EDQM in International Harmonisation Initiatives

2019 Training Session
"The European Pharmacopoeia"
Mrs Cathie Vielle
EDQM Head of European Pharmacopoeia Department

10 – 11 September 2019, Iselin, New Jersey, USA
Update on Recent PDG Developments

PDG meeting

Pro memoria, PDG reforms approved in 2017:

- Restructuring meeting format to engage more at the technical level and introduce more direct exchange between the experts in the regions.
- Streamlining of working procedure, reducing complexity => elimination of two stages to increase efficiency and improve focus.
- Strategic review of harmonization areas and individual work items currently in progress and for future consideration still ongoing.
- Cleaning of the work programme => identification of items to be considered outside of PDG (e.g. bilateral discussion).

![Diagram showing Nb of harmonised texts for Excipients and General chapters](chart.png)
Work programme => the review continues

Prioritisation scheme for excipient monographs and general chapters:
• Strategic review conducted on 10 excipient monographs and 5 general chapter
• Extension to remaining general chapters
• Need for further discussion for excipient monographs

Transparency => another PDG priority

• Towards other Pharmacopoeias:
  • Discussion on how information on progress made by the PDG should be shared amongst the PDG member pharmacopoeias and other pharmacopoeias participating in the International Meeting of World Pharmacopoeias (IMWP) => to be continued at the next face-to-face meeting which will be hosted by the JP on 1-2 October 2019 in Tokyo (Japan)
• Towards other harmonisation initiatives:
  • New Maintenance Procedure on the ICH Q4B Annexes Adopted by the ICH Assembly
• Towards users:
  • PDG harmonization policy to be further updated to provide additional clarity to users.
How can you know if a monograph is harmonised?

Indication of harmonisation:

1. This monograph has undergone pharmacopoeial harmonisation. See chapter 5.8.

Pharmacopoeial harmonisation

The non-harmonised attributes/provisions are placed between black diamonds (♦♦)

The local requirements are placed between white diamonds (◊◊)

Ph. Eur. Chapter 5.8 Pharmacopoeial harmonisation

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Ph. Eur.</th>
<th>EP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Identification by HPLC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Conductivity</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Melting point</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Reducing sugars</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Related substances</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Metal</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Loss on drying</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Maximum content of moisture</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Residual solvents</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Labelling</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inspected</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Harmonised attributes

- with and implant
- will not escape

Non-harmonised attributes

Characters/Description, Heavy metals, Container and storage/Package and storage

Local requirements

Second identification (specific optical rotation, melting point, TLC) (Ph. Eur.), Absence of Salmonella (Ph. Eur.)

Pharmaceutical harmonisation

Appearance: white or almost white crystals or powder.
Solubility: freely soluble in water, practically insoluble in ethanol (96% per cent).

It shows polymorphism (5.9) •

Identification

Composition: mannitol CRS.
Chapter 5.8 : will change in 10th Edition

10th Edition:

NOTE ON THE GENERAL CHAPTER
With a view to increasing transparency on the texts harmonised by the PDG, it is proposed to stop mentioning the harmonised and non-harmonised items, as well as the local requirements, in this chapter; conversely sign-off coversheets signed off by the PDG will be made available on the EDQM website. This chapter has been revised accordingly.

• Chapter 5.8 will no longer give details on harmonisation of individual monographs, PDG process explained in general

• List of harmonised monographs will be published separately

• It remains the ultimate responsibility of the user to verify the current content of the texts in force in the respective pharmacopoeias

New Maintenance Procedure on the ICH Q4B Annexes Adopted by the ICH Assembly
### PDG Chapter ↔ ICH Q4B Annex

<table>
<thead>
<tr>
<th>PDG</th>
<th>PDG Number</th>
<th>PDG Name</th>
<th>Q4B Annex</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>Q-08</td>
<td>Extractable Volume</td>
<td>Q4B Annex 2R1: Test for Extractable Volume of Parenteral Preparations</td>
</tr>
<tr>
<td>EP</td>
<td>Q-09</td>
<td>Particulate Contamination</td>
<td>Q4B Annex 3R1: Test for Particulate Contamination: Sub-Visible Particles</td>
</tr>
<tr>
<td>EP</td>
<td>Q-05a</td>
<td>Test for Specified Microorganism</td>
<td>Q4B Annex 4A1: Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests</td>
</tr>
<tr>
<td>EP</td>
<td>Q-05c</td>
<td>Limits for Non-sterile Products</td>
<td>Q4B Annex 4C1: Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use</td>
</tr>
<tr>
<td>USP</td>
<td>Q-02</td>
<td>Disintegration</td>
<td>Q4B Annex 5B1: Disintegration Test</td>
</tr>
<tr>
<td>USP</td>
<td>Q-03/04</td>
<td>Uniformity of Content/Mass</td>
<td>Q4B Annex 6 Uniformity of Dosage Units</td>
</tr>
<tr>
<td>USP</td>
<td>Q-01</td>
<td>Dissolution</td>
<td>Q4B Annex 7R2: Dissolution Test</td>
</tr>
<tr>
<td>EP</td>
<td>B-06</td>
<td>Polyacrylamide Gel Electrophoresis</td>
<td>Q4B Annex 10R1: Polyacrylamide Gel Electrophoresis</td>
</tr>
<tr>
<td>EP</td>
<td>B-02</td>
<td>Capillary Electrophoresis</td>
<td>Q4B Annex 11 Capillary Electrophoresis</td>
</tr>
<tr>
<td>USP</td>
<td>G-01</td>
<td>Analytical Sieving</td>
<td>Q4B Annex 12: Analytical Sieving</td>
</tr>
<tr>
<td>JP</td>
<td>Q-06</td>
<td>Bacterial Endotoxins</td>
<td>Q4B Annex 14: Bacterial Endotoxins Test</td>
</tr>
</tbody>
</table>
Why a new maintenance procedure? Some history

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>1989</td>
<td>PDG formed (EP, JP, USP)</td>
</tr>
<tr>
<td></td>
<td>establishment of ICH</td>
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<tr>
<td></td>
<td>=&gt; harmonisation of several compendial test chapters (&quot;general chapters&quot;) considered as critical by the ICH SC =&gt; PDG requested to include these general chapters in its work program.</td>
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<td>1999</td>
<td>approval of ICH Q6A</td>
</tr>
<tr>
<td></td>
<td>&quot;Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances&quot; by ICH SC</td>
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<td>2003</td>
<td>establishment by ICH of the Q4B EWG to evaluate selected PDG harmonised chapters to facilitate their recognition by regulatory authorities for use as interchangeable in the ICH regions</td>
</tr>
<tr>
<td>2010</td>
<td>evaluation of all texts on the work program was concluded and 14 ICH Q4B annexes had been adopted. They are published on the website of ICH and of individual regulatory authorities, e.g. the EMA.</td>
</tr>
<tr>
<td>2018</td>
<td>PDG new maintenance procedure of ICH Q4B annexes approved by the ICH Assembly [14-15 Nov. 2018, Charlotte, NC, USA]</td>
</tr>
</tbody>
</table>

Future Maintenance process of the ICH Q4B Annexes

As with the former ICH Q4B process, the need to revise a Q4B annex would be triggered by PDG’s sign-off of a revised text subject to Q4B. Potentially non-harmonised and/or local requirements are highlighted in the sign-off coversheet.
Future Maintenance process of the ICH Q4B Annexes

**Step 1:**
- PDG compares the corresponding current ICH Q4B Annex, the PDG sign-off text as well as the corresponding Ph. Eur., JP and USP chapters as published in the respective Pharmacopoeias. All other pharmacopoeias are informed of the ongoing review via the contact list of the International meeting of World Pharmacopoeias (IMWP).
- Based on this review, the PDG prepares a revised Q4B annex, which is submitted to the ICH Secretariat for proceeding to Step 2. Depending on the case, revision could be limited to an update on the pharmacopoeial reference texts (i.e. updated versions of the pharmacopoeia).

**Step 2 (former ICH Q4B Step 3):**
The draft Q4B annex is submitted to the ICH Secretariat to initiate regulatory consultation (generally for 3 months). The regulatory consultation and discussion should focus on the Q4B Outcome in the annex, i.e. regulatory interchangeability; comments on the harmonised pharmacopoeial text itself are not expected. Comments will be evaluated by PDG and the annex revised by PDG, where necessary.
**Future Maintenance process of the ICH Q4B Annexes**

**Step 3 (former ICH Q4B Step 4):**
PDG submits the revised annex to the ICH Assembly for adoption and publication on the ICH website.

**Future Maintenance process of the ICH Q4B Annexes**

**Step 4 (former ICH Q4B Step 5):**
The annex moves to the regional regulatory implementation step. The corresponding PDG chapter moves to PDG stage 5 (inter-regional acceptance). All other pharmacopoeias are informed via the contact list of the International meeting of World Pharmacopoeias (IMWP).
Some other initiatives

Quick walk through

Sharing Vs Harmonisation & Convergence ....

PDG

MoU

Informal
Prospective Harmonisation

IMWP
Informal prospective harmonisation

Ph. Eur. & USP: 19 monographs harmonised:
- 13 monographs on API
- 6 on finished products

Further 15 monographs on the work program
Sharing Vs Harmonisation & Convergence ....

**PDG**

**Prospective Harmonisation**

- **MoU on collaboration and exchanges** e.g. EDQM – ChP; EDQM – IPC; EDQM – ANVISA etc...
- Involvement of observers in the elaboration/revision of texts.
- Information sharing (of data, know-how...); co-organisation of events.

**IMWP**

International Meeting of World Pharmacopoeias

*cf information provided by WHO at the last PDA conference*

- International Meetings of World Pharmacopoeias
  - Opportunity for greater collaborative work
  - Opportunity for sharing of information between world pharmacopoeias
  - Development of good pharmacopeial practices (GPhP), applying WHO's standard-setting processes and procedures
  - Outcome presented to WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECGPP) + through ECGPP also to WHO’s 184 Member States
Call for experts 2019

Provide a vital and invaluable contribution to the elaboration and maintenance of Ph. Eur. texts by taking part in the work of the Ph. Eur.

• Expand your knowledge of the Ph. Eur. and the European regulatory system
• Network with peers and other professionals with various backgrounds and from all over Europe and beyond
• Help shape Ph. Eur. texts, internationally-recognised quality standards for medicines
• Share information and experience

Nomination process now open to all experts!

• Ph. Eur. member states: via your respective National Pharmacopoeia Authorities.
• Non Ph. Eur. member states: via EDQM Helpdesk service.

Thank you for your attention

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Thank you for your attention

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