GPhP - PDG and its future interactions with ICH & IMWP

Cathie VIELLE
Head of the Ph. Eur. Department – EDQM - CoE
The main emerging suggestion was the development of "Good Pharmacopoeial Practices" to favour prospective harmonization, which procedure WHO could facilitate. An initial drafting group was formed during the meeting and is composed of: Argentina, Brazil, European Pharmacopoeia, India, Japan, Mexico, Russian Federation, Ukraine, United States Pharmacopeia, with editorial assistance being provided by the United Kingdom. The whole process is intended to be open to all pharmacopoeias. It was agreed to draft such a document under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

GPhP – the story!

1st IMWP
Feb 2012

1st GPhP Draft outline sent by WHO to the draft group
Oct 2012

GPhP concept paper Initial GPhP draft Sent to all IMWP in prep. Of the 2nd meeting
Jan. 2013

The primary objectives of the WHO Good Pharmacopoeial Practices (GPhP) guidance are to support regulatory authorities in controlling the quality of medicinal products and to provide a means by which the user or procurer of medicinal products can make an independent judgement regarding quality, thus safeguarding the health of the public. GPhP is designed to promote the standardization of processes and ensure that robust quality systems underpin these processes, leading to the recognition of published standards between national (NPhAs) and regional pharmacopoeial authorities (RPAs).
GPhP – 2012 [concept] => 2015 [outcome]

Feb 2012

1st IMWP

1st GPhP Draft

Oct 2012

1st GPhP Draft sent by WHO to the draft group

Sept 2015

6th IMWP

Rev. 7 of the GPhP Draft

Sent to all Ph. for final review
Incl. chapters on monographs for pharmaceutical substances and on monographs for finished pharmaceutical products

Oct. 2015

Rev. 7 of GPhP presented at the 50th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) and adopted, subject to final concurrence being granted by the pharmacopoeias

Nov. 2015

Final approved of all participating Ph.

GPhP => launch of public consultation

2014

GPhP approved

GPhP – the story continues...

2016

Draft GPhP chapters on monographs on herbal medicines and the one on compounding (+ glossary)

Q2 => Survey launched!

2017

Discussion of outcome of survey on GPhP

Adoption of the GPhP chapters on monographs on herbal medicines and the one on compounding, in principle, by the WHO ECSPP at its Oct. meeting, subject to its final revision and adoption by the pharmacopoeias by the end of 2017.

e.g. Need to promote more widely the GPhP by for ex. creation of a section in the IH webpage on each Ph. website

GPhP chapters on monographs on herbal medicines and the one on compounding formally adopted in Dec.
Outcome of the Survey

WHO Expert Committee on Specifications for Pharmaceutical Preparations
TRS 1010 - Fifty-second report

Authors: WHO

Publication details
Number of pages: 624
Publication date: May 2018
Language: English

Downloads
- English
  pdf, 1.96Mb

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Survey on GPhP

During the eighth international meeting of world pharmacopoeias it was decided to conduct a survey on the use of the GPhP. The survey questions were developed and sent out by several agencies including by Brazil, the European Pharmacopoeia, USP and WHO to their stakeholders.

Dr. Sabine Kopp presented the outcomes of a survey on the use of the new GPhP guidance, which was coordinated by WHO in collaboration with the world pharmacopoeias. Approximately two thirds of the respondents identified in the survey stated that they were aware of the GPhP. Some stated that elements of the GPhP guidance had been incorporated into national practice, and a number of other users of the GPhP were described. There did not seem to be a great demand for more technical details or illustrative examples.

The USP presented an overview of the responses received through the survey sent to the USP’s marketing research distribution list. Responses came predominantly from industry. The feedback received through the survey suggested that the GPhP guidance is of interest to a limited group of professionals. The European Pharmacopoeia and the Brazilian Pharmacopoeia had presented the responses they received to this survey at the eighth meeting of world pharmacopoeias.

The Committee noted the update. It was recommended that the use of GPhP guidance, as well as the International Pharmacopoeia and national pharmacopoeias, should be more widely advocated within WHO and among stakeholders and partners.

https://www.who.int/medicines/services/quality_safety/quality_assurance/expert_committee/trs_1010/en/
Annex 1

Good pharmacopoeial practices

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What do you find in the GPhP?

Annex 1

Good pharmacopoeial practices

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FIP/WHO Workshop on Pharmacopoeias
Oct. 7/8 2012

To Conclude...

- ... start with the fundamentals / building blocks (clear objectives ➔ tangible outcomes), otherwise:
Purpose of the GPhP:

- to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization.
- To describe a set of principles that provide guidance for national pharmacopoeial authorities (NPAs) and regional pharmacopoeial authorities (RPAs) that facilitates the appropriate design, development and maintenance of pharmacopoeial standards.

Objective => establishing common practices => facilitate collaboration among pharmacopoeias

Status of the GPhP?

- Voluntary basis
- recommended and encouraged.

What to find? Info on:
- Open and transparent process
- Harmonization
- Legal recognition
- Compliance with a pharmacopoeial monograph
- Analytical requirements
- Acceptance criteria

https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209950-eng.pdf?sequence=1
Open and transparent process

i. Stakeholders engagement
ii. Timely development and revision and/or withdrawal;
iii. publicly available work programmes;
iv. communication (forums, workshops and other interactions);
v. timely response to user enquiries;
vi. training and education;
vii. rapid correction of errors

Harmonisation

including, but not limited to:
• adoption or adaptation of existing standards;
• development of a new standard through coordinated consideration (prospective harmonization);
• revision of a standard between two or more pharmacopoeias (bilateral or multilateral harmonization);
• creation or revision of standards through a harmonization initiative (e.g. PDG).
Technical guidance

- Monographs for pharmaceutical substances
- Monographs for finished pharmaceutical products
- Monographs for herbal medicines
- Monographs on compounding

PDG and its future interactions with ICH & IMWP
Concerning PDG texts

PDG procedure

Stage 1: Preparation of 1st draft
Stage 2: Official enquiry
Stage 3: Consensus
Stage 4: Regional adoption and implementation
Stage 5: Inter-regional acceptance
PDG Stage 2 (Official Inquiry)

1. Stage 2 draft is agreed by PDG

2. Coordinating Ph. (« CP ») shares Stage 2 draft to IMWP Ph. (list maintained by WHO) on date when it is published in the fora of the CP, with the deadline for responses (=> the deadline is the end of publication for public enquiry of CP).

3. Review Stage 2 draft shared by CP (if of interest)

4. If any comments, each IMWP pharmacopoeia to submit comments to CP directly.

5. CP receives comments from:
   - Public/Users
   - PDG pharmacopoeias
   - IMWP pharmacopoeias

6. PDG works according to PDG working procedure

Stage 4 (After sign-off by PDG)

1. PDG text signed-off at face-to-face meeting or by correspondence

2. Host Pharmacopoeia of previous PDG meeting shares the press release and meeting highlights with IMWP Pharmacopoeias (list maintained by WHO) which includes the list of most recent sign off texts.

3. Each Ph. to decide whether or not to adopt and publish the text under conditions that the source of the text i.e. PDG is indicated.

4. If a Ph. would reproduce the PDG signoff text:
   - PDG shall be informed via CP
   - The source of the text shall be clearly indicated (per GPhP)
   - The potential divergences to the signoff (non-harmonised requirements or local requirements) shall be communicated to PDG via CP.

5. PDG works according to PDG working procedure
Next steps

- Presentation at the 11th IMWP (18 – 19 February 2020)
- Agreement to go for a pilot phase

Concerning ICH Q4B annexes
Concerning ICH Q4B annexes

Elaboration & revision of pharmacopeial text (technical content)

Revision of content of Q4B annexes (regulatory interchangeability)

PDG procedure

ICH procedure

Why a new maintenance procedure? Some history

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>PDG formed (EP, JP, USP)</td>
</tr>
<tr>
<td>1990</td>
<td>establishment of ICH</td>
</tr>
<tr>
<td>1990</td>
<td>WHO observer to PDG</td>
</tr>
<tr>
<td>1999</td>
<td>ICH SC approved Q4B Work Plan</td>
</tr>
<tr>
<td>2001</td>
<td>ICH SC established Q4 EWG with a scope to address 11 General Test Chapters (-&gt; 11 Annexes) discussed during development of ICH Q6A Guideline</td>
</tr>
<tr>
<td>2003</td>
<td>ICH SC approves limited expansion of scope -&gt; 16 annexes</td>
</tr>
<tr>
<td>2004</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>2008</td>
<td>ICH SC decided not to further expand the ICH Q4B work programme and to disband the ICH Q4B EWG</td>
</tr>
<tr>
<td>2010</td>
<td>PDG new maintenance procedure of ICH Q4B annexes approved by the ICH Assembly [14-15 Nov. 2018, Charlotte, NC, USA]</td>
</tr>
<tr>
<td>2018</td>
<td>Ph. texts not cast in stone / need to keep them state-of-the-art</td>
</tr>
</tbody>
</table>

Ph. texts not cast in stone / need to keep them state-of-the-art

Tablet Friability - Bulk and tapped density - Analytical Sieving - Capillary Electrophoresis - PAGE
Why a new maintenance procedure? Some history

Founding Regulatory Members: EC (Europe), FDA (USA), MHLW/PMDA (Japan),
Standing Regulatory Members: Health Canada* (Canada), Swissmedic** (Switzerland)
* No active Ph. – ** member of the Ph. Eur.

New Regulatory members:
- (ANVISA) Brazil, HSA (Singapore),
- MFDS (Republic of Korea), NMPA (China)
- TFDA (Chinese Taipei)...
- Some having active Pharmacopoeias

Ref: Increasing international outreach, changing ICH's governance structure, disseminating more information on ICH processes to a wider number of stakeholders, and establishing ICH as a legal entity to provide for a more stable operating structure (https://www.ich.org/page/history)

Table: PDG Chapter ↔ ICH Q4B Annex

<table>
<thead>
<tr>
<th>CP</th>
<th>PDG Number</th>
<th>PDG Name</th>
<th>Q4B Annex</th>
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</thead>
<tbody>
<tr>
<td>JP</td>
<td>Q-10</td>
<td>Residue on Ignition</td>
<td>Q4B Annex 1R1 Residue on Ignition/Sulphated Ash</td>
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<td>EP</td>
<td>Q-08</td>
<td>Extractable Volume</td>
<td>Q4B Annex 2R1 Test for Extractable Volume of Parenteral Preparations</td>
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<tr>
<td>EP</td>
<td>Q-09</td>
<td>Particulate Contamination</td>
<td>Q4B Annex 3R1 Test for Particulate Contamination: Sub-Visible Particles</td>
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<tr>
<td>EP</td>
<td>Q-05a</td>
<td>Test for Specified Microorganism</td>
<td>Q4B Annex 4R1 Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests</td>
</tr>
<tr>
<td>EP</td>
<td>Q-05b</td>
<td>Microbial Enumeration</td>
<td>Q4B Annex 4R1 Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms</td>
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<tr>
<td>EP</td>
<td>Q-05c</td>
<td>Limits for Non-sterile Products</td>
<td>Q4B Annex 4R1 Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use</td>
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<tr>
<td>USP</td>
<td>Q-02</td>
<td>Disintegration</td>
<td>Q4B Annex 5R1 Disintegration Test</td>
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<tr>
<td>USP</td>
<td>Q-03/04</td>
<td>Uniformity of Content/Mass</td>
<td>Q4B Annex 6 Uniformity of Dosage Units</td>
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<td>Dissolution</td>
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<td>Sterility Test</td>
<td>Q4B Annex 8R1 Sterility Test</td>
</tr>
<tr>
<td>USP</td>
<td>G-06</td>
<td>Tablet Friability</td>
<td>Q4B Annex 9R1 Tablet Friability</td>
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<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>EP</td>
<td>G-02</td>
<td>Bulk Density and Tapped Density</td>
<td>Q4B Annex 13 Bulk Density and Tapped Density of Powders</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>

Added by ICH SC to Q4 EWG scope in Nov. 2008
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.

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 1: PDG interaction with other Ph.

1. PDG compares the corresponding current ICH Q4B Annex, the PDG sign-off text as well as the corresponding EP, JP and USP chapters as published in the respective Ph.

2. CP informs IMWP pharmacopoeias of the ongoing review via the contact list maintained by WHO.

3. Based on the PDG review and feedback provided by the other Ph. (in any), the CP prepares a revised Q4B annex (technical comparison), which is submitted to the ICH Secretariat for proceeding to Step 2 (timelines for CP: 3 months).

4. Depending on the case (e.g. no feedback received from other Ph.), revision could be limited to an update on the pharmacopoeial reference texts of EP, USP and/or JP.

5. Each Ph. to inform CP if it has implemented the PDG sign-off text or considers its text as harmonised with PDG sign-off.

6. To be provided to CP:
   - English copy of the Ph. text
   - Harmonization status (incl. potential residual discrepancies)

Future Maintenance process of the ICH Q4B Annexes

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

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).
Step 4: PDG interaction with other Ph.

The corresponding PDG chapter moves to PDG stage 5 (inter-regional acceptance).

Coordinating Pharmacopoeias within PDG (= CP) informs the IMWP Pharmacopoeias (list maintained by WHO)

Each Ph. to decide on next steps

Pharmacopoeias of ICH member states (other than PDG members)

Next steps – ICH Q4B annexes

• Submission of this proposal by PDG to ICH MC / Assembly (May 2020)
• Recommendation to go for a pilot phase (proof-of-concept on some selected annexes)
Thank you for your attention

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