How to participate in the Elaboration and Revision of Monographs

Dr Mihaela Buda
European Pharmacopoeia Department
European Directorate for the Quality of Medicines & HealthCare

Basis for monographs

✓ Monographs take account of currently approved products
✓ Approved specification(s) are the main basis backed up by batch data
✓ Draft monographs are checked by regulatory authorities at Pharmeuropa stage
✓ Policy for monograph development is given in:
  • *Guide for the elaboration of monographs on synthetic peptides and recombinant DNA proteins* (2010) (available on the EDQM website)
Creation or revision of a text

Chair of the Ph. Eur. Commission
Delegation of a member state
Experts, EDQM

Stages in elaboration or revision (1)

All procedures:

- Addition to work programme – endorsed by the Ph. Eur. Commission: public announcement
- Interested parties can (and should!) express an interest
- Elaboration, experimental verification of the draft
- Publication in Pharmeuropa (3-months comment period)
Stages in elaboration or revision (2)

- **Study of comments** by group of experts/working party
- **Submission to Commission** for adoption
- **Publication** in the Ph. Eur. within 6 months
- **Implementation** 1 year after adoption
  (see publication schedule available on website)

<table>
<thead>
<tr>
<th>Commission Session</th>
<th>Submission Date</th>
<th>Review Date</th>
<th>Publication Date</th>
<th>Implementation Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>195</td>
<td>November 2015</td>
<td>30 Oct 2015</td>
<td>1 Jan 2016</td>
<td>1 Jan 2017</td>
</tr>
<tr>
<td>196</td>
<td>June 2016</td>
<td>30 June 2016</td>
<td>1 July 2017</td>
<td>1 Jan 2018</td>
</tr>
<tr>
<td>197</td>
<td>November 2016</td>
<td>30 Nov 2016</td>
<td>1 Dec 2017</td>
<td>1 Jan 2019</td>
</tr>
<tr>
<td>198</td>
<td>March 2017</td>
<td>30 Mar 2017</td>
<td>1 Apr 2018</td>
<td>1 Jan 2020</td>
</tr>
<tr>
<td>199</td>
<td>June 2017</td>
<td>30 June 2017</td>
<td>1 July 2018</td>
<td>1 Jan 2021</td>
</tr>
<tr>
<td>200</td>
<td>November 2017</td>
<td>30 Nov 2017</td>
<td>1 Dec 2018</td>
<td>1 Jan 2022</td>
</tr>
<tr>
<td>201</td>
<td>March 2018</td>
<td>30 Mar 2018</td>
<td>1 Apr 2019</td>
<td>1 Jan 2023</td>
</tr>
<tr>
<td>202</td>
<td>June 2018</td>
<td>30 June 2018</td>
<td>1 July 2019</td>
<td>1 Jan 2024</td>
</tr>
</tbody>
</table>

Work programme (1)

> Based on proposals from:
  - National delegations
  - Groups of experts
  - EDQM

Manufacturers can submit proposals via one of the above
Work programme (2)

• **Additions** announced on:
  - EDQM website 
  - Pharmeuropa-on-line 

• **Status (steps 1-5)** displayed on the **website**

---

Work status: see Knowledge database

Key to information on State of Work (SoW):

- **0** = on the work programme, no first draft
- **1** = first draft (new or revised monograph)
- **2** = published (or in press) in Pharmeuropa
- **3** = submitted to the Commission
- **4** = adopted, ready for publication
- **5** = published
Creation or revision of a text

Chair of the Ph. Eur. Commission
Delegation of a member state,
Experts, EDQM

Monographs: how?

**Procedure 1  (group of experts):**
- Multi-source products and monograph revisions
  On request, data are handled confidentially by EDQM

**Procedure 4  (working party of regulators):**
- Single-source products, direct co-operation with innovator
  Data are handled confidentially by EDQM
Groups of experts and working parties: Procedure 1

• >720 experts in pharmaceutical sciences from the Ph. Eur. members states and observers.

• **New:** the Ph. Eur. Commission has revised its working procedures to open up to the nomination of experts from non-European Pharmacopoeia member states and non-observers states (November 2016)


Monographs: how?

**PROCEDURE 1**: Revision

**MONOGRAPH** valid for A, B, C & D

**PROCEDURE 4**: Revision

**MONOGRAPH** applicable to B, C, D ....
**P4 procedure: aim**

- Create monographs for **single-source** substances/finished products (still under patent) with a potential for further generics
- Based on authorised products
- Monograph ready ≥ 2 years before patent expiry (ideally)
- Possibility of starting elaboration work 5 years after first MA approval
- **Protection of proprietary information**: expert group P4 solely composed of regulators, OMCLs and EDQM

**P4 procedure: steps (1)**

1. Ph. Eur. Commission: addition to work programme
2. Manufacturer: submits data package/samples
3. Rapporteur from expert group P4 and EDQM staff member prepare first draft
4. Discussion with manufacturer
5. Experimental verification (EDQM/OMCL(s))
6. Report and questions to manufacturer
7. Rapporteur/EDQM: draft for Pharmeuropa

P4 procedure: steps (2)

8. Group P4 approves draft for public consultation
9. Comments collected via National Pharmacopoeia Authorities
10. EDQM compiles comments
11. Rapporteur and EDQM examine comments, prepare revised draft, after approval by group P4
12. Presented for adoption (or re-publication)


New monographs: actives

- Addition to programme depends on:
  - therapeutic importance
  - extent of use
  - number of countries in which product is approved
Proposing a new monograph

- Contact your National Pharmacopoeia Authority (in Europe) or EDQM (outside Europe)

- **Initial data**: countries where the product is approved

- **Data package**:
  - Current specifications
  - Analytical procedures (SOPs)
  - Method validation reports
  - Batch and stability data
  - Samples of substance and impurities; *in-house reference standard*
  - Full description of data package is available

P4Bio Pilot Phase

- Numerous exchanges between manufacturer, P4Bio Experts and EDQM

- Critical initial evaluation of the data package

- Laboratory resources, workload (≥ 2 OMCLs involved in experimental verification of the methods described in the data package).

- Time of elaboration – longer compared to P4 chemicals
## P4Bio Pilot Phase: 2008-2016

<table>
<thead>
<tr>
<th>Structure</th>
<th>Monograph</th>
<th>Ph. Eur. edition</th>
<th>Implementation date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insulin glargine (2571)</td>
<td>8.0</td>
<td>January 2014</td>
</tr>
<tr>
<td></td>
<td>Human coagulation factor VIIa (rDNA), concentrated solution (2534)</td>
<td>8.0</td>
<td>January 2014</td>
</tr>
<tr>
<td></td>
<td>Human coagulation factor IX (rDNA), concentrated solution (2522)</td>
<td>8.2</td>
<td>July 2014</td>
</tr>
<tr>
<td></td>
<td>Human coagulation factor IX (rDNA), powder for solution for injection (2994)</td>
<td>9.3</td>
<td>January 2018</td>
</tr>
<tr>
<td></td>
<td>Teriparatide (2829)</td>
<td>9.0</td>
<td>January 2017</td>
</tr>
<tr>
<td></td>
<td>Etanercept (2895)</td>
<td>9.x</td>
<td></td>
</tr>
</tbody>
</table>

## Revision: why? (1)

- **Developments in Regulatory Environment**
  - e.g. Guidelines, ICH Q3D, elemental impurities
  - ICH Q8/Q9/Q10/Q11, REACH

- **Increased demand for Biosimilar products**
  - e.g. New sources

- **Scientific / technical evolutions**
  - e.g. Fast LC, PAT, new molecules, new therapies
  - e.g. CT

- **Developments in Manufacture and Globalisation**
  - e.g. continuous manufacturing, changed routes of synthesis

- **New risks to Public Health**
  - e.g. TSE, contamination/falsification (heparins)

---

*Revision: 20 Mihaela BUDA ©2017 EDQM, Council of Europe. All rights reserved.*
Revision: why? (2)

- New sources have **new impurity profiles**
- **New quality issues** arise
- **Analytical methods change/development**: more convenient methods, more powerful/sensitive methods, more reliable methods become available
- **International harmonisation** (PDG, ICH, VICH)

---

How can manufacturers request revision?

- **Europe**: via National Pharmacopoeia Authority (address list on EDQM website and in Pharmeuropa)
- **Outside Europe**: contact EDQM which will refer the matter to a group of experts or to the Commission

Make clear what needs revising and if possible make a **concrete proposal**
Data for revision

• Revision can only be undertaken if the request is backed up by sufficient data
• Provide batch data, sample chromatograms, etc. to enable a decision on the need for revision
• Supply validated methods (if possible, cross-validated against official Ph. Eur. method) and samples, notably for all impurities controlled by the new method

Revision programme

✓ Work programme is announced via EDQM website and to industry associations and pharmacopoeia liaison contacts (http://www.edqm.eu/en/european-pharmacopoeia-work-programme-607.html). Stakeholders to:
  ▪ Declare an interest for relevant items
  ▪ Make sure they see Pharmeuropa for revision proposals
  ▪ Provide samples, test the draft proposal
After revision: why?

FAQ: “Why did you revise the monograph on...?”

The answer can be found out via:

- Briefing notes in Pharmeuropa
- Collected briefing notes posted on the website for each new edition/supplement (http://pharmeuropa.edqm.eu/home/menupage/English/Useful%20Information/Supplementcomments82.pdf)
- Knowledge database (monograph history)

No briefing notes for corrections

Knowledge database

History: contains information concerning certain technical modifications to some revised/corrected texts published since Ph. Eur. 5.0. This information complements the modifications indicated by lines in the margin in the supplements and is not necessarily exhaustive.
Monograph under elaboration

0 The monograph has been authorised but work has not started yet
1 Work has started (first draft)
2 The monograph has been authorised for publication in Pharmeuropa (see Pharmeuropa number)
3 The monograph has been submitted for adoption to the European Pharmacopoeia Commission
4 The monograph has been adopted
5 The monograph is about to be published, or has been published (see the supplement number indicated and the calendar of the editions below)

The number of the last issue of Pharmeuropa into which a draft of the monograph was published

The section reflects the status of the text with regard to the work of:
• the Pharmacopoeia Discussion Group (PDG), a joint collaboration between the United States Pharmacopeia, the Japanese Pharmacopoeia and the European Pharmacopoeia.
• the International Conference on Harmonisation (ICH) Quality Guideline on Evaluation and Recommendation of Pharmacopoeial Tests for Use in the ICH (Q4B).
Further information can be found in chapter 5.8 (Pharmacopoeial Harmonisation) of the European Pharmacopoeia.

Monograph under revision

Two on-going revisions

- Aim of the revision
- State of work
- The number of the last issue of Pharmeuropa into which a draft of the monograph was published

The number of certificate(s) of suitability have been granted for the substance in question, their list is shown. This is an excerpt from the online List of CEP.
How to participate?

- Participation depends on the procedure used
- For all procedures - provide samples for testing and participate as early as possible (i.e. before the text is published for comments in Pharmeuropa so at state of work 0 or 1)
- Only information on actives and excipients used in already approved products licensed in Europe is considered

Pharmacopoeia liaison

- EDQM wishes to have a pharmacopoeia liaison contact for each major manufacturer/user
- Channel information and requests from manufacturer to EDQM
- Reception point for contact by EDQM
- Benefits for both sides
Thank you for your attention!

How to participate in the Elaboration and Revision of Monographs

Dr Mihaela Buda
European Pharmacopoeia Department
European Directorate for the Quality of Medicines & HealthCare