New Frontiers in the Quality of Medicines

Workshop
Pharmacopoeial Discussion Group (PDG)
& the ICH Q4B

Moderators:
Dr Michael Morris
Dr Costin Camarasu

EDQM International Conference
13-15 June 2007
Strasbourg, France
ICH Q4B: Programme of Activities

PDG and ICH Q4B

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New Frontiers in the Quality of Medicines
Strasbourg, France
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Presentation Outline

- Short history and overview of ICH Q4B
- The Pharmacopoeias and the Regulators
- The Q4B Process and Annex
- Interaction: Q4B EWG and PDG
- Current Activities for the Q4B Expert Working Group (EWG)
Background

• The harmonisation of specific compendial test chapters has been considered as critical by the ICH Steering Committee to attaining full utility of the ICH Q6A guideline.

• Industry asks ICH SC to create an EWG to address how the regulatory authorities (3 regions) will recognize the interchangeability of harmonised pharmacopoeial methods from EP/JP/USP (PDG) – July 2003

• ICH SC establishes Q4 EWG with a scope to address 11 General Test Chapters discussed during development of ICH Q6A Guideline - November 2003

• SC approves Q4B Work Plan – April 2004

Background (Continued)

• SC approves development of an ICH Guideline – June 2004

• Q4B EWG begins evaluating PDG harmonised text – November 2004

• Step 2 ICH Q4B Guideline approved by SC – June 2006

• 1st Annex (Residue on Ignition/Sulphated Ash) approved (ICH Step 2) – June 2006

• Regulatory consultation (ICH Step 3) completed by each regulatory region (60-day comment period) – October 2006

• Documents reworked based on constituent comments; ICH Step 4 documents being finalised for ICH signoff
### Q₆A-related General Chapters

<table>
<thead>
<tr>
<th>Dissolution</th>
<th>Disintegration</th>
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<tbody>
<tr>
<td>*Uniformity of Content</td>
<td>*Uniformity of Mass</td>
</tr>
<tr>
<td>Extractable Volume</td>
<td>Particulate Matter</td>
</tr>
<tr>
<td>Sterility</td>
<td>Microbiological Quality</td>
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<tr>
<td>Bacterial Endotoxins</td>
<td>ROI/Sulphated Ash</td>
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<tr>
<td>Colour and Clarity (per ICH SC, work will just be on &quot;Colour&quot;)</td>
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* Harmonised to Uniformity of Dosage Units

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### The Pharmacopoeias and the Regulators

Different Approaches for Moving Forward

<table>
<thead>
<tr>
<th>JP (PMDA)</th>
<th>Ph. Eur. (EDQM)</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Governmental</td>
<td>Governmental</td>
<td>Independent of Government</td>
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</table>

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Strasbourg – June 2007
FDA and USP – A Unique Relationship

• Federal regulation (Food, Drug, and Cosmetic Act) establishes the relationship and role of each:
  – The Food and Drug Administration (FDA) approves drug products and specifications, to ensure safety and efficacy, to include post-approval changes, inspection and enforcement, and conducting post-market surveillance.
  – The United States Pharmacopeia (USP), a non-governmental, not-for-profit private organization, is recognized as a developer of public standards to demonstrate identity, strength, and purity of pharmaceutical products.

• FDA participates on several of the USP Stakeholder Forums  
• Established FDA-USP Working Group specific for PDG matters

The Q4B Process  
Value of the Q4B Activity

• A component of international harmonisation efforts
• A savings in time and effort:
  – Industry: to globally unify testing strategies [for applications and other regulatory (compliance) needs] – one test rather than three
  – Regulators: to reduce or eliminate the need to go through a justification procedure as to the use of other compendial methods (done one time to eliminate repetitive justifications)
PDG Process Results in Harmonised Text

Individual Pharmacopoeial Approval & Official Printing Process

JP Version

USP Version

Ph. Eur. Version

Challenges for the regulators:
Do differences impact on the ability to achieve same result with same accept/reject capability?
Are they interchangeable?

Q4B Process Steps

FOR EACH TOPIC:
• PDG provides to Q4B Expert Working Group:
  – PDG-harmonised text
  – JP/Ph. Eur./USP draft version of how harmonised text will be implemented in their compendia
  – Briefing note to delineate any local differences or potential issues
  – Printing timeline to move each pharmacopoeia to official status
• Q4B member parties bring the documents back to their constituents for independent evaluation
Q4B Process (continued)

- Q4B EWG reviews the evaluations
- Issues discussed within Q4B EWG for possible resolution
- Evaluation results and possible resolution mechanisms conveyed back to and/or discussed with PDG
- Once issues are resolved, Q4B EWG recommends approval (ICH Step 2) to the ICH SC
- Start of Annex process – Moving the Q4B Outcome into the regulatory mechanisms for each region

Topic Specific Annex Process

PDG Process

PDG Document Submission

Regional pharmacopoeial implementation

Inter-regional Acceptance

ICH Process

Step 1: Q4B EWG assessment and annex development

Step 2: ICH Sign off on draft Q4B annex

Step 3: Regulatory Consultation on annex

Step 4: Annex adopted by ICH Steering Committee

Step 5: Regional regulatory implementation
Q4B EWG and PDG Interaction

- Dedicated time (generally) at each formal ICH meeting venue to discuss issues
- Stakeholder partnering – all parties focused to achieve interchangeability
- Direct feedback mechanisms to resolve issues
- Clear delineation of what steps are necessary for problem resolution
- Success more likely versus single, independent efforts

Current Status – Q4B EWG

- Residue on Ignition/Sulphated Ash ...............Draft ICH Step 4
- Extractable Volume .............................Draft ICH Step 2 in preparation
- Particulate Matter
- Sterility
- Dissolution
- Disintegration
- Uniformity of Dosage Units
- Microbiological Tests
- Bacterial Endotoxins
- Colour

Initial Q4B EWG evaluation completed – issues being resolved with PDG

PDG submissions recently received – Q4B EWG evaluating

PDG submissions to come
Acknowledgements

My thanks to:

Continuing support of the PDG Member Pharmacopoeias!

Current members of the Q4B EWG

Cindy Buhse (FDA)                  Tsueno Okubo (JPMA)
Costin Camarasu (IGPA)             Stéphanie Parra (Health Canada)
Martine Draguet (EFPIA)            Chris Potter (EFPIA)
Takao Hayakawa (MHLW)              Hideki Sasaki (JPMA)
Nobukazu Igoshi (JPMA)             Judy Shimek (PhRMA)
Robert King (FDA, Rapporteur)      Janeen Skutnik (PhRMA)
Sabine Kopp (WHO)                  Hiroshi Tsuji (MHLW)
Osamu Morita (JPMA)                Kiyomi Ueno (MHLW)
Michael Morris (EU)                Petar Vojvodic (WSMI)
New Frontiers in the Quality of Medicines
International Conference, Strasbourg
June 13-15, 2007
ICH Q4B: the viewpoint of EFPIA

Martine DRAGUET
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UCB Pharma SA

ICH Q4B: the viewpoint of EFPIA

Overview of the presentation

I. Need for “pharmaceutical harmonisation”
II. ICH Q4B background and concept
III. ICH Q4B current status
IV. EFPIA viewpoint
ICH Q4B: the viewpoint of EFPIA

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ICH Q4B: the viewpoint of EFPIA

I. Need for “pharmaceutical harmonisation”

- More and more pharmaceutical companies are developing “global” products intended for submission worldwide to regulators.
- ICH Q6A guideline’s objective is “to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products ... which have not been registered previously in the US, the EU, or Japan”.

Martine Draguet
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• Currently
  – FDA reviewers have different attitudes (some do not accept EU and JP, some are less reluctant)
  – MHLW generally requests JP monographs in the Marketing Authorisation files
  it is nearly impossible for industry to use one set of standards in the different regions, and to fully benefit from ICH Q6A.

• This situation leads to redundant testing by suppliers and pharmaceutical industry to meet differing standards.

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ICH Q4B: the viewpoint of EFPIA

II. ICH Q4B background and concept

- Harmonisation among the 3 major pharmacopoeias in the world (USP, EP, JP) in progress since 1990 when the Pharmacopoeial Discussion Group (PDG) started.
- PDG’s activities very slow over a decade.
- Adoption of necessary revisions too slow for industry.
- Acceptance by Regulatory Authorities of harmonised monographs remains difficult.
- In November 2003 an Expert Working Group was created to understand the implications of implementation of “regulatory interchangeability” and to develop ICH Q4B guideline.

- Goals of this EWG and Q4B guideline:
  - Facilitate the regulatory acceptance of PDG-harmonised texts.
  - Clearly indicate the regulatory interchangeability status of harmonised text for each of the regulatory regions, as well as to indicate the effective date to begin use on applicable regulatory documents.
  - Ensure that from a regulatory perspective the interchangeability is based on sound science.
  - Facilitate regulatory and industry access to the harmonised text, ensuring that all are aware of exactly what text has been reviewed and given a status for interchangeability.
  - Working with the Pharmacopoeial Discussion Group to expedite the implementation for the interchangeability.
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III. ICH Q4B Current status
1. Current Status
   • Q4B guideline
     → Step 2 in June 2006
     → Comments analysed by EWG in Oct. 2006
     → Step 4 in October 2007?
   • Initial title of Q4B guideline
     “Regulatory Acceptance of Pharmacopeial Interchangeability” has been modified to “Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria” to take regional specificities into account.
   • Agreement on objectives of the guideline and on implementation principles has been reached.
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• Q4B Annex 1 on Residue on Ignition
  → Step 2 in June 2006
  → Step 4 in October 2007 (impossible before main guideline reaches step 4)

• Other annexes in progress between PDG and Q4B EWG
  • Extractable volume
  • Particulate matter
  • Microbiological quality of non-sterile products
  • Uniformity of dosage units
  • Disintegration
  • Dissolution

2. Structure of Q4B guideline
• Main Guideline describing the process
• Topic Specific Annexes describes for each topic considered:
  – Q4B outcome, interpretation of how APAC should be used
  – Implementation date
  – Reference of
    • PDG document (published by Pharmacopoeia lead)
    • Pharmacopoeia supplement (USP, EP, JP) where the content of the topic-specific annex is published.
3. **Q4B Evaluation Process**

- Q4B EWG evaluates scientifically pharmacopoeial text proposals and assesses the regulatory impact of the proposals.
- The text proposals are provided by PDG (or one or more Pharmacopoeia at stage 5B of the harmonization process (= document submission).
- Classical ICH steps (1 to 5) are followed, leading to a topic-specific annex. This annex provides the “Q4B outcome” explaining to stakeholders when they can begin referencing the pharmacopoeial text and in which conditions.
ICH Q4B: the viewpoint of EFPIA

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IV. EFPIA Viewpoint

• Progresses are slow (PDG and Q4B)
• Q6A general chapters (Uniformity of dosage Units, Dissolution, Disintegration, extractable volumes, particulate matter, sterility, microbiological quality, bacterial endotoxins, residue on ignition, sulphated ash, colour) need to be completed by other monographs and methods
• Maintenance of Q4B topic-specific annexes will require additional work (in case of update by pharmacopoeias)
• Recent ICH guidelines (Q8/Q9) would also benefit from better “interchangeability” of compendial texts in the 3 ICH areas.
ICH Q4B: the viewpoint of EFPIA

• FDA initiative on “Acceptability of Alternative Compendia” in the MAPP (Manual of Policies and Procedures published in February 2007 on FDA website and withdrawn shortly after) gives an encouraging signal
• EFPIA is currently considering the best way to
  - address difficulty to reach agreement on
    "Pharmacopoeial interchangeability"
  - address the lack of significant progress on Q4B despite huge involvement of parties
  - e.g. by revisiting Q4B objectives?
    • Short term?
    • When Q6A general chapters are completed?
    • Under PDG umbrella?

ICH Q4B: the viewpoint of EFPIA

• Legal and regulatory constraints cannot not be underestimated
  – EU Directive (e.g.)
  – Definition of “equivalent or superior” analytical procedures and acceptance criteria
• Clearly EFPIA does want to decrease the analytical burden for industry
• No “golden solution” immediately available
• Thinking process is going on
THANK YOU!

Any question?