Current Status and Perspectives on QbD implementation in Japan
Disclaimer

- The information in this presentation is not intended to create any new expectations beyond current regulatory requirements.
- Is not official views of PMDA.
- Contains my personal point of view.
Introduction of PMDA

NAME:
Pharmaceuticals and Medical Devices Agency (PMDA)

Date of Establishment:

Outline

- What is QbD?
- PMDA experience with QbD
- Example: Edxaban Tosilate Hydrate
- QbD assessment project
- Japanese CMC Review System
- The most important things to implement the QbD approach
- Challenges
Transition of requirement in drug review

ICH Q8, Q9, Q10, Q11

Former

Current

Specifications

Manufacturing

Specifications

Manufacturing
The New Paradigm Emphasize

- Quality must be mainly built in and it will not only improve by additional testing and inspection
- Better utilization of modern science throughout product lifecycle
- QRM is a key enabler throughout product lifecycle
- Robust PQS, with appropriate knowledge management, assures quality throughout product lifecycle
- An integrated approach to development, manufacturing and quality for both industry and regulator
Quality by Design (Q8(R2))

- Quality cannot be tested into products; i.e., quality should be built in by design.
- A systematic approach to development begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management.
Example QbD Approach

- Define Quality Target Product Profile (QTPP)
- Determine “potential” critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space (optional and not required)
- Design and implement a control strategy
- Manage product lifecycle, incl. continual improvement

Modified from http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10/presentations.html
PMDA Experience with QbD

- **Approved products with QbD in Japan**
  Number of approved products

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- **Consultations with PMDA on QbD**
  Number of consultations

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<th>2008</th>
<th>2009</th>
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<td>2</td>
<td>2</td>
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<td>3</td>
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Example:

Edoxaban Tosilate Hydrate (1)

Report on the Deliberation Results

March 1, 2011

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name] Lixiana Tablets 15 mg and 30 mg
[Non-proprietary name] Edoxaban Tosilate Hydrate (JAN*)
[Applicant] Daiichi Sankyo Company, Limited
[Date of application] March 29, 2010

Some review reports are translated into English.

http://www.pmda.go.jp/english/service/drugs.html
Example:
Edoxaban Tosilate Hydrate (2)

2.A.(3).4) Control of drug product
The proposed specifications for the drug product include description (appearance), identification (HPLC, ultraviolet-visible spectrophotometry [UV]), uniformity of dosage units (content uniformity), dissolution (paddle method, UV), and assay (HPLC). For [blanks], an alternative test or a real-time release test (RTRT) performed as [blanks] test are defined as follows as the release acceptance criteria for the drug product.

- Approved in April 2011
- RTRT: Uniformity of dosage units, Dissolution and Assay
- The first case where RTRT for Dissolution was approved in Japan
What is Real Time Release Testing (RTRT)?

- Real time release testing can replace end product testing.
- Enhanced understanding of product performance can justify the use of alternative approaches to determine that the material is meeting its quality attributes.
- The use of such alternatives could support real time release testing.
2.B.(2) Design space to ensure dissolution

Regarding the design space for ensuring the dissolution, the applicant explained as follows:
At the time of the regulatory submission, [removed] had been determined as the factor affecting the dissolution, based on the results from [removed] to the commercial-scale production. After the submission, the concept of the control strategy on dissolution was changed from [removed] to [removed], and the dissolution-related risks were re-evaluated. As a result, a total of [removed] factors, [removed], were extracted as factors affecting dissolution. The subsequent systematic analysis of the above [removed] factors based on the design of experiments provided an equation for calculating the dissolution rate that contains [removed] as input variables. [removed] was not included in the variables of the equation, which showed that [removed] did not affect the dissolution within the range studied. With the above results taken into consideration, [removed] were identified as factors that constitute the design space for ensuring the dissolution and then a design space for ensuring the dissolution was re-constructed.
Example:
Edoxaban Tosilate Hydrate (4)

- Identification of factors affecting the dissolution
- The subsequent systematic analysis of the factors based on the design of experiments (DoE) provided an equation for calculating the dissolution rate

- Is it possible to ensure the dissolution by the mathematical model in fact?
Example:
Edoxaban Tosilate Hydrate (5)

What reviewers focused on

- Is the dissolution method adequately set?
- Is it sufficient to determine the factors affecting the dissolution?

In this case, the concept of the control strategy was changed by applicant after NDA.

What is the reason why applicant needed to change the concept?

How will the changes influence the construction of the model?
What reviewers focused on

- Is the validation/verification of the model adequate?
  - The verification of the model throughout the lifecycle is essential.

- How reliable is the model?
  - Limits of the prediction model needs to be investigated
  - Uncertainty of the model should be considered
Example:
Edoxaban Tosilate Hydrate (7)

Since the re-constructed design space for ensuring the dissolution of the drug product is configured based on the mathematical model, it is useful to ensure the performance of the model by confirming that the drug product with the appropriate dissolution rate is manufactured as expected. Therefore, PMDA considered that it was necessary to perform the dissolution test included in the specifications at release from the early post-marketing phase, and asked the applicant to confirm the performance of the equation for calculating the dissolution rate, by simultaneously carrying out the dissolution test on the commercial lots after approval, based on the production plan for the drug product as well.

- PMDA considered that this case is the highest impact model among the High-Impact Models in ICH Q-IWG Point to consider because the judgment for release is based on the indirect indicator.
To facilitate innovation, regulators and industry need to work in cooperation

- PMDA assessed
  - The relationship between each of the extracted variables and dissolution had been investigated appropriately.
  - The maintenance program was established to ensure the model’s continuity.
Example:

Edoxaban Tosilate Hydrate (9)

- However this was the first case in Japan and PMDA had little experience to ensure the dissolution by indirect indicators.

- Finally PMDA required the applicant to perform the dissolution test included in the specifications at release from the early post-marketing phase, and to confirm the performance of the equation for calculating the dissolution rate, by simultaneously carrying out the dissolution test on the commercial lots after approval, based on the production plan for the drug product as well.

One of our challenges and the best way to move forward
In November 2011, PMDA launched a new project team to handle the participation in the EMA-FDA pilot program as an observer.

The project team consisted of reviewers, inspectors, etc..
- Office of New drug I~V, GMP&QMS Inspection, International Programs, Standards and Guidelines Development

PMDA participated in • • •

- 1 parallel assessment application
- 1 biotech product that followed the consultative advice pathway
- Comments on 2 sets of Q&As that have been published
What PMDA learnt from our experience in the pilot program

- Our concerns about QbD are basically the same as FDA and EMA.
- There are no great differences in the evaluation approaches of QbD, FDA, EMA or PMDA.
- Reviewers still need a lot of time to assess the QbD approach and we tend to ask more questions than with the traditional approach.
- Regulatory actions, especially post approval change actions, might be a little different because the regulatory framework of each regulatory agency is different.

But we have realized that...
# Post-authorization procedure

<table>
<thead>
<tr>
<th>Risk of Changes</th>
<th>Japan</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Partial change (Application for approval of variation)</td>
<td>Major change (Prior approval supplement)</td>
<td>Type II variation (Application for approval of variation)</td>
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</table>
| Moderate        | Minor change (Notification within 30 days after implementation or shipping) | Moderate change  
1) Supplement-changes being effected (CBE) in 30 days  
2) Supplement-changes being effected (CBE) | Type IB variation (Notification before implementation and MAHs must wait a period of 30 days) |
| Low             | Minor change (Annual report)              | Minor change (Annual report)               | Type IA variation (Notification within 12 months after implementation) |
Relationship between Application Form and CTD Documents in Japan

Application Form

Extracted

Module 2 (QOS)

Summarized

CTD Module3

Approval Matters

Major review document

Raw data
Matters to be described in manufacturing section of Application Form

- All processes from raw material(s) to packaging process
  - A flow diagram of manufacturing process including:
    - Raw materials
    - Charge-in amounts
    - Yields
    - Solvents
    - Intermediate materials
    - Process parameters (e.g. Target Value/Set Value)

- A narrative description of manufacturing process
  - Acceptance criteria of starting material(s) and intermediate materials
  - In process control, Design Space, RTRT etc.
How to describe partial change matters and minor change matters

- Enter target/set values of process parameters and standard charge-in amounts in
  - 《 》: partial change matter
  - 『 』: minor change matter

- Enter items other than target/set values in
  - “ ”: minor change matter
  - No parentheses: partial change matter
Step 1 (Critical Step)

CP-6 (230kg), tetrahydrofuran (1300L), sodium carbonate (42.4kg) are combined. Ethyl chloroformate “158 ~ 592kg” is added and the mixture is heated at temperature up to reflux. ・・・・

Water (“25 to 35%” *weight per weight of ethanol) is added and the mixture is stirred at 20℃

* Water quantity is relative to the ethanol quantity, ethanol volume and crystallization temperature are parameters establishing Design Space which controls the quantity of total impurities.

Reference : Sakuramil (Sakuramil S2 mock)
What are the most important things to implement the QbD approach?

- **Understanding** the drug character at a deeper level.
  - for example, manufacturing and developing process

- **Using the knowledge**, consider a way to develop strategy and manage the risk.

- **Sharing** the information with one another.
  - regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc.
Quality risk management

- Provides a proactive means to identify and control potential quality issues during development and manufacturing
- Further ensure the high quality of the drug (medicinal) product to the patient
- Facilitates better and more informed decisions
  - Provide regulators with greater assurance of a company’s ability to deal with potential risks
  - Beneficially affect the extent and level of direct regulatory oversight
Risk communication

- Sharing of information about risk and risk management
- Between the decision makers and others
- Parties can communicate at any stage of the risk management process
- Communications might include regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc.

Risk communication between applicant and regulator is important in NDA review
Challenges

- **How to decrease our burden?**
  - Share our experience and knowledge
    - QbD Pilot Program, Workshop, Training
    - Take advantage of Module 2 (over all summary)

- **How to encourage continuous improvement?**
  - Increase flexibility in post approval changes
    - Application form, annual reporting system, post approval change management protocol

To be discussed at ICH Q12 (Life cycle management)
Following the quality assurance policy based on guidelines not only from Q1 to Q7 but also from Q8 to Q11,

A harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science will be finally built up.

Better quality medicines to patients
Thank you for your attention

QbD Assessment Project at PMDA

http://www.pmda.go.jp/english/service/qbd_e.html