EDQM: 50 YEARS OF LEADERSHIP IN THE QUALITY OF MEDICINES

PAVING THE WAY FOR THE FUTURE

6-8 October 2014
Strasbourg, France

WORKSHOP
FINISHED PRODUCT MONOGRAPHS
Finished Product Pilot Project - Background and Outcomes

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Background

• The question “if the European Pharmacopoeia (Ph. Eur.) should elaborate Finished Products (FP) monographs” has been raised and discussed at several occasions since 1999.

• The European Pharmacopoeia Commission took a decision June 2000 not to elaborate FP monographs for Chemicals
  – This decision was based on a note from the Joint CHMP/CVMP Quality working party who had discussed this item and they did not see a need for such monographs.
Background

- Discussion continued at meetings with the National Pharmacopoeia Authorities (NPA:s) and the Official Medicine Control Laboratories (OMCL:s) which both expressed a need for FP monographs
- The need has also been expressed by users via EDQM:s helpdesk and during international conferences
- The absence of FP monographs has also been highlighted on several occasions by other Pharmacopoeias

Background

- FP monographs are already elaborated by other Pharmacopoeias, such as the USP, but also by pharmacopoeias from European Pharmacopoeia member states
- Times are changing ..........
  - globalisation of the supply chain
  - more and more finished products are imported from countries outside Europe
  - cost-pressure in healthcare systems leads to an increased demand for generics
Reflection paper

- The Presidium of the European Pharmacopoeia Commission decided 2011 to take up the discussion again and prepared a reflection paper

- The purpose was to
  - providing guidance to the industry and facilitating the development of generics
  - support the assessment of marketing authorisation applications
  - support the OMCL:s in testing marketed products

European Pharmacopoeia Commission

- The reflection paper was presented at the meeting with the European Pharmacopoeia Commission in April 2012
  - the proposal from the Presidium was to start with a pilot phase and based on its outcome decide whether the Ph. Eur. shall elaborate FP monographs or not.
  - start with P4 - products (products which contain a chemical substance still under patent)

- A first discussion took place and a lot of questions was raised.
European Pharmacopoeia Commission

• Example of questions raised
  – flexibility when assessing a generic application
  – possible to ask for more appropriate specifications
  – flexibility for the manufacturer when choosing methods
  – resources to do the job
  – legally-binding? which parts of the monograph?
  – retrospectively applied
  – scope of the monographs
  – how will different excipients be covered
  – benefits for the patient?
  – QbD?

European Pharmacopoeia Commission

• Questions raised
  – release and/or shelf-life specifications?
  – cover different strength and
  – different salts/esters
European Pharmacopoeia Commission

• The item was further discussed at the June - meeting in 2012
  – where additional information was given to answer some of the questions
  – all couldn’t be answered at this stage but should be forwarded to the working party if the Ph. Eur. Commission decided to follow the proposal from the Presidium

European Pharmacopoeia Commission

• One of the main argument against was the flexibility needed by the assessors when they assess applications but this is already taken into account in the European Pharmacopoeia
  – “With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.”,
European Pharmacopoeia Commission

• and in the EU Directive 2001/83:
  – “In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder.” [EU Directive 30 2001/83/EC as amended]

European Pharmacopoeia Commission

• At the June - meeting 2012 the Commission agreed to start a pilot and to
  – create a FP Monographs Working Party whose purpose would be:
    • to address the issues raised by the QWP and by the delegations at the 142nd and 143rd sessions of the Commission relating to the elaboration of chemically-defined FP monographs
    • to deliberate draft monographs in order to gain hands-on experience.
  – add at least one single-sourced and at least one multi-sourced product to the work programme of the proposed FP Monographs Working Party
FP monographs - Working Party

Terms of reference:

• Members of the working party are exclusively part of
  – a National Pharmacopoeia Authority,
  – a competent authority
  – an official medicines control laboratory.

• One observer from QWP

• One Observer from EMA

• Industry representatives are not appointed to this
  Working Party, although they may contribute by
  submitting data and interacting via the Secretariat.

FP monographs - Working Party

• The mission was to
  – draft two monographs
    • one single-source (Sitagliptin Phosphate tablets) and one
      multi-source product (Clopidogrel Tablets)
  – to answer all questions raised by the Commission and
    QWP
  – to draft a proposal for the scope and the content of such
    FP monograph with the mandatory and non-mandatory
    sections identified.

  • based on this, a guidance document for assessors and
    applicants on how to use FP monographs should been
    drafted and considered as appropriate by the Commission.
FP monographs - Working Party

• Chair: Dr. Marianne Ek
• 6 assessors
• 1 inspector
• 6 from OMCL
• 2 from NPA
• 3 from OMCL/NPA
• 1 observer from QWP
• 1 observer EMA

Intense and goal-focussed discussions took place within the group.

Practical work in elaboration and testing of the two specific monographs was conducted smoothly and efficiently by the authors.

The working party showed that monographs on finished products containing chemically defined active substances could be elaborated with high quality for single-source and multi-source products providing quality standards for different formulations from different manufacturers.
Outcome

• The working party accomplished its mission during only 3 meetings and 2 teleconferences and drafted
  – 1 monograph on a single-source product, Sitagliptin phosphate monohydrate tablets (active substance still under patent protection)
  – 1 monograph on a multi-source product, Clopidogrel hydrogen sulphate tablets (broad range of finished product from different manufacturers on the European market)
  – a Note on the Guidance on Finished Product Monographs for assessors and applicants where mandatory and non-mandatory sections are identified
  – Feedback to all issues raised by the Commission

Outcome

• The working party recommended to start with FP monographs of single source-products and continue with multi-source products when more experience are gained

• The working party had to outstanding questions to be answered by the Commission
  – would FP monographs be applied retrospectively?
  – would the dissolution test be mandatory?
Outcome

• The results from the Working party was presented to the Commission at its meeting in March 2014
• After discussions
  – the guidance document was accepted with some modifications
  – it was decided to start with single-source products

Outcome

• The outstanding questions
  – retrospectively applied will be discussed later because for the moment only single-source products will be elaborated
  – dissolution test: testing procedure (test conditions, limits and acceptance criteria), if specified in the monograph, shall be mandatory unless otherwise justified and authorised.

➢ Sitagliptin phosphate monohydrate tablets is published in Pharmeuropa 26.3 for comments
I want to thank all Members of the working party, the Observers and the participants from the European Pharmacopoeia Secretariat who have all contributed to the positive outcome.

Thank you for listening
Finished Product Monographs
The opinion of a regulator

DI Susanne Stotter
Head of Department
Department Quality Assessment of Medicinal Products
Institute Marketing Authorisation of Medicinal Products & LCM
BASG / AGES / Austrian Medicines and Medical Devices Agency

EDQM 50 YEARS OF LEADERSHIP IN THE QUALITY OF MEDICINES
MAKING THE WAY FOR THE FUTURE
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www.ages.at

Historical details ...

- QWP October 1999
  - initial discussion started

- QWP January 2000
  - survey on the need of specific monographs in the Ph. Eur. was performed

- QWP June 2000
  - conclusion of the survey was that QWP is of the opinion that there is no need for the elaboration of specific dosage form monographs in the Ph. Eur. because a simplification in the authorization process cannot be seen
Times are changing ...

- QWP February 2012
  - Reflection paper summarizing the need for finished product monographs in the Ph. Eur. was presented
  - QWP member comments were asked
- QWP May 2012
  - Discussion in break out session and plenary
  - QWP agreed on a pilot phase
- QWP December 2013
  - Draft guidance document was presented to QWP
  - Two main questions were asked to QWP
- Guidance document finalized by the Finished Product Working Party at its January 2014 meeting

Initial thoughts by regulators ...
QWP February 2012

... replace drug product assessment
... avoid generics
... preclude alternative analytical methods
... prevent higher standards
... open doors for CEPs for finished products
... impair innovations
... be a barrier for development
... trigger reassessment of marketed products

finished product monographs should not ...
Times are changing ...

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Major issues discussed ...

QWP May 2012

- retrospective application?
- a mandatory requirement?
- scope of the procedure?
- pharmaceutical development still necessary?
- Further applicability of QbD/PAT
- analytical methods
- dissolution testing
- setting specifications
**Times are changing ...**

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**Questions asked to QWP ...**
**QWP December 2013**

- **Should FP monographs be applied retrospectively?**
  - carefully selected substance: YES
  - revision subject of public consultation: ☹️

- **Should the dissolution test be mandatory?**
  - unless otherwise justified and authorised: ☹️
  - dissolution test and limits should be sufficiently discriminatory to assure batch to batch consistency: YES
Times are changing ...

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  - Reflection paper summarizing the need for finished product monographs in the EP was presented
  - QWP member comments were asked
- QWP May 2012
  - Discussion in break out session and plenary
  - QWP agreed on a pilot phase
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Guidance document finalized by the Finished Product Working Party at its January 2014 meeting

Benefits acknowledged ...

By assessors

- recognized common standards
- support CAs in their duties
- facilitate assessment
- ease the comparison of medicinal products
- will not hinder or have a negative impact on assessment as EU Directive and Ph. Eur. general Notices provide for the needed flexibility of assessors
FINISHED PRODUCT MONOGRAPHS
The Opinion of an OMCL

Andreas Mayrhofer
OMCL-AT

Int. Conference „EDQM: 50 years of leadership in the quality of medicines“
Strasbourg, 7 Oct. 2014

Content

1. Introduction
2. OMCL tasks and strategies
   - Use of pharmacopoeias
   - Wish for FPMs
3. FPM pilot project: OMCL experiences
4. FPM: Future perspectives
Introduction

• Prague 2010
  - Int. Conference „Quality of Medicines in a globalised World“
  - Swissmedic – OMCL: Presentation
  - **Is Ph.Eur. prepared for the Future?**
    - Wish for Finished Product Monographs (FPM)
    - FPMs are frequent in national pharmacopoeias
    - Ease for generic testing and MA

OMCL tasks and strategies

• 3 Tasks
  1. **Market surveillance:** Testing of medicines (ff.)
  2. Analysis of falsified medicines
    - *Heparin case:* OSCS adulteration
    - Rapid revision of monograph (NMR + HPLC-SAX)
    - Used also for FP
  3. **Pharmacopoeia development**
    - Challenge: 1 monograph / API
    - Rapporteurs team: Study with samples comprising
      - All manufacturers
      - Different synthesis routes
      - Different national licenses (imp. limits)
OMCL task Market Surveillance

• Economic strategy for big market > spot checks
  1. Risk based sampling plan
  2. Work sharing in OMCL network
     - CAP + MRP + DCP
  3. Campaigns, e.g. all diclofenac products (AT >80 MA)
     - OMCL specific validation guideline - 3 categories, eg.
     - Method transfer (9 types), eg.
       2. Pharmacopoeial method for medicinal product: BP, USP
       3. API method used for medicinal product: MSS

Market Surveillance Studies (since 1995)

• Europe wide supervision
• Important medicinal product classes
• OMCL Network (planning at annual meeting)
  - Scientific advisor - Feasibility study (AT: 10/46)
    - Pharm.-technical tests: Ph.Eur. mandatory
    - Assay + imp.s: Ph.Eur. - API method
      - Validation for diff. excipients, dosage forms etc.
      > Test protocol in Ph.Eur. style ("FPM like")
• Outcome from 46 MSS:
  - > 2 800 samples tested
  - Robust methods for similar FPs
<table>
<thead>
<tr>
<th>MSS of OMCL Network</th>
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<tbody>
<tr>
<td>1 Amoxicillin solid preparations</td>
</tr>
<tr>
<td>2 Beclometasone f. inhalation</td>
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<tr>
<td>3 Salbutamol f. inhalation</td>
</tr>
<tr>
<td>4 Ranitidine oral solid forms</td>
</tr>
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<td>5 Lithium modified release</td>
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<tr>
<td>6 Diclofenac gastro-resistant</td>
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<tr>
<td>7 Nifedipine oral imm. release</td>
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<td>8 Tamoxifen tablets</td>
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<tr>
<td>9 Salbutamol f. inhalation</td>
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<td>10 Dihydrostreptomycin f. inj.</td>
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<tr>
<td>12 Nifedipine retard prep.s</td>
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<td>13 Trimethoprim: API + tab.s</td>
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<tr>
<td>14 Doxycyclines in oral prep.s</td>
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<td>15 Erythromycin: API + solid pr.</td>
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<tr>
<td>16 Valerian root</td>
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<td>17 Matricaria flower</td>
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<td>18 Linseed: Cadmium contam.</td>
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<tr>
<td>19 Liquorice root</td>
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<tr>
<td>20 Aciclovir tablets</td>
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<td>21 Amoxicillin oral suspensions</td>
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<tr>
<td>22 Ibuprofen + Dex- tab.s</td>
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<tr>
<td>23 Omeprazole tabs. + cap.s</td>
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<td>24 Piroxicam tab. - unfinished</td>
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<td>25 Tablets with subdivisions</td>
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<tr>
<td>26 Erythromycin liquid prep.s</td>
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<tr>
<td>27 Equisetum stem</td>
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<tr>
<td>28 Sulfasalazine t. - unfinished</td>
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<tr>
<td>29 Trimethoprim: API + tab.s</td>
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<td>31 Cadmium in herbal drugs</td>
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<td>32 Diclofenac retard prep.s</td>
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<td>33 Procaine injections</td>
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<tr>
<td>34 Essential oils in herbals</td>
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<tr>
<td>35 Lisinopril tablets</td>
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<tr>
<td>36 Amoxicillin, clavulanic acid and prednisolone intramammary suspensions</td>
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<tr>
<td>37 Levothyroxine tablets</td>
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<td>38 Opioid analgetic oral retard</td>
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<td>39 Omeprazole gastroresistant</td>
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<td>40 Simvastatin tablets</td>
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<tr>
<td>41 Acetylsalicylic acid oral pr.</td>
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<tr>
<td>42 Alkyl mesylates in APIs + FDFs</td>
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<tr>
<td>43 Clopidogrel: API + tab.s</td>
</tr>
<tr>
<td>44 Telmisartan - started</td>
</tr>
<tr>
<td>45 Pramipexole - started</td>
</tr>
</tbody>
</table>
FPM pilot project: OMCL experiences

• 3 tasks from COM
1. Sitagliptin phosphate monohydrate tablets
   - API: P4 monograph (under patent > single source)
2. Clopidogrel hydrogen sulfate tablets
   - Multisource substance (CAP, CAP generic, MRP/DCP, nat. MA)
3. Guidance document on FPM
   - Structure: Similar API monographs
   - Validation of testing procedures: Influence of excipients
   - Related substances: Degradation products (stability)
   - Dissolution: Mandatory, no replacement for bioequivalence

OMCL experience (DE, PT, RS)
Sitagliptin phosphate tablets

Draft monograph for COM, strength: 25 – 100mg
• Identification: HPLC, A: UV spectrum (DAD), B: RT
• Related substances: HPLC, unspec. + total imp.: max. 0.2%
• Dissolution: 0.01m HCl, 50 rpm, 30 min., HPLC; Q = 75%

• Assay: HPLC, 95.0 – 105.0%
• Impurities: A - E
OMCL experience (AT, FR, RS, UK, DE)
Clopidogrel hydrogen sulfate tablets

- Results from MSS 43 – Clopidogrel tablets + APIs
  - 4 API forms: hydrogen sulfate, besilate, hydrochloride, base
  - 173 samples (121 tablets + 52 APIs) tested in 26 OMCLs
  - Result: 4 tablets + 1 API OOS
    - Identity: isocratic HPLC
    - Enantiomeric purity: isocratic chiral HPLC, imp. C
    - Related substances: gradient HPLC, imp. A + B
    - Assay: isocratic HPLC
  - Feasibility study for the 3 HPLC methods
    - Ca. 20 exc.: No interferencies, BHA well separated

Clopidogrel hydrogen sulfate tablets
Draft monograph for COM

Based on
- Results MSS 43 (2011-2012, whole eur. market, exp.: 2011-2014)
- Additional lab studies (identity A, dissolution, uniformity 2.9.40)
- Strength: 75mg, extension to 300mg possible

- Identification: isocratic HPLC (assay)
  - A: UV spectrum (DAD: 200 – 350nm)
  - B: RT

- Related substances: gradient HPLC (Ph.Eur./API)
  - Imp. A: max. 0.5% (API: 0.2%, USP: 1.2%, nat. MA: 1.2%)
  - Imp. B: max. 0.3% (API: 0.3%, USP: -), degrad.?
  - Total imp.: max. 1.0% (API: 0.5%, USP: 2.5% excl. B, nat. MA: 2.5%)
Clopidogrel hydrogen sulfate tablets
Draft monograph for COM

- Enantiomeric purity: isocratic chiral HPLC (Ph.Eur./API)
  - Imp. C: max. 1.5% (API: 0.5%, USP: 1.5%, nat. MA: 1.5%)
- Dissolution: HCl buffer pH 2.0, 50 rpm, 30 min., UV
  - Selected from 12 similar methods, (10 MA + USP + JP)
    - Differences: time 30-60min., rpm 50-100
    - Validation: MAH method + spiking
  - Results (rapp. markets + PT): Q = 75% (USP: 80%)
    - Hydrogen sulfates + hydrochlorides + bases fit
      - Selective (MA: 50-75 rpm)
    - Besilate failed (1 sample, disintegr. incomplete, MA: 100 rpm)
- Assay: isocratic HPLC, 95.0 – 105.0% (USP: 90.0 – 110.0%)
- Impurities: A - C

FPM: Future perspectives

- Sitagliptin in Pharmeuropa
  - API: published 1/14, consolidated comments 6/14
  - Tab.s: published 7/14, waiting for comments

- 4 new P4-FPMs started in COM 6/14
  - Raltegravir, 2x
  - Deferasirox, 2x

- Clopidogrel stays model for future
FPM: Future perspectives

- **OMCLs in favor of FPMs**
  - Equal standard/test methods for similar FPs
- **FPMs should ease MA (manufacturer + assessor)**
- **FPMs will boost Ph.Eur. in a globalized market**

- **Start soon with generic block buster APIs**
  - Keeping the high standard of Ph.Eur.
  - Needs big MSSs with participation of OMCL Network
  - Max. 5 FPMs/year - challenging for EDQM + OMCLs
  - Approx. 15 years for 50 FPMs

Thanks

- **For your attention**
- **For the good cooperation of the rapporteurs team „clopidogrel tablets“**
Ph.Eur. Monographs on Finished Products

An Industry Viewpoint
Laure Girard, Head Global Pharmacopoeial Affairs
EDQM, Strasbourg, 7th October 2014

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Novartis

- One of 25 largest companies by market capitalization
- Global presence in over 140 countries with approximately 133,000 employees
- Six divisions: Pharma, Sandoz, Alcon, Vaccines, Consumer Health and Animal Health
- Headquarters in Basel, Switzerland

Thank you!
Brainstorming and constructive exchanges

- Novartis Group Pharmacopoeia Network
- External Relations team
- Quality Control experts
- Analytical Science and Technology experts
- Experts at Authorities and Pharmacopoeias
- EFPIA team, PhRMA team
Finished Product (FP) Monographs in Ph.Eur.?  
*From idea to first draft FP monograph published*

**How to move forward?**

- Great uncertainty
- Lack of clarity
- Questions
- Confusion
- Unrest

**Extremely complex...**

**Hours of brainstorming...**

**Animated discussions...**

**Controversial topic...**
Frequent stumbling points

**Purpose and Scope**
- Does / Can FP monograph achieve a purpose for all stakeholders?
- Can we create FP monograph for multi-source products?
  Or can we only manage single-source (‘P4’)?
- How is the subsequent revision process foreseen?

**Status**
- Would FP monograph be mandatory or not? In all, or in parts?
- Can we achieve single mandatory dissolution at the same time as ensuring the test is discriminatory?

**Applicability**
- How would FP monograph be implemented to existing products?
- What happens to existing national monographs?
- Could we wake up the Adaptation of National Monographs procedure?

---

**Market Surveillance**
- Use standard as authoritative method and specifications, in the interest of patient protection (Q,S,E)
- Demonstrated quality of products with same active
- Eliminate ‘sub-standard’ medicines
- Robust methods

**Innovator Industry**
- Set standard
- Collaborate with Pharmacopoeia(s)
- Assure the ‘state-of-the-art’ quality is reflected, based on approved pre-clinical data to justify specifications

**Non-Innovator Industry**
- Rely on available public standard
- Facilitate marketing authorisation and speed to market
- Reduce duplication of efforts
- Could lead to further simplification

**Marketing Authorisation**
- Facilitate MA, increase access to multi-source drugs
- Optimise use of limited resources
- Could lead to collaboration with Pharmacopoeia(s)

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Weaknesses and Threats

Creation of FP Monographs

Different HAs have approved / requested different specs
Lack of harmonisation, recognition or convergence
Different rules and principles leading to (more!) non-harmonised monographs
Constitute trade barriers
Increase supply chain complexity
Increase supply disruption risk
Decrease independence and flexibility
Impede technical development
Competing pharmacopoeias and their business models

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Competing pharmacopoeias and their business models

Sections and Dilemmas

Pilot Draft Tablets, Pharmeuropa 26.3, July 2014

• Naming policy needed (e.g. ‘active moiety’ tablets)
• Would different hydrates or salts come into the same monograph?
• If not, what is the benefit of FP monograph?

• Which salts or hydrates are covered in one monograph?
• What would be the purpose of a monograph if specific to each API?

• Identify active moiety or complete salt(s)?
• Technology in draft is not widely-spread (DAD)

• Dilemma on status. Impossible to satisfy all? Align with approved innovator specs vs. offer an authoritative single method
• Separate monographs for modified-release forms?
• Could we imagine a non-mandatory test (e.g. FRC-like, production section) or prescribe a method but no specs?
Related Substances and Assay Dilemmas

Pilot Draft Tablets, Pharmeuropa 26.3, July 2014

- Alignment with ICH Q3B/Q6A principles seems essential
- API impurities should not be included in the sum of impurities
- Innovator unlikely to support elaboration if multiple different data interpretations are needed for different Pharmacopoeias (e.g. data integrity, resources)
- Dilemmas on how to set a policy acceptable from industry, regulator and patient standpoint

**Related Substances**

- What to do about enantioner impurities that are controlled in API but not in DP (co-elute)?
- What happens if SST depends on API impurities related to excipients?
- This case was lucky to prepare it in-situ
- How can peaks be identified (with reasonable use of CRS)?
- Why are total 0.2% and any other also 0.2%?
- Do we really need the “any other 0.2%”?
- Could we imagine only sum of unspecified, and individual limits for specified?
- ...
Recommendations

Opportunity for prospective harmonisation

Establish partnership between pharmacopoeias, share the work... Or recognise each other’s... but don’t multiply it

Partner with authorisation agencies, brainstorm on a Certification-like procedure

Ensure regulatory acceptance

Invest time to align principles such as impurity testing and dissolution within GPhP

Make a strong commitment to apply future WHO Good Pharmacopoeial Practices (GPhP)

Thank you!

“A good standard is one that saves time, money, and problems in the long run”

International Regulatory Harmonization Amid Globalization... Workshop (Feb 2013)