ICH Q8: Pharmaceutical Development

Pharmaceutical Quality Forum
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Outline

- Background to Q8
- Q8 - an opportunity for change
- Progress to date
- Implications for the future
High level purpose of Q8

To provide [harmonised] guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development) for new drug products

- **Scope**
  - Products as defined in scope of Module 3 of the CTD
  - May also be appropriate for other categories of products.
    - Consult with the appropriate regulatory authorities.

For a better understanding we need to examine the drivers and deliverables.
**Life before Q8**

- **US - design and development information submitted is variable**
  - Some submitted via INDs
  - Some companies submit EU report
  - Information also distributed around NDA
    - Variable levels of information given by Industry, due to concerns over consistency of review and questions

- **EU - Development Pharmaceutics**
  - Describes formulation development, the critical product attributes, and design of the manufacturing process

- **Japan - limited expectations**
  - More detail expected for complex dosage forms
What’s wrong with the status quo?

- **US CTD** focuses on future regulatory commitments
  - Sponsor generally doesn’t describe how they designed their product
    - Creates a “check-list” submission and review paradigm
    - Current ‘Development Report’ aimed at successful PAI
- **EU CTD** has Dev Pharmaceutics as a ‘cornerstone’ of submission
- **Japan** has greater emphasis on Module 2 yet P2 is in Module 3 and only summarised in Module 2

- **Regional disharmony**
  - We have a P2 section in the CTD
    - Harmonised guidance on content would be helpful

Limited (regulatory) incentive to truly understand our processes and products, and optimise them
Q8 – an opportunity for change

• Adoption of Q8 philosophies can create a new paradigm and set of opportunities for Industry and Regulators

A manufacturing sciences based approach to Registration and Approval

FROM
Data
TO
Information
& Knowledge
Adoption of Q8 delivers a new state:
(as agreed by EWG)

1. Product **quality and performance achieved and assured by design** of effective and efficient manufacturing processes

2. Product **specifications based on mechanistic understanding** of how formulation and process factors impact product performance

3. An ability to effect **Continuous Improvement and Continuous "real time" assurance of quality**

Q8 presents the opportunity to tell a great story
Adopted as ICH topic October 2003
4 Expert Working Group meetings
Step 2 (Draft for Public Consultation) achieved in Yokohama
Q8 was envisaged as a 2 part guideline

Part 1
- Core document
- Baseline expectations
- Optional information
- Regulatory Flexibility

Part 2
- Annexes relating to specific dosage forms
- Appropriate examples of risk management
  - Using Q9 toolbox

ICH partners discussing revision of Q6a vs. Part II of Q8

Step 2: Nov 2004
Not all information “mandatory”

Guideline constructed to avoid potential misunderstanding that may evolve from this

Guideline describes one system with different levels of design focus

we use the “design space - predictive ability” principles as a means to create a continuous framework and avoid “two different systems”
Pharmaceutical development is a learning process
- We can describe both successes and failures as part of the story which demonstrates QbD

Information from pharmaceutical development studies is a basis for risk management

Critical attributes and parameters carry the risk
- Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product

This assessment helps define ‘design space’
Design space is the established range of process parameters that has been demonstrated to provide assurance of quality.

In some cases design space can also be applicable to formulation attributes.
Industry and the Regulatory Agencies need to think differently

- Industry submissions change
- Agency reactions change

What’s in a name?

When is a change is not a change....

Work in progress
Design Space facilitates regulatory flexibility

Traditional process – limited knowledge – 3 batches, any change needs new data and new approval

New paradigm: influence of factors explored creating knowledge. Risk analysis of impact of change possible. Approval to move within defined area post-approval could give flexibility for continuous improvement without need for further approval
Can we reduce the post-approval change burden?

- Can comparability protocols allow change outside known factor space?
- What if a region doesn't have such protocols?

Factor space explored at initial filing

Industry wants ability to explore new regions based on pre-approved design space, protocols and criteria
Industry’s Desire
- Should be consistent around the world

Regulators’ views
- EU & FDA - movement in the agreed design space is not a change
- Japan - would need notification (minor change) within 30 days of ‘change’
  - Data held at site
FDA - several ways - e.g. can use SUPAC or comparability protocols (prior approval) - demonstrate no impact on spec and performance

EU - could be Type 1 or Type 2 variation, but use the opportunity to provide updated P2 information to give future flexibility (would force a Type 2)

MHLW - Partial change, and update to P2 is attractive to enable potential future flexibility

Can we reduce the post-approval change burden?
- Can comparability protocols allow change outside known factor space?
- What if a region doesn’t have such protocols?

Factor space explored at initial filing
- a-b inside space
- b-c inside space
- c-d explores new space – comparability protocol?
- OK to do if spec not impacted?

Industry wants ability to explore new regions based on pre-approved design space, protocols and criteria
**Q8 & Regulatory Flexibility**

**IF**

- Relevant (scientific) understanding (e.g., stability and bioavailability)
- Ability to predict quality/ performance
- Confidence that product and process critical variables are controlled
  - with an appropriate ability to detect and prevent deviations
- High confidence in the value of regulatory specifications and process validation

**THEN**

- Faster CMC review more likely (no clock stops)
- Process optimisation possible without prior approval
- Risk-based Inspections feasible
  - Based on identification of critical product and process parameters
  - Systems focused
Q8 & Pharmaceutical QbD

Q8

- Fully characterised product
- Well defined process
- Assessed (& mitigated) risk
- Process monitoring plan

Framework for continuous improvement

Regulatory Flexibility

Product & Process Knowledge + Risk Management

= Manufacturing Sciences
**Future State Vision:**

**Both Regulators and Industry need to change**

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<tr>
<th>REGULATORS</th>
<th>INDUSTRY</th>
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<tbody>
<tr>
<td>Promote open communication</td>
<td>Be open and transparent in sharing knowledge: success and failure</td>
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<td>Reviewers who are accessible, engaged, and expert</td>
<td>Scientists who understand the needs of the Regulators</td>
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<td>Change the content of applications</td>
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<td>- Encourage knowledge sharing</td>
<td>- Share the knowledge</td>
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<tr>
<td>- Eliminate non-value added information</td>
<td>- Focus on manufacturing sciences</td>
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<td>More science &amp; risk-based evaluation of applications</td>
<td>Move to science-based, risk mitigated applications</td>
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<td>Reduce post-approval change regulatory hurdles</td>
<td>Provide insight into manufacturing sciences so as to reduce need for post-approval change</td>
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Q8 opens the door to the new state, but fuller flexibility needs “Q10”
Remaining Uncertainties

● Industry
  ■ What level/depth of information in P2
    ▪ P2 is a summary report so what goes in the QOS?

● Regulatory process
  ■ Incentives for Industry to do and submit the work
    ▪ More flexible manufacturing descriptions and fewer post approval submissions
  ■ Consistent review of P2 section
    ▪ Information provided may vary in depth
    ▪ Not a compliance document
    ▪ Give the flexibility & incentive
  ■ Definition of roles and responsibilities for Assessors and Inspectors

● Both
  ■ Further development of Q8
Conclusion: A Revolution is Underway

- Agencies and Industry are moving from ‘blind’ compliance to ‘science and risk-based’ compliance
  - Industry wants this to be global
- This (r)evolution is based on process understanding and continuous improvement throughout the product life cycle
- Traditional process validation being replaced by a much better alternative
  - Building in quality
  - Continuous quality verification and improvement
- Moving from ‘Quality by Testing’ to ‘Quality by Design’ should, in principle, allow significant regulatory flexibility
  - Helps both regulators and industry focus on higher risk or added value activities.

Are we all ‘on board’?