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Quality of Medicines in a Globalised World: Dreams and Reality

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Plenary Session

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“QbD and Analytical Considerations – Opportunities and Challenges”

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Quality of medicines in a globalised world:
Dreams and reality

International conference Organized by EDQM
Prague, Czech Republic
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Outline

• Introduction
  – International Collaboration
  – Role of EP in US Drug Regulations
• QbD and Analytical Considerations
  – Key Opportunities and Challenges
• Concluding remarks
FDA 21st Century Initiative

Guiding Principles:

• Risk-based orientation
• Science-based policies and standards
• Integrated quality systems orientation
• International cooperation
• Strong public health protection

September 2004 Report - International Cooperation

• Enhanced collaboration with international health and regulatory partners to harmonize pharmaceutical quality standards and requirements
  – Multilateral and international forums
  – ICH/VICH
• Development of bilateral and multilateral confidentiality agreements
• Seeking membership in the Pharmaceutical Inspection Cooperation Scheme (P.I.C/s)
Role of EP in US Drug Regulations

• Q4(B) Process
• MAPP 5310.7 - Acceptability of Standards from Alternative Compendia (BP/EP/JP)
  – This MAPP applies to the CMC evaluation of new drug applications performed by ONDQA
  – FDA accepts proposals to use a quality standard from the BP, EP, or JP as part of the specifications for an excipient, drug substance, or drug product in the drug application
    • Providing that BP, EP, or JP standards are equal to or better than the corresponding standard in the USP/NF
  – Applicants are responsible to justify the use of a standard from the BP, EP, or JP in lieu of the USP/NF standard in the application

FDA and ICH Guidance

Sept 2004
Guidance for Industry
Quality Systems Approach to Pharmaceutical CGMP Regulations

Sept 2006
Guidance for Industry
Pharmaceutical Development

Nov 2005 & Nov 2008
Guidance for Industry
Quality Systems Approach to Pharmaceutical CGMP Regulations

November 2005
Guidance for Industry
Process Validation: General Principles and Practices

June 2008
Guidance for Industry
Process Validation: Specific Process Areas

April 2009 & Ongoing
Guidance for Industry
Process Validation: Specific Process Areas
Recent ICH Quality Guidances –

- Pharmaceutical Development - Q8(R2)
  - Describes good practices for pharmaceutical product development
  - Introduces concepts of design space and flexible regulatory approaches
  - Introduced and elaborated on QbD concepts

Example QbD Approach - Q8(R2)

- Quality Target product profile (QTPP)
- 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
Role of Analytics in QbD

- **Pharmaceutical Development**
  - Enhances understanding of process chemistries
  - Continual Improvement
    - Monitor trends in product quality
  - Process Monitoring & Control
    - Makes corrections before failures occur
    - Allows implementation of RTRT

**Analytics in Pharmaceutical Development**

- **Drug substance synthesis and manufacturing**
  - As a screening tool to identify optimal chemistry
  - Continuous monitoring of crystal growth to select optimal reaction conditions
- **Drug product manufacture**
  - Understanding excipient - active interactions
  - Defining design space
    - Measuring CQAs during experimentation
    - Identifying optimal manufacturing conditions
- **Examples**
  - Analytics in Process Monitoring & Control
  - Analytics in Continuous Monitoring
Example #1: Analytics in Process Monitoring & Control

Collect in-process information for timely control decisions

- Tablet potency measured by on-line NIR
- Potency measured on individual tablet samples at timed intervals
  - Provides fast response
  - Early detection of potential problems
  - Highly automated - less resource requirement

Example #2: Analytics in Process Monitoring & Control

Continuous in-process monitoring of Critical Quality Attributes

- Raw materials & API dispensing
  - Specifications based on product
- NIR Monitoring
  - Blend Uniformity
- Laser Diffraction
  - Particle Size
- NIR Spectroscopy (At-Line)
  - Identity
  - Assay
Example #3: Analytics in Process Monitoring & Control

Multivariate models as surrogates for traditional release tests

PROCESS DATA

RAW MATERIAL DATA

Qualitative Assessment by PCA

Manufacturing Data

Quantitative Prediction by PLS

Calibration Data

Examples of Analytics in Continuous Monitoring

- Continuously trending process parameters
  - Multivariate Statistical Process Control (MSPC)
  - New batches projected onto the MSPC model to demonstrate conformance

- Develop information rich assays of raw materials, to monitor integrity of supply chain

- Chemometrics to analyze data from various analytical methods (e.g. enzymatic assay + LC-MS)
Considerations for QbD based Analytical Method Development

Sampling Considerations

- Probe/sample location representative of entire vessel
- Sample interface
  - Remains constant over the process (e.g., no fouling)
  - Environmental factors (e.g., temperature, humidity)
- Sample volume/mass
  - Determine amount of sample measured
  - Compare to unit dose
- Sample acquisition time
  - Suitable for system dynamics/mixing
Considerations for Regulatory Documentation of Spectroscopy/Chemometric Methods

ICH Q2(R1) is mostly applicable to multivariate methods
- Specificity
- Linearity
- Range
- Accuracy
- Precision
- Detection Limit
- Quantitation Limit
- Robustness
- Model Maintenance
- Representative Sample
- Reference Method

Chemometric Model Development Considerations

- Calibration data
  - Include potential sources of variance (e.g., operating conditions, raw materials, scale)
  - Uniform distribution of spectra over the analysis range
- Calibration Model
  - Model development
    - Appropriate data pre-treatment, preferred to have physical basis
    - Appropriate spectral ranges
    - Number of model factors justified
    - Avoid overfitting
  - Model validation
    - Internal validation using subsets of calibration data
    - External validation using an independent data set
- Robust and representative reference method
Chemometric Model Maintenance and Update Considerations

- NIR model results may change with time as new sources of variability are introduced
  - Changes in raw material suppliers, process changes
- Evaluation of outliers as part of maintenance
  - Can detect bad spectra or interface problems
  - Usually implemented through examination of residuals
- Procedures in place to monitor and update the model
  - Done under the manufacturer's quality system
  - Include frequency and methods of periodical model evaluation
- Depth of validation done on updated model, depending on level of change

Considerations for Models Serving As Surrogates for Release Tests

- Demonstrate discriminatory power of the model
  - Compare model to a robust and discriminatory reference method for a statistically acceptable number of batches
- Demonstrate model performance at commercial scale
  - Understand model limitations and model assumptions
- Robust calibration model
  - Include as many possible variations in raw materials/process conditions to cover the entire design space
- Include an independent dataset for validation
Considerations for Maintenance of Models

• Develop and document procedures on how to evaluate and update the calibration model
  – How to deal with OOS results
  – Develop criteria for model re-calibration
• Verify or recalibrate the model for process changes:
  – Revising the operating ranges
  – Change in raw materials
  – Change in manufacturing equipment or measuring instrument
• Include plans for model maintenance/update in the firm’s Quality System
  – Tracking/trending (for process monitoring) included within the Quality System

Challenges in Applying QbD Principles for Analytical Methods
Implementing QbD for Analytical Methods – Industry Approach

- Defining ATP (Analytical Target Profile)
  - What is the method intended to do?
- Defining analytical Method Operable Design Region (MODR)
  - Risk assessment techniques to identify parameters that have significant impact on method performance
  - Use of in silico procedures for method optimization
  - Statistically based Design of Experiments (DOE) to define MODR
- Flexibility to implement alternate analytical methods that meet the defined ATP
  - Changes managed under the firm’s internal quality system
- Risk based approach to maintain/improve analytical method over the product life cycle

Implementing QbD for Analytical Methods – Regulatory Perspective

- Availability of adequate data to support proposed MODR
  - Includes variation in raw materials, sites, analysts
- Primary analytical method should be identified
- Inappropriate to use alternate methods upon detection of failure by primary methods
- Proposals to switch to alternate analytical methods implemented via Comparability Protocols
  - Methods that have similar operating principles
Areas For Further Research

- Development of additional PAT tools for feed-back or feed-forward control
- Defining techniques for implementing model predictive controls
- Establishment of robust procedures for analytical data handling over the product life cycle
- Defining representative sampling to consistently assure product quality over time
  - Location of sampling probes
  - Sample size and sampling frequency
- Updating existing public standards to allow leveraging of modern analytical methods
- Harmonizing global regulatory approaches for reviewing QbD implementation in analytical methods

Importance of the Updated Public Standards

- Provide better assurance of the quality of marketed products by using appropriate and modern analytical methods
- Prevent fraudulent suppliers from adding components that in the past have eluded existing identity tests due to similar properties
- Provide significant improvement to the safety nets that keep substandard drugs from reaching the marketplace
Concluding Comments

• Implementation of modern analytical methods in the QbD paradigm, is progressing well
• There is a need to address remaining gaps and to encourage innovation and new technologies
• Opportunities for global harmonization of regulatory expectations
• Need to revise existing standards to include modern analytical methods to meet global supply chain challenges

Thank you!

Questions, comments, concerns:
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International Harmonization and Scientific Development of Quality Practices

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NIHS, MHLW
EDQM International Conference on Quality of Medicines in a Globalized World, Prague, Czech Republic, October 14, 2010

Outline of presentation

• Development Needs with International Harmonization and under the 2005 Pharmaceutical Affairs Law
• Regulatory Sciences Studies
  Quality System, GMP guidance, Tech Transfer
  GMP inspection policy, guidance and Quality System
  Manufacturing process commitment in Approval Letter
• Health Science Studies
  Analytical Methods Development to support product development and manufacturing controls
Revision of the Pharmaceutical Affairs Law
(effective April 2005, published in 2002)

- **Revision of the Approval and Licensing System**
  - From Manufacturing (or Importation) Approval/License to **Marketing Authorization**

- **Enhancement of Post-marketing Measures**
  - To clarify the Market Authorization Holder’s (MAH) responsibility of the safety measures as well as quality management (GVP, GQP)

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**Revision of the Quality Regulation and Needs for Practice Development**

1. MAH’s responsibility for the Quality management
2. Requirement Changes in Approval Matters
3. Drug Master File system to support CTD based application
4. Consolidation of the Legal Positioning of GMP
5. Revision and Consolidation of GMP standards
Revision of the Quality Regulation and Needs for Practice Development

1. MAH’s responsibility for the Quality management
   New Ministerial Ordinance (GQP), Guidance- ICH Q10
2. Manufacturing process commitment
   Policy Notification, Guidance- Case study, Mock
3. Drug Master File system
   Policy Notification
4. Consolidation of the Legal Positioning of GMP
   Revise GMP Ministerial Ordinance,
   Policy Notification: Pre-approval and Foreign inspections
5. Revision and Consolidation of GMP standards
   Revise GMP Ministerial Ordinance,
   Guidance: Product GMP, Change Control

Regulatory Science Studies

- Quality System, GMP guidance (2002-2010)
  QS, Regulations, Product GMP, Information Flow/Tech Transfer, Lab Control, Change Management, Quality System
  Policy, System Base, Check (Reference) list, Inspection Scenario, Quality System
- Manufacturing Process Commitment (2003-2011)
  Survey, Technical Elements, Policy Notification, Mock for AL and P2
- Clinical Supply GMP Policy
- Sterile Manufacturing GMP guidance
Expected Outcome

For Industry

- Establishment of quality management system from development to post-marketing

For regulatory authority

- Improvement of the approval review system by integration of the review and the GMP inspection
- To concentrate on higher risk products
- The establishment of effective, efficient, and streamlined quality regulation

The 2003 ICH Quality Vision

Industry parties and regulatory authorities of the ICH Quality met in Brussels in July 2003 and agreed on the ICH Quality vision “A harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science”.

In order to develop a modern pharmaceutical quality system, discussions on two topics, 1) Pharmaceutical Development (Q8) and 2) Quality Risk Management (Q9) started. The guidelines on the two topics were published in 2006 in the three ICH regions. Pharmaceutical Quality System (Q10) was published in 2008.
**Pharmaceutical Affairs Law (PAL), ICH Q8/Q9/Q10 and MHLW Grant Regulatory Science Studies**

<table>
<thead>
<tr>
<th>PAL regulation changes</th>
<th>ICH discussion</th>
<th>Regulatory science groups</th>
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<tbody>
<tr>
<td><strong>2002</strong></td>
<td><strong>2002</strong></td>
<td><strong>2002</strong></td>
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<tr>
<td>Revised PAL published</td>
<td>CTD Q&amp;A</td>
<td>QS/GMP guidance</td>
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<td><strong>2004</strong></td>
<td><strong>2003</strong></td>
<td><strong>2003</strong></td>
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<td>PMDA established</td>
<td>GMP workshop in Brussels</td>
<td>CTD mock</td>
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<tr>
<td>New GMP standards</td>
<td>Q8 and Q9 started</td>
<td>Approval matters</td>
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<tr>
<td><strong>2005</strong></td>
<td><strong>2004</strong></td>
<td><strong>2004</strong></td>
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<tr>
<td>Approval matters policy</td>
<td>Revised PAL enforced</td>
<td>Inspection Policy</td>
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<tr>
<td>Inspection policy published</td>
<td>Q8 reached step 2</td>
<td><strong>2005</strong></td>
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<td><strong>2006</strong></td>
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<tr>
<td>Product GMP guidance</td>
<td>Q9 reached step 2</td>
<td>Inspection Policy</td>
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<tr>
<td>Sterile process guidance</td>
<td>Q8 and Q9 reached step 4</td>
<td><strong>2006</strong></td>
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<td><strong>2008</strong></td>
<td><strong>2007</strong></td>
<td><strong>2007</strong></td>
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<tr>
<td>Clinical Supply GMP</td>
<td>Q10 reached step 2</td>
<td><strong>2008</strong></td>
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<td>Q10 and Q8R reached step 2</td>
<td>Sterile process guideline</td>
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<td></td>
<td>Q10 and Q8R reached step 4</td>
<td><strong>2008</strong></td>
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<tr>
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<td>Q-IWG and Q11 started</td>
<td>P2/application mock</td>
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<td>Change management system</td>
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<td>GMP for IP</td>
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**Application Form after the Enforcement of Revised Pharmaceutical Affairs Law**

- **OLD APPLICATION**
  - Manufacturing Application
  - Approval Matter (Specification)
  - GAIYO
  - Batch Data etc
  - Quality Information

- **CTD-BASED APPLICATION**
  - Marketing Application
  - Partial Change (application)
  - Minor change (notification)
  - Module 2
  - Batch Data etc
  - Quality Information

**Application form**
- Specification + Manufacturing (Process Control)

**Module 3**

10
Distinctions between Partial Change Approval Application and Minor Change Notification

<table>
<thead>
<tr>
<th>Partial Change Approval Application</th>
<th>Minor Partial Change Notification</th>
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<tr>
<td>Change in the principle of unit operation of critical process</td>
<td>Process parameter to control the quality endpoint criteria</td>
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<td>Change in process control criteria as quality endpoint criteria</td>
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Classifications are determined based on the level of understanding provided in the submission.

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P2 mock for enhanced approach
-discussion purpose-

- Risk Assessment before Development, after Process Development and after Risk Control
- Design Space and Real Time Release

- DS and RTR into Approval Letter
  - Decision tree for RTR
  - Description of in-process NIR into a test method

The initial data for the P2 mock was kindly provided by AstraZeneca. The story was modified by the group. Then the case study was finalized through international public comment.
MHLW Grant (Health Science) study on Evaluation Methods for Pharmaceutical and Process Development (2004-)

- The needs-quality assurance based on science and risk management, gap between desired state and current status, rPAL and ICH
- The group structure- Industry, Academia and Government (NIHS) Joint
  (Industry: Nikki-JGC, Pfizer, Powrex, Shionogi, Santen, Takeda and Tanabe 2009 member)

List of topics in the Health Science Program (2009)

- Characterization of granulated powders by NIR and Raman imaging (NIHS)
- Characterization of formulations by Teraherz (NIHS)
- Real time monitor of chemical reaction by P-31 NMR and Raman (Santen)
- Real time monitor of MgSt in mixing process by thermal effusivity (Toho University)
- Ultra Performance Liquid Chromatography for PAT (NIHS)
- Tablet hardness and distribution of MgSt in intermediate by SEM and EDAX (Pfizer)
- Development of reproducible dissolution methods with USP stationary basket (Takeda)
- Raman spectrometric application in API crystallization process (Tanabe)
- Survey on bio process monitors (Nikki JGC)
- Quantitative analysis of crystal forms in tablet by XRD (Shionogi)
- Real time process control of coating process (Powrex)
Summary and Conclusions

• Needs of the 2005 PAL regulation changes presented.
• Challenges for implementation of the PAL with ICH guideline presented
• Challenges we face are mostly common in all regions. Hope to solve the problems with more work and international collaboration.