New Frontiers in the Quality of Medicines

Workshop Homoeopathy

Moderators:
Dr Michael Morris
Dr Emiel Van Galen

EDQM International Conference
13-15 June 2007
Strasbourg, France
Homoeopathy
The European Pharmacopoeia work programme and its achievements

Emmanuelle Charton, Ph. D.
Deputy Head, European Pharmacopoeia Department

ACHIEVEMENTS SO FAR...
“Homoeopathy” chapter of the European Pharmacopoeia (since the 4th edition)

Introduction
All general texts and monographs of the Ph. Eur. that are relevant to homoeopathy are applicable.

The “Homoeopathy” chapter of the Ph. Eur. contains general monographs and preparations used virtually exclusively for homoeopathic medicines.

II. Introduction of Ph. Eur.

- It is understood that when the same substance is used in both homoeopathic and other preparations then the monograph in the main body of the European Pharmacopoeia applies.
Achievements: general monographs, 5th Edition

- Homoeopathic preparations
- Mother tinctures for homoeopathic preparations
- Herbal drugs for homoeopathic preparations

Apply to all relevant homoeopathic preparations (having a Ph. Eur. specific monograph or not)

E. Charton, Strasbourg, June 2007

Supplement 5.8, 5th edition

- Homoeopathic preparations: Reference to new chapter 5.1.7 (Viral safety)

- New chapter 2371 (Methods of preparation of homoeopathic stocks and potentisation) Methods 1a to 4b of HAB and 2 from Ph. Fr. (MT from plants/animal materials)

E. Charton, Strasbourg, June 2007
Achievements: inorganic monographs, 5th edition

- Arsenious trioxide
- Barium chloride dihydrate
- Cadmium sulphate 2.7 hydrate
- Calcium iodide tetrahydrate
- Copper
- Copper acetate monohydrate
- Iron

Achievements: herbal and other monographs, 5th edition

- Common stinging nettle
- Garlic
- Hedera helix
- Hyoscyamus
- Hypericum
- Oriental cashew
- Saffron
- Honey bee
CURRENT ACTIVITIES

MANUFACTURING METHODS

Homoeopathic medicinal product

• Any medicinal product prepared from substance called homoeopathic stocks in accordance with a homoeopathic manufacturing procedure described in the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States.

Homoeopathic Manufacturing Methods Working Party (“HMM”)

• Appointed since November 2006
• Terms of reference: Drafting and revision of monographs allocated to the group by the Commission in the field of HMM
• Membership restricted to national authorities
HMM WP: April 2007 meeting

- Fr. Ph. method on glycerol macerates
- HAB methods 5-8, 10, 40 a & c, 42
  - 5 a Solutions from the raw material and a liquid vehicle
  - 5 b Solutions from the raw material and water for injections
  - 6 Triturations of solid raw material with lactose
  - 7 Solid preparations with lactose
  - 8 a Liquid preparations from triturations
  - 8 b Aqueous preparations from triturations
  - 10 Pills
  - 40 a, b & c Co-potentised mixtures
  - 42 a & b MT and dilutions thereof from animal material

HMM WP: Sept. 2007 meeting

- Finalise discussions from the April meeting
- Resume discussions on pillules
- Continue work on more HAB methods (nosodes = low priority)
MONOGRAPHS ON RAW MATERIALS

Homoeopathic Raw Materials and Stocks Working Party (“HOM”)

- Appointed since November 2006
- Terms of reference: Drafting and revision of monographs allocated to the group by the Commission in the field of raw materials and stocks
- Membership opened to manufacturers
HOM WP Future activities

- Meeting in the fall of 2007
- 37 monographs on the work programme (based on a priority listing made by industry)
- Rapporteurs identified

Thank you for your attention!
Starting the new legal framework for homeopathic medicinal products.

Emiel van Galen

New Frontiers in the Quality of medicines, 14 Jun 2007
Homoeopathy

Speeding up the legal procedures for homeopathic medicinal products.

A simple plan

Tinctures,
Monographs,
Certificates of suitability
National submissions and assessments:

<table>
<thead>
<tr>
<th>applicants</th>
<th>submissions</th>
<th>assessments</th>
<th>registrations</th>
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National submissions and assessments:

applicants → submissions → assessments → registrations

MA → MA → MA → MA → MA
Current regulatory practice

- A broad range of homeopathic remedies used
- Several manufacturers are submitting dossiers for identical homeopathic products, in several MS, for separate national registrations;
- Several regulatory agencies perform similar assessments, sometimes with slight differences in outcome;
- Mutual feeling of dissatisfaction

- Use Mutual Recognition, or even better: DCP
Mutual recognition:

registration    submissions    assessments    registrations

Mutual recognition:

registration    submissions    assessments    registrations
Mutual recognition:

- One dossier to be compiled,
- First positive assessment should be sufficient
- One registration can be used for next submissions

Particular attention:
- Several homeopathic manufacturers and a large amount of different homeopathic stocks.
- in 27 Member States.
- No legal way for arbitration in case of disagreement
Speeding up the process: Can EDQM be of any help?

Recognize the benefits of certificates of suitability

Monographs for tinctures in Ph. Eur.
Request for certification of tinctures
Certification by EDQM

To be used in national submissions
To be used in MRP/DCP

To be used in a free market for tinctures as intermediate products

The homeopathic tincture is the real homeopathic active substance

Towards Certificates of Suitability

(¢ refers to both HAB ¢ and Ph.Franc. TM)
Towards Certificates of Suitability

(¢ refers to both HAB ¢ and Ph.Franc. TM)

Certification
assessment

submissions

assessment
registrations

Towards Certificates of Suitability

(¢ refers to both HAB ¢ and Ph.Franc. TM)
Towards Certificates of suitability:

Certification submissions assessment registrations

Ø refers to both HAB ø and Ph.Franc. TM

Certification of Quality:

Certification assessment registrations

submissions assessment registrations
Monographs for tinctures:
(€ refers to both HAB € and Ph.Franc. TM)

Certification assessment

1 Proposal

Assessment Draft Monograph In Ph. Eur

1 Monographs for tinctures:
(€ refers to both HAB € and Ph.Franc. TM)
Monographs for tinctures:
(¢ refers to both HAB¢ and Ph.Franc. TM)

Certification assessment
 Proposal 1 Assessment Draft Monograph In Ph. Eur
 Ø Ø Ø

Monographs for tinctures:
(¢ refers to both HAB¢ and Ph.Franc. TM)

Certification assessment
 Proposal 1 Assessment Draft Monograph In Ph. Eur
 Ø Ø Ø

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New Frontiers in the Quality of Medicine

Expectations and MRP

Helena Pinto Ferreira

Mutual Recognition
What expectation?

• Introduction
• Regulatory framework
• Harmonization
• Challenges
Homeopathic Medicinal Products

What expectation on the Mutual Recognition?

Homeopathy

• Samuel Hahneman
  – 1755-1843
200 years - Homeopathy
Development of different:
Homeopathic stocks
Manufacturing methods
Pharmacopoeias
Homeopathic traditions
Homeopathic Schools
Interested parties

European legislation
Directive 92/73/EEC

↓
National Legislation

15 years of Regulatory Action
National Legislation

With tradition

EU Member States

Without tradition

Different criteria

Different access to HMP

Regulatory framework

• Some positive points
  – More guarantee of quality and safety of the medicinal products on the market
  – Improvement of the manufacture procedure by the industry.
  – Work in the sense of harmonization
Regulatory framework

• Some restraints
  – HMP rejected or cancelled
    • Lack of quality and safety data
    • Lack of commercial interest for the industry

Regulatory framework

HMP withdrawn from the market

Less possibilities of treatment both for the patients and for the health professionals
Harmonization is required

- HMPWG
  - Formal mandate in November 2004 by the Head of Agencies
    - Exchange of scientific and regulatory expertise
    - Provide guidance and advice
    Sense of harmonization

Art. 13
MRP and DCP
Registration

Art. 14
Art. 28
Art. 29 (1) to (3)

Art. 16
Art. 28 to 34 shall not apply

Mutual Recognition
Decentralised procedure

- Same timeframes as other MP
- CTD structure
- Assessment report by the reference MS
  - Avoid duplication of work
Mutual Recognition/DCP

- MRP and DCP - art. 14
  - No referral to CHMP in case of disagreements
    - Serious risk to public health

CMD(h) Standard Operating Procedure
Disagreement in Procedures – Referral to CMD(h)
Q&A on the SOP on disagreements in procedures

Don’t give up Fight

Routes to Harmonisation

Guidance documents

- Points to Consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin for human use
- Points to Consider on Safety of Homeopathic Medicinal Products from Biological Origin
- Guidance document on Module 3 of the Homeopathic Medicinal Products Dossier (draft)
Expecting Harmonisation

• Common interpretation of requirements
  – Regulatory issues
    • Administration routes
      – Oral and external
    • Labelling
  – Quality items
    • CTD
      – Stability data
      – Concepts European Pharmacopoeia / Directive

According to 2003/63/EC Directive (page 61):

- "... Starting materials mean all the materials from which the active substance is manufactured or extracted."
- "Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials."
Expecting Harmonisation

• Concepts Pharmacopoeia / Directive

  – Eur. Ph monographs "Homeopathic preparations" and "Mother tinctures for homeopathic preparations“:
    • different concepts for raw and starting materials.

  – Source material?
    • Not defined on the Eur. Pharm and on the Directive

Expecting Harmonisation

• Common interpretation of requirements
  – Justification of the Homeopathic use
    • Anthroposophic justification
    • Other “homeotherapies”
Expecting Harmonisation

- Safe dilution grade
  - Toxicological concerns
- Safety of material of biological origin
  - Nosodes
- Pharmacopoeia issues
  - Same name / different manufacture method / different HMP

Challenges

Expected problems

High number of HomMP

High number of Assessment Reports
Resources?
Timeframes?
Challenges

• Disagreements between MS
  – Serious Risk to Public health
    • Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC – March 2006

Challenges

• Disagreements between MS
  – Advisable for agreement
    • Good Quality of data from the applicant
    • Good assessment report of each MS concerned

• If no agreement is reached at the end of the CMD (h)
  – Possibilities?
    • HMPWG?
    • Final decision by the NCAs?
The rules relating to the manufacture control and inspection of homeopathic medicinal products must be harmonized to permit the circulation throughout the Community of medicinal products which are safe and of good quality.

Challenges

Achieving more harmonization → European market
Challenges

• Exchange of information /Cooperation
  – HMPWG
  – European Commission
  – National Authorities
  – Manufacturers, Applicants
  – Other Interested parties – Professional Associations, patients…

Helena Pinto Ferreira
Challenges

• Exchange of information /Cooperation
  — Progress

  – Save time and resources
  – Improve the quality, safety and effectiveness
  – More cooperation between interested parties
    • Work together for solving difficult issues
  – Future harmonization for Article 16 (2)

• Let’s keep on working together
Homoeopathic medicinal products in Europe: Developing a regulatory environment for a long-standing European tradition

Viewpoint of ECHAMP

Speaker  Nand De Herdt
          Industrial pharmacist
          General Secretary of ECHAMP

Conference  EDQM Conference
            “New Frontiers in the Quality of Medicines”

Place / Date  Strasbourg, June 14, 2007

Manufacturing Methods

• **We appreciate**
  - Establishment of the HMM working party
  - Publication of methods 1a – 4d in edition 5.8
  - Work on methods HAB 5 – 8, 40, 42 & glycerine macerates

• **We have questions** about the working procedure

• **We recommend** that the final outcome should reflect the tradition of homoeopathic preparations on the market in the member states and the reality of ’Homoeopathy’.
Priorities of Monographs

• *We appreciate*
  - Establishment of a monograph working party
  - Consideration of ECHAMP list proposal
• *We propose* the following criteria for definition of priorities by EDQM
  - Manufacturing method included in Ph. Eur.
  - Raw material identical in DE & FR
  - High priority for all interested stakeholders
• *We are ready* for pro-active input and participation in Pharmeuropa consultations, representing 52 companies in 17 member states

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Herbal homoeopathic preparations

*What are*

• appropriate standards to describe quality of mother tinctures?
• the differences to phytotherapeutic products?

⇒ *Basic Principle*

Quality is defined as an instrument to guarantee the suitability of a medicinal product for its intended use

• How to apply this principle?

⇒ *Learn from existing phytotherapeutic models*
Types of herbal extracts (Ph. Eur.)

- **Standardised extracts**
  - ± isolated substances of known therapeutic activity
  - *adjusting to a given content*

- **Quantified extracts**
  - group of constituents of relevant therapeutic activity & extract
  - *adjusting to a defined range*

- **Other extracts**
  - whole extract
  - defined by production process & specification

Function of assays in herbal extracts

- Batch conformity regarding active principle => relevant to extracts
- Quantifiable parameter as starting-point of batch related control => relevant to finished products

- Standardised extracts (a) + (b)
- Quantified extracts (a) + (b)
- Other extracts (b) only
Homeopathic MT - technical aspects

- MT of fresh plants are qualitatively different compared to extracts of dried drugs.
  Examples:
  - Echinacea angustifolia, echinacoside (Ph. Eur.)
  - Pulmonaria, rosmarinic acid (DAB)
  - Chamomilla, apigenin-7-glucoside (Ph. Eur.)
- MT generally less concentrated
- Availability of reference substances

Assays not relevant for QC of MT

- There are no therapeutically relevant constituents
  - active principle: MT as a whole
  - no dose-effect relationship
- Quality of MT defined by
  - Control of the starting material
  - Constant manufacturing process
  ➔ This is comparable to extract type „other extracts“ (Ph. Eur.)
Assays not relevant for QC of homoeopathic finished product?

- Are assays here a starting-point of batch related control of the finished product?
  => => => No

- Dir 2001/83/EC, Annex I
  - “If possible, an assay is required if toxic components are present…”
  - “…the quality shall be demonstrated by complete validation of the manufacturing and dilution process”

Future suitable parameters for MT

- “Assay”: Only in case of toxic components
- Why still quantitative “tests” for non toxic MT?
  - Variability of TLC fingerprints
  - Clarity of interpretation of TLC fingerprints
- Group determinations of secondary metabolism (prevalent groups like flavonoids, polyphenols)
  - More objective and more precise description
  - Reflecting MT as a whole better than a specific marker
- Specifications to cover biological variability
Proposal of monograph structure
- Herbal drug

- Definition
- Identification, e.g. pharmacognostic description
- Tests,
  - Falsification, if applicable
  Not useful for fresh plants:
  - Loss on drying
  - Foreign matters
- Assay, if dried drug

Proposal of monograph structure
- Mother tincture

- Production: Manufacturing method
- Characters
- Identification
  - TLC
  - Additional tests, if applicable
- Tests
  - Relative density or Ethanol
  - Dry residue
  - Quantitative determination, if no toxic compounds are present
- Assay, only if toxic compounds are present
THANK YOU

• EDQM for the organisation

• Colleagues for your excellent presentations

• Audience for your interesting questions and input in the discussion
EDQM International Conference

Strasbourg

Homoeopathic Medicinal Products in Europe: Developing a Regulatory Environment for a long-standing European Tradition

Irène CHETCUTI
June 14th, 2007

The CIPH was founded in 1955, with 13 members representing 7 countries. One of the primary objectives of the CIPH is to Compare and, if possible, harmonize our manufacturing and control techniques.
I. Reminder of EDQM Homeopathy Symposium, Strasbourg, 15 Feb. 2005

- The symposium was held by the EDQM following the end of the mandate of the homoeopathic medicinal product working group of the European Pharmacopoeia.

- The objective of the symposium was to define approaches to harmonising homeopathic medicinal products manufacturing processes and launching a new working program on fresh bases.

 Two different visions were presented:

The first vision defended the concept of manufacturing process harmonisation through standardisation and rationalisation, while the second recommended juxtaposition of existing methods, respecting their diversity.
While we would have preferred the first solution, the second found favour with the majority and was adopted for the subsequent work of the European Pharmacopoeia.

However, it is also clear that the choice will have the **coexistence** of two different systems as a **consequence**.

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**II – Consequences**

Safety issues could arise from this situation

**Example:** Aconitum napellus, two products bearing the same label

<table>
<thead>
<tr>
<th>Aconitum napellus Pharmacopée française</th>
<th>Aconitum napellus German Homeopathic Pharmacopoeia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloid content determined as aconitine in Aconitum napellus 1X = 1 DH</td>
<td>0.002 % - 0.005 %</td>
</tr>
</tbody>
</table>
Unnecessary Burden for companies

International companies manufacture different products under the same label, depending on the country where the product is intended to be marketed. This results in unnecessary efforts dedicated

- to prepare double manufacturing procedures, double documentation for registration, double stability studies etc., to separate the products physically

Limits the feasibility of establishing a common list of first safe dilutions

- Establishment of first safe dilutions of plant raw material necessitates in most cases to identify and quantify toxicologically relevant markers. This is only possible if common, harmonised manufacturing methods are used.
III. Proposal for achieving progress

- The coexistence could apparently not be rigorously managed without using differentiated special labelling stating the manufacturing process used for the medicinal product.
- We are in favour of a system designed to **enhance the reliability of homoeopathic medicinal products** and ensure their **suitability for traditional homoeopathic use**, where a uniform definition of homoeopathic medicinal products is provided.
- Differentiated labelling is therefore not justified for homoeopathic medicinal products.

Harmonisation of homoeopathic processes is possible

- In our opinion, the special labelling is only a superficial and provisional solution and would not resolve the basic difficulty which resides in the fact that real harmonisation of homeopathic medicinal product manufacturing processes is necessary. The harmonisation may be implemented using the processes common to the two systems.
- This would necessitate each side, the German and French sides, taking a step forward.
III.1. What is already in common

- The manufacturing processes for medicinal products obtained from chemical raw materials.

III.2. What is already common and requires nomenclature adjustment

- The manufacturing processes for medicinal products prepared from dried herbal drugs and from fresh herbal drugs, expressed as dry weight.
Given the similarity between the manufacturing processes for mother tinctures prepared from dried herbal drugs or fresh herbal drugs expressed as dry weight, as defined in the new section 4c of monograph 2371 of the European Pharmacopoeia, and the manufacturing processes for mother tinctures prepared from dried herbal drugs as defined in the new section 4a of the same European Pharmacopoeia monograph, a common method can certainly be envisaged.

To fully pursue harmonisation, we recommend that the rule:

\[
1:10 \text{ Mother Tincture} = 1 \text{ DH}
\]

be applied to all the medicinal products manufactured as per methods No. 4a and 4c, irrespective of whether they are of French or German origin.

The commitment will be nil for the German manufacturers who use process 4a. The commitment will be considerable for the French manufacturers who use process 4c.

No differentiated labelling will then be necessary for those medicinal products.
III.3. What requires a change in process

- The manufacturing processes for medicinal products prepared from fresh herbal drugs not expressed as dry weight.
- This involves processes 1, 2 and 3 of monograph 2371 of the European Pharmacopoeia. There is no French equivalent and the processes therefore cannot be harmonised.

In this case, the commitment will be considerable for German manufacturers who use processes 1, 2 and 3 of monograph 2371 of the European Pharmacopoeia and who make the effort to replace those processes by a future harmonised process 4a / 4c.
The harmonisation of the German and French methods of manufacturing homeopathic medicinal products is feasible. The methods share more points in common than they have points of divergence.

In short

- In order to prevent the juxtaposition of methods and the marketing of different products under the same labelling, we recommend that efforts are made so that the following conditions are all fulfilled:
  - processes 4a and 4c of European Pharmacopoeia 2371 monograph are harmonised and
  - the rule 1:10 mother tincture = 1 DH is generalised and
  - the differentiated labelling is restricted to homeopathic medicinal products manufactured using non-harmonised processes.
Conclusion

- Tradition?
- Tradition is respected and adapted to 2007 reality.

Thank you for your attention