



42nd
Annual Meeting



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QbD Pilot Program Experience

Patricia C. Tway, PhD

Vice President

Regulatory & Analytical Sciences

Merck

Product Introduction

- **Drug substance**
 - Stable, highly soluble
- **Drug product**
 - Immediate release film-coated tablet
 - 3 potencies, weight multiples
 - Rapidly dissolving
 - Simple direct compression process



History

- **June 2004**
 - Introduced QbD examples for various products
- **June 2005**
 - Discussed QbD for Drug Product MK-X and Streamline NDA documentation
- **Sept 2005**
 - Accepted into Pilot
- **Nov 2005**
 - Built upon June 2005 discussion
 - Also presented QbD for Drug Substance



NDA Filing

- **Preparation of the CTD w/ relevant information**
 - Increased level of detail in 3.2.P.2 in lieu of executed batch records
 - Simplified analytical method development and analytical validation sections
 - Provided stability summary data in lieu of individual data
 - Pursued streamlined approach to final product quality testing



III. Testing Strategy

Traditional Release Approach

MK-X Release Testing Approach

API Blend

Lubricant Blend

Compress

Film coat

Laboratory

Manufacturing Floor
Composite Assay
Dosage Uniformity by Weight

Manufacturing Floor
Disintegration
ID
Appearance

No laboratory testing required

Lab Tests

HPLC
Content Uniformity
Composite Assay
Degradates
ID
Dissolution
Appearance



Risk – Based Process Development

- Identify the process risks
- Conduct experiments to probe the risks
- Evaluate potential critical parameter sensitivities
- Define operating ranges for process parameters to establish the “design space”



Drug Substance

- **Monohydrate salt selected**
 - Stability
 - Sticking
- **Design Space**
 - Asymmetric hydrogenation
 - Kinetics vs. selectivity
 - Crystallization of penultimate intermediate
 - Assure appropriate enantiomeric excess
 - Crystallization of drug substance
 - Assure monohydrate
 - Particle size control through seeding and knowledge of crystal growth kinetics
 - Control of final drying
 - Assure monohydrate



Drug Product

- **Risks proactively identified for the MK-X DC process included:**
 - Segregation during blending and compression
 - Sticking to tooling during compression
 - Breakage during film coating



Risk – Based Process Development

- **Development focused on segregation risk:**
 - Considered segregation potential when selecting grades of key excipients
 - Thoroughly characterized blending process, looking for evidence of segregation
 - Used conventional blend sampling and NIR
 - Conducted detailed sampling at beginning and end of compression step
 - Developed an at-line NIR method for detailed characterization of core tablet composition across the batch



Risk – Based Process Development

- **Development focused on sticking risk:**
 - Optimized lubricants to minimize sticking tendency
 - Probed effect of lubrication process parameter variation on sticking tendency
 - Probed effect of tool design and tool surface condition on sticking tendency
 - Probed effect of API particle size changes on sticking tendency



Pilot Program

- **IR Letter Received**

- Focus of Questions:

- How design space/control space can be captured at operational level
 - How design space would be redefined when change occurs
 - For each unit operation clear definition of design space, control space, critical and non-critical parameters
 - Regulatory agreement – not in original filing
 - Request for NIR details



Pilot Program

- Teleconference/face-to-face meetings to obtain clarification arranged quickly
- Good science based dialog based on understanding the needs of both partners.
- Responses to IR letter will be grouped



Pilot Program

Saga to be continued!

