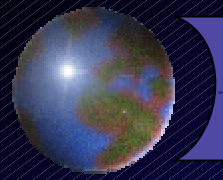

ICH Q8: Pharmaceutical Development

Pharmaceutical Quality Forum
November 2004

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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

FROM
Data
TO
Information
& Knowledge

A manufacturing sciences based approach to Registration and Approval

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

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

Q8: Progress to Date

- Adopted as ICH topic October 2003
- 4 Expert Working Group meetings
- Step 2 (Draft for Public Consultation) achieved in Yokohama

Structure of Q8

Q8 was envisaged as a 2 part guideline

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

Step 2: Nov 2004

- 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

Q8 applicable to all products -but at applicant's discretion

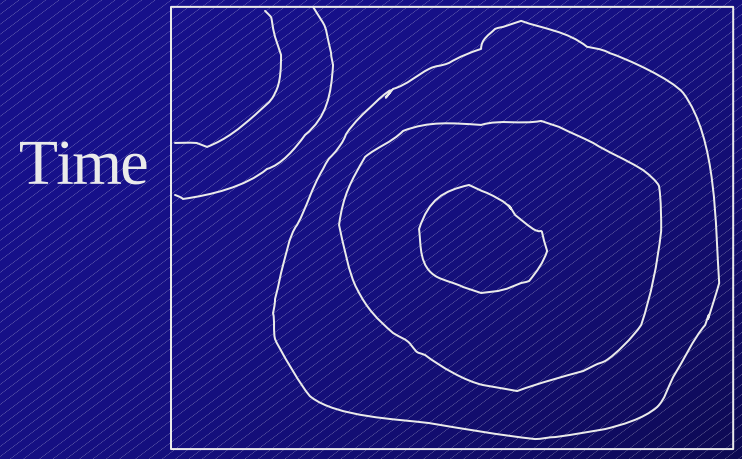
- Not all information "mandatory"
  - Guideline constructed to avoid potential misunderstanding that may evolve from this
- Guideline describes one system with different levels of design focus
  - we use the "design space – predictive ability" principles as a means to create a continuous framework and avoid "two different systems"

Q8 Key Concepts

- 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

- 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.



Future Implications

- Industry and the Regulatory Agencies need to think differently
  - Industry submissions change
  - Agency reactions change

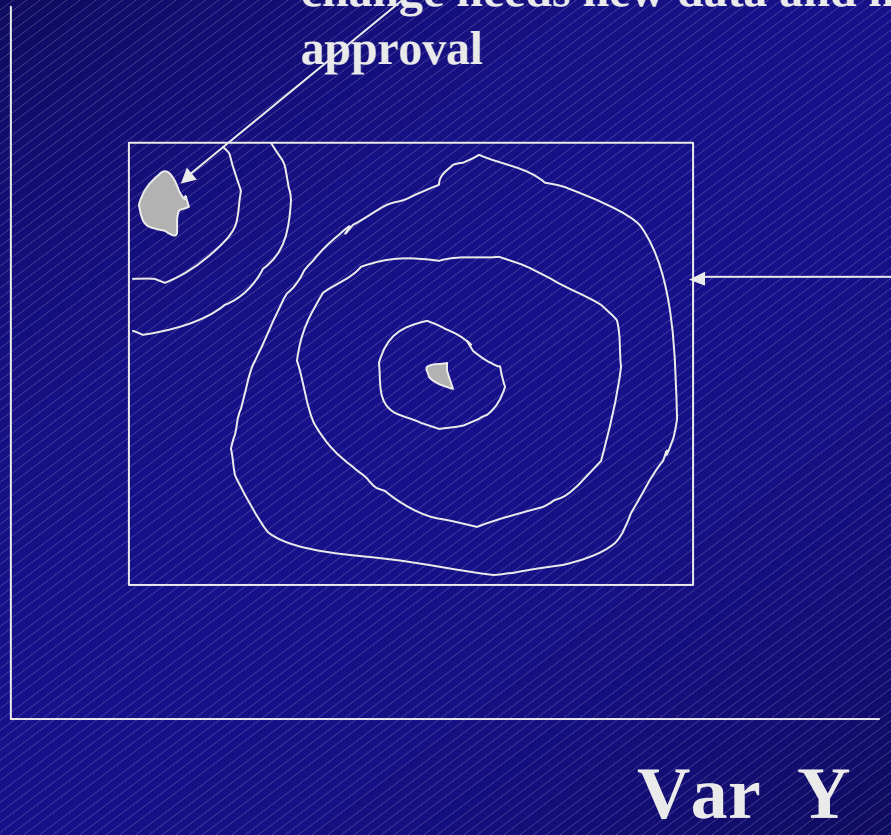
What's in a name?

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

Work in progress

Design Space facilitates regulatory flexibility

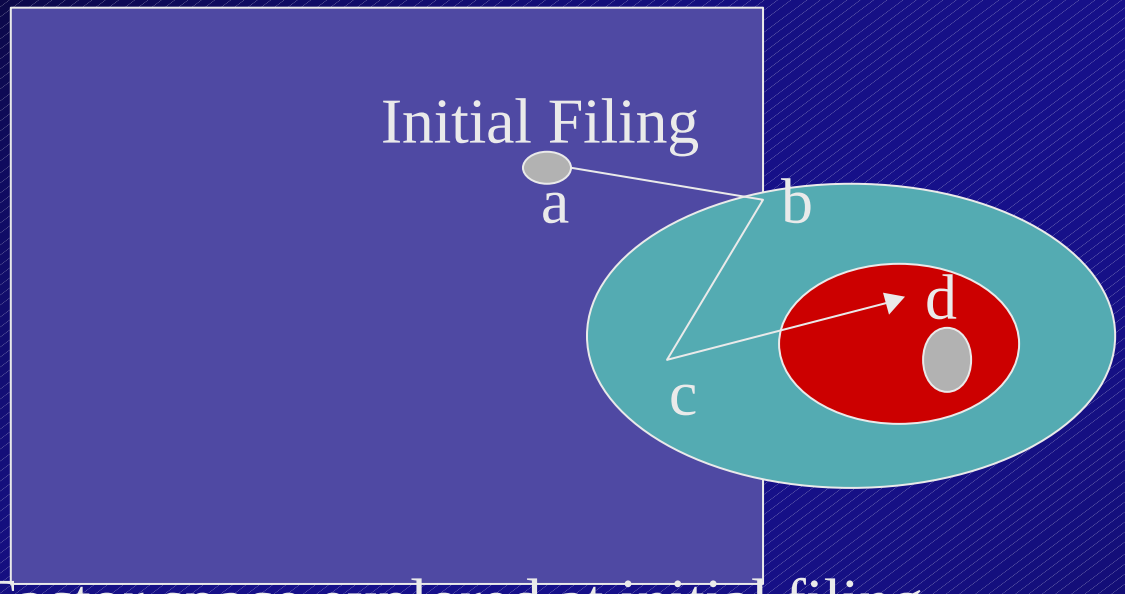
Traditional process – limited knowledge – 3 batches, any change needs new data and new approval



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?

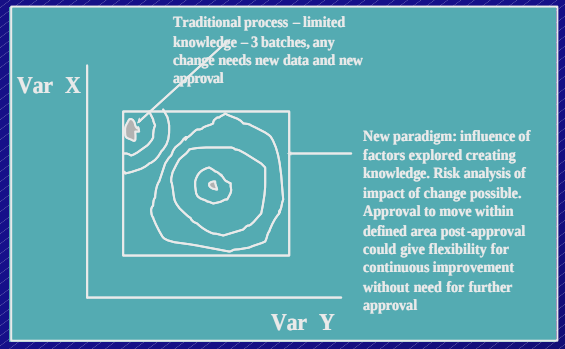


Factor space explored at initial filing

- 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

Regulatory Flexibility – within design space



- 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

Change outside design space

- 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

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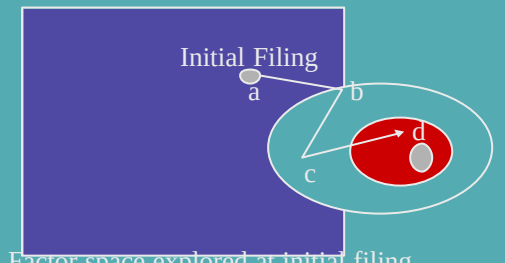

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Q8 & Regulatory Flexibility

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

REGULATORS

- Promote open communication
- Reviewers who are accessible, engaged, and expert
- Change the content of applications
  - Encourage knowledge sharing
  - Eliminate non-value added information
- More science & risk-based evaluation of applications
- Reduce post-approval change regulatory hurdles

INDUSTRY

- Be open and transparent in sharing knowledge: success and failure
- Scientists who understand the needs of the Regulators
- Change the content of applications
  - Share the knowledge
  - Focus on manufacturing sciences
- Move to science-based, risk mitigated applications
- Provide insight into manufacturing sciences so as to reduce need for post-approval change

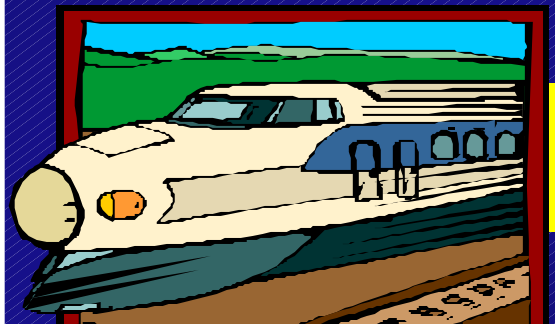
Q8 opens the door to the new state, but fuller flexibility needs “Q10”

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 Asessors 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’?