

# EDQM Conference

## Quality of Medicines in a Globalised World: Dreams and Reality

14-15 October 2010  
Prague, Czech Republic



©2010 EDQM, Council of Europe, All rights reserved



## Plenary Session

 Dr Moheb M. Nasr

 Dr Yukio Hiyama



©2010 EDQM, Council of Europe, All rights reserved





# “QbD and Analytical Considerations – Opportunities and Challenges”

Moheb M. Nasr, Ph.D.

Office of New Drug Quality Assessment  
(ONDQA/CDER/FDA)

**Quality of medicines in a globalised world:  
Dreams and reality**

International conference Organized by EDQM

Prague, Czech Republic  
October 14, 2010

1



## Outline

- Introduction
  - International Collaboration
  - Role of EP in US Drug Regulations
- QbD and Analytical Considerations
  - Key Opportunities and Challenges
- Concluding remarks

2

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health [www.fda.gov](http://www.fda.gov)

## FDA 21<sup>st</sup> Century Initiative

*PHARMACEUTICAL CGMPs  
FOR THE 21<sup>ST</sup> CENTURY —  
A RISK-BASED APPROACH*

*FINAL REPORT*

Department of Health and Human Services  
U.S. Food and Drug Administration  
September 2004

*September 2004*

**Guiding Principles:**

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

3

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health [www.fda.gov](http://www.fda.gov)

## 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)

4

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health www.fda.gov

## 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

5

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health www.fda.gov

## FDA and ICH Guidance

The collage includes the following documents:

- Sept 2004**: Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- Sept 2006**: Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations
- Nov 2008**: Guidance for Industry Process Validation: General Principles and Practices (DRAFT GUIDANCE)
- Nov 2005 & Nov 2008**: ICH HARMONISED TRIPARTITE GUIDELINE PHARMACEUTICAL DEVELOPMENT Q8(R2) (Current Step 4 version dated August 2009)
- November 2005**: ICH HARMONISED TRIPARTITE GUIDELINE QUALITY RISK MANAGEMENT Q9 (Current Step 4 version dated 9 November 2005)
- June 2008**: ICH HARMONISED TRIPARTITE GUIDELINE PHARMACEUTICAL QUALITY SYSTEMS Q10 (Current Step 4 version dated 4 June 2008)
- April 2009 & Ongoing**: ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (Current version dated October 20 2009)



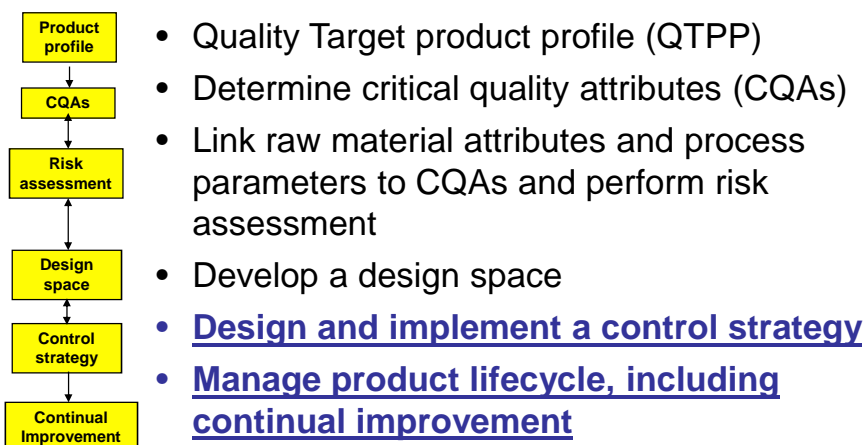
## Recent ICH Quality Guidances –

- **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

7



## Example QbD Approach - Q8(R2)



8

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health [www.fda.gov](http://www.fda.gov)

## Role of Analytics in QbD

**Key Role Throughout Drug Product Life Cycle**

**Continual Improvement**  
Monitor trends in product quality

**Process Monitoring & Control**  
Makes corrections before failures occurs  
Allows implementation of RTRT

**Pharmaceutical Development**  
Allows enhanced understanding of process chemistries

9

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health [www.fda.gov](http://www.fda.gov)

## 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

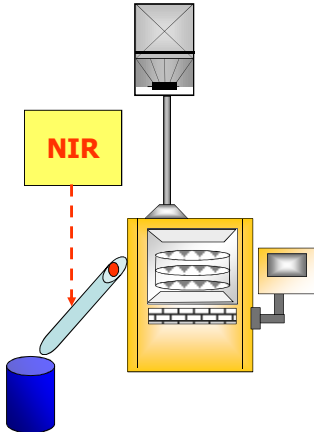
10

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

### 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

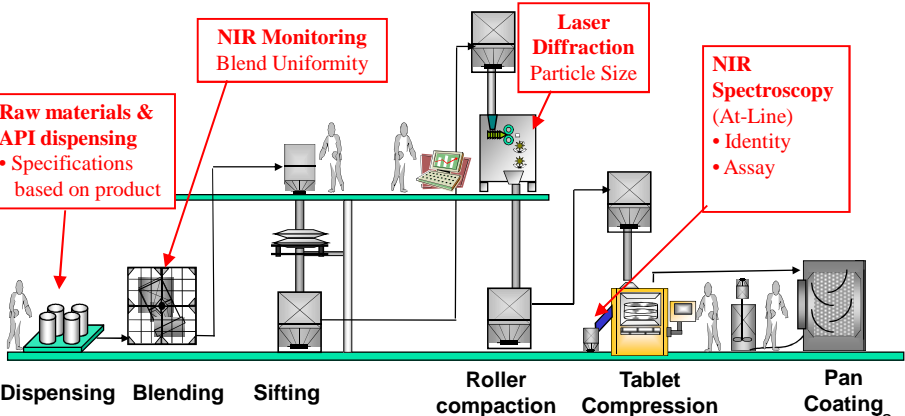


11

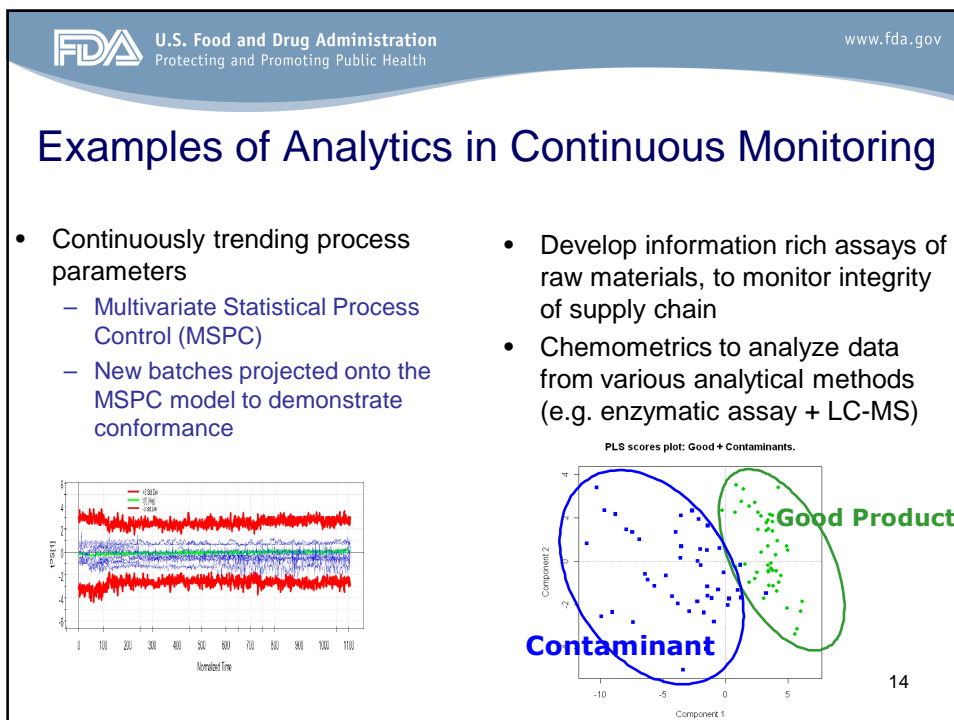
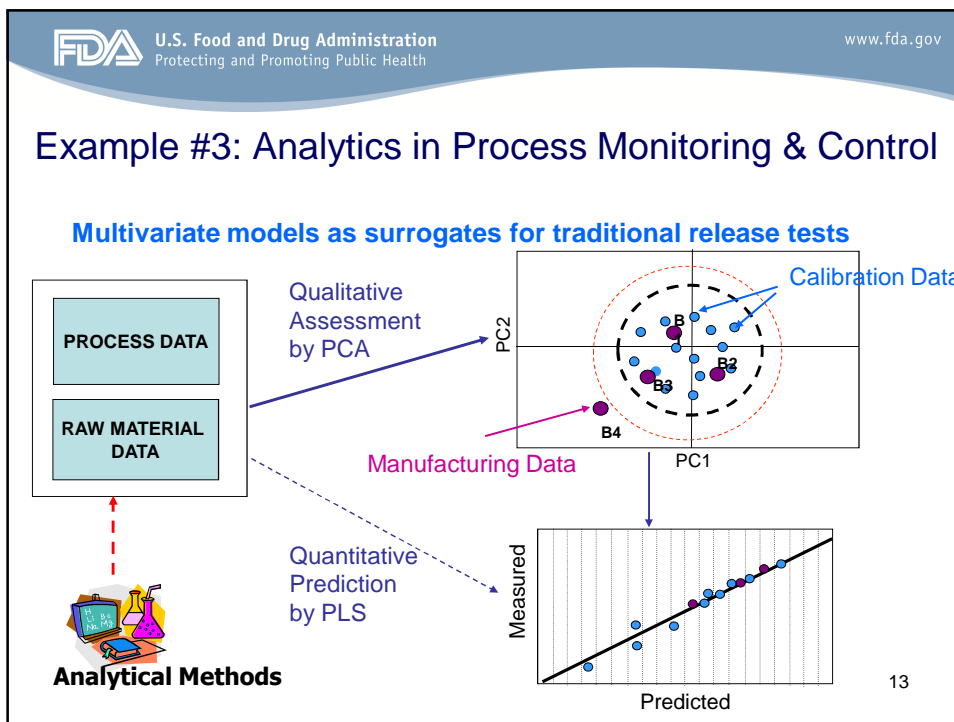
FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

### Example #2: Analytics in Process Monitoring & Control

**Continuous in-process monitoring of Critical Quality Attributes**



12





## Considerations for QbD based Analytical Method Development

15



## 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

16



## Considerations for Regulatory Documentation of Spectroscopy/Chemometric Methods

ICH Q2(R1) is mostly applicable to multivariate methods

- Specificity
- ~~Linearity~~ → Calibration Model
- Range
- Accuracy
- Precision
- Detection Limit
- Quantitation Limit
- Robustness
- Model Maintenance
- Representative Sample
- Reference Method

17



## 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

18



## 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

19



## 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

20



## 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

21



## Challenges in Applying QbD Principles for Analytical Methods

22



## 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

23



## 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

24



## 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

25



## 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

26



## 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

27



# Thank you!

Questions, comments, concerns:  
[NewDrugCMC@fda.hhs.gov](mailto:NewDrugCMC@fda.hhs.gov)

28

# International Harmonization and Scientific Development of Quality Practices

Yukio Hiyama  
Chief, 3<sup>rd</sup> Section, Division of Drugs  
NIHS, MHLW

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

1

## 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

2

## 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)

## 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

4

## 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

5

## Regulatory Science Studies

- Quality System, GMP guidance (2002-2010)  
QS, Regulations, Product GMP, Information Flow/Tech Transfer, Lab Control, Change Management, Quality System
- GMP Inspection Policy, Manual, System (2003-2011)  
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

6

MHLW slide at 2003 workshop 14/15

## 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

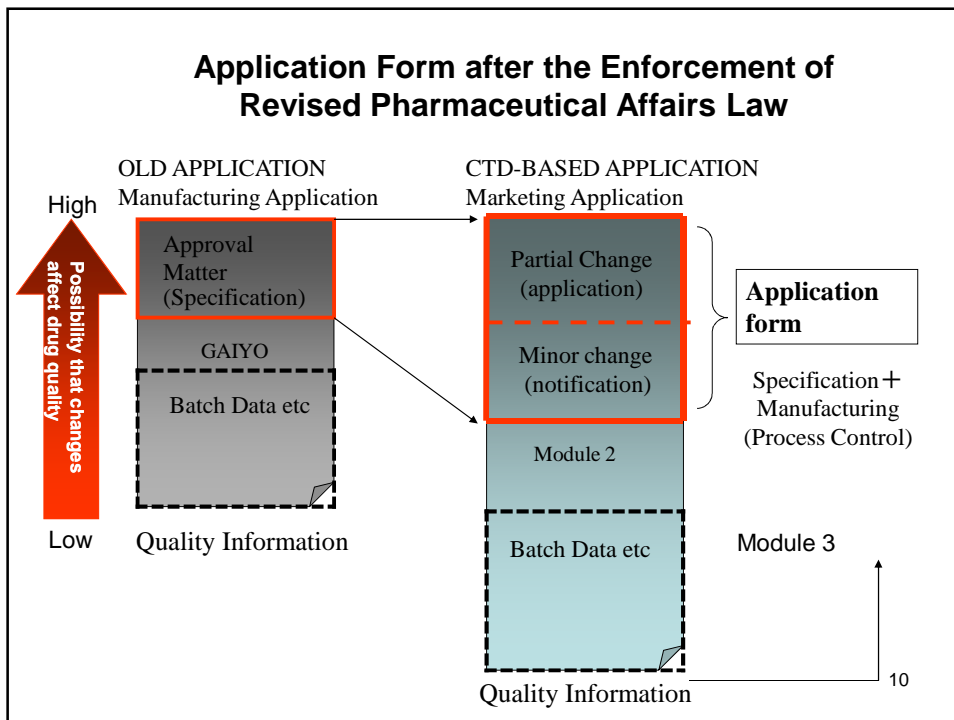
7

## 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 <b>Regulatory Science Studies</b>		
<p>PAL regulation changes</p> <p><b>2002</b> Revised PAL published</p> <p><b>2004</b> PMDA established New GMP standards</p> <p><b>2005</b> Approval matters policy <b>Revised PAL enforced</b> Inspection policy published</p> <p><b>2006</b> Product GMP guidance Sterile process guidance</p> <p><b>2008</b> Clinical Supply GMP</p>	<p>ICH discussion</p> <p><b>2002</b> CTD Q&amp;A</p> <p><b>2003</b> <b>GMP workshop in Brussels</b> Q8 and Q9 started</p> <p><b>2004</b> Q8 reached step 2</p> <p><b>2005</b> Q9 reached step 2 Q8 and Q9 reached step4</p> <p><b>2007</b> Q10 started</p> <p><b>2007</b> Q10 and Q8R reached step 2</p> <p><b>2008</b> Q10 and Q8R reached step4 Q-IWG and Q11 started</p>	<p>Regulatory science groups</p> <p><b>2002</b> QS/GMP guidance</p> <p><b>2003</b> CTD mock Approval matters Inspection Policy</p> <p><b>2004</b> Approval matters GMP guideline</p> <p><b>2005</b> Inspection Policy Skip Test guideline</p> <p><b>2006</b> Inspection Checklist</p> <p><b>2008</b> Sterile process guideline</p> <p>P2 /application mock</p> <p>Change management system</p> <p>GMP for IP</p>



## Distinctions between Partial Change Approval Application and Minor Change Notification

Partial Change Approval Application	Minor Partial Change Notification
Change in the principle of unit operation of critical process	Process parameter to control the quality endpoint criteria
Change in process control criteria as quality endpoint criteria	

Classifications are determined based on the level of understanding provided in the submission

11

## P2 mock for enhanced approach -discussion purpose-

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

The mock(2009version Sakura Tablet) is posted at

<http://www.nihs.go.jp/drug/DrugDiv-E.html>

- 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)

13

List of topics in the Health Science Program (2009)

Characterization of granulated powders by NIR and Raman imaging(NIHS)  
 Characterization of formulations by Terahertz (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)

14

## 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.