievements Summary

• Published 45 Q&As
• Training has been a major achievement
  – ICH regions:
    • EU: Tallinn June 2-4, 2010
    • US: Washington October 6-8, 2010
    • Japan: Tokyo October 25-27, 2010
  – ASEAN, Kuala Lumpur: July 2010
  – IFPMA/DIA, Seoul April 2011
  – HC, Ottawa September 2011
  – APEC/AHC, Seoul October 2011
• Training material available at ICH website
(Adapted from: M. Nasr, J-L Robert, 2011 DIA Annual Meeting)
ICH Q-IWG Achievements Summary (cont)

• ‘Points to Consider’ endorsed June 2011
  – Criticality of Quality Attributes and Process Parameters
  – Control Strategy
  – Level of Documentation in enhanced (QbD) Regulatory Submissions

• ‘Points to Consider’ document to be developed
  – Process validation/process verification
  – Role of modeling in QbD
  – Design space

• IWG work to be completed by end of 2011

(Adapted from: M. Nasr, J-L Robert, 2011 DIA Annual Meeting)
FDA Efforts in International Collaboration (Outside of ICH)

• FDA-EMA Parallel Assessment Pilot
  – Set up a pathway for knowledge sharing between FDA/ONDQA and EMA reviewers/assessors
  – Ensure consistent implementation of ICH guidelines
  – Encourage FDA-EMA joint pre-approval inspections
  – At least one application will include Japanese regulators as observers

• Pharmaceutical Inspection Cooperation Scheme (PIC/S)
  – Collaboration between regulatory agencies on pharmaceutical inspection and training

• CDER Forum for International Drug Regulatory Authorities
  – Training and information exchange forum for non-US pharmaceutical regulators
  – Typically offered twice per year; no registration fee
Summary of Progress in Global Harmonization

• Progress has been made in harmonizing implementation of ICH Q8, 9, 10
  – Both in ICH and non-ICH regions

• Efforts are ongoing within FDA and other regulatory agencies to increase global collaboration and harmonization

• Challenges still remain, including
  – Establishing an enhanced global quality culture
  – Clarity of global regulatory and GMP expectations
  – Role of compendial standards and lack of harmonization among pharmacopeias
Concluding Thoughts

• New drug development is becoming more complex
• Using a science and risk based approach for product development can facilitate successful products, throughout product lifecycle
  – Quality built into product design for its intended use
  – Can increase product and subsequent process robustness
• In some cases, regulatory flexibility can result from increased product and process understanding and controls
  – Good progress through ICH documents and IWG activities
  – Increased global coordination will be necessary to fully harmonize these approaches
Thank you!

Questions, comments, concerns:
NewDrugCMC@fda.hhs.gov