Introduction to a debate on Industry participation in the elaboration of Pharmacopeia monographs

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Summary

- Given that the first reason to have Ph. Monographs is the public health.
- Elaboration, benefit and weaknesses of existing drug substance monographs. Two short stories:
  - Heparin crisis
  - Somatropin saga
- Lessons to learn from these examples
- Participation of the Industry to the elaboration of a monograph: Why, when and how
Short example 1

A useful monograph
Heparin crisis
Heparin crisis

- Heparin is extracted from Pork intestine (or Beef lung) mast cells and used as a drug substance or as a raw material in Low Molecular Mass heparins production

- Heparin crisis in US
  - 1,000 adverse events in the United States, including 81 confirmed deaths since January 2008 after heparin injection (Fatal cases with Baxter heparin)
  - In contrast, there were just three deaths due to allergic reactions to heparin in all of 2006
Sequence of events (cont.)

- Worldwide alert
  - USP (and other Pharmacopeia monographs methods as well) failed to detect the contaminant
  - In an emergency situation FDA asked to perform 2 screening methods (March 2008): H1 NMR and capillary electrophoresis (CE).
  - Many other companies had contaminated batches:
    - None of these companies had the same bad consequences as Baxter
    - Some had several LMMH contaminated heparin batches
- Presence of Oversulfated chondroitin sulfate (OSCS) was identified as a contaminant and associated with the adverse event.
- Note that addition of OSCS occurred after Heparin shortage linked to blue hear disease in China in 2007
Isolation/Structure of the contaminant

Isolation and characterization of contaminants in recalled unfractionated heparin and low-molecular-weight heparin
Limitations of the current monograph

- **Optical rotation specification:** ≥+35°
  - Pure heparin ~ +55°
  - OSCS ~ -8°
  - The monograph could allow ~ 30% of OSCS

- **Potency assay specification:** 140U/mg
  - Pure heparin > 175U/mg
  - OSCS ~ 40 U/mg
  - The monograph could allow ~ 25% addition of OSCS
  - In addition OSCS mixed with heparin produces a strong interaction resulting of a disproportionately higher activity (50% mixed resulted in 200U/mg)

- Absence of any specific purity test for related substances (*e.g.* HPLC, Electrophoresis…)

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1. P. Soon Shiong, 2. J. Walenga, 2d Workshop on the characterization of heparin products 19-20 June in EDQM Strasbourg
A list of « all? » possible impurities or contaminants

<table>
<thead>
<tr>
<th>Heparinoids</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondroitin sulfate A (CS-A)</td>
<td>Animal tissues</td>
</tr>
<tr>
<td>Dermatan sulfate (DS, CS-B)</td>
<td>Animal tissues</td>
</tr>
<tr>
<td>Chondroitin sulfate C (CS-C)</td>
<td>Animal tissues</td>
</tr>
<tr>
<td>Chondroitin sulfate D (CS-D)</td>
<td>Animal tissues</td>
</tr>
<tr>
<td>Hyaluronic acid (HA)</td>
<td>Animal tissues and bacteria</td>
</tr>
<tr>
<td>Heparan sulfate (HS)</td>
<td>Animal tissues</td>
</tr>
<tr>
<td>Heparosan</td>
<td>E. coli K5</td>
</tr>
<tr>
<td>Chitosan sulfate</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>Dermatan disulfate (DS-diS)</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>Oversulfated IIA (OSIIA)</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>Oversulfated DS (OSDS)</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>Oversulfated CS (OSCS)</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>Dextran sulfate</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>κ-Carrageenan</td>
<td>Seaweed</td>
</tr>
<tr>
<td>Fucoidan</td>
<td>Seaweed</td>
</tr>
<tr>
<td>Pentosan sulfate</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>PlI88</td>
<td>Semi-synthesis</td>
</tr>
<tr>
<td>Poly(vinyl sulfate)</td>
<td>Synthesis</td>
</tr>
<tr>
<td>Polyanetholesulfonic</td>
<td>Synthesis</td>
</tr>
<tr>
<td>Sucrose octasulfate (SOS)</td>
<td>Semi-synthesis</td>
</tr>
</tbody>
</table>

What are the methods on the shelf

- **Separation methods** (provided by Sandoz, GSK, Sanofi, Baxter)
  - Plate electrophoresis after nitrous acid hydrolysis of heparin
  - Ion exchange chromatography with and without nitrous acid hydrolyzed heparin
  - Analysis of GAGs (monosaccharides) after complete HCl hydrolysis
  - Capillary electrophoresis of the intact molecule

- **Spectroscopic methods** (FDA, Academic laboratories, Baxter)
  - $^{1}$H NMR
  - $^{13}$C NMR
  - 2D NMR
Criteria for the choice

• Define a rationale instead of the addition of all possible methods

• Retained methods are applicable by all manufacturers and OMCLs

• Key messages to upgrade the Ph. Monographs
  • Separation method
    • “Better is the resolution of a given method better is its chance to detect contaminants with a structure close to the structure of the drug substance”
    • “Preference for analytical methods resolving intact molecules rather than products from hydrolysis (e.g. sugar monomers)”
  • “A second orthogonal method was desirable” (e.g. NMR)
H NMR of OSCS Contaminated Heparin

Note Hep. Methyl At 2.04 and DS methyl at 2.08
Hep.: SAX-HPLC method.

<table>
<thead>
<tr>
<th>Sample name</th>
<th>Retention time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharide K5</td>
<td>10.5</td>
</tr>
<tr>
<td>Heparan sulfate</td>
<td>17.9</td>
</tr>
<tr>
<td>Chondroitin AC sigma</td>
<td>20.9</td>
</tr>
<tr>
<td>Dermatan sulfate sigma</td>
<td>21.2</td>
</tr>
<tr>
<td>Chondroitin sulfate CRS (EP)</td>
<td>21.3</td>
</tr>
<tr>
<td>Pure heparine WS</td>
<td>33.8</td>
</tr>
<tr>
<td>Persulfated poly-K5</td>
<td>38.3</td>
</tr>
<tr>
<td>Persulfated hyaluronic acid</td>
<td>41.5</td>
</tr>
<tr>
<td>Persulfated dermatan sulfate</td>
<td>41.6</td>
</tr>
<tr>
<td>Oversulfated chondroitin sulfate</td>
<td>49.1</td>
</tr>
</tbody>
</table>

Method: P. Mourier, C. Viskov, P. Anger and C. Houiste
Conclusion

- The usefulness of an Heparin monograph is obvious but a monograph based only on global tests/assay is not enough

- A monograph is only one piece of the quality system (traceability, Inspections are also key)

- Keep in mind this story for other biological products for new and old monographs.

- Are we capable to detect (any?) adulteration or to detect counterfeit products with a Ph. Monograph. Is it the role of a monograph?
Short example 2

Somatropin
Somatropin monograph
(Purity and assay)

Identification by peptide mapping


Aggregates and assay by SEC
**Assay**  
(A great simplification for routine control)

- Absence of bioassay:
  - The in-vivo bioassay in hypophysectomized rats is imprecise, costly and invasive.
  - It has been removed from the routine product specification with an acceptable degree of security demonstrated by a collaborative study with the participation of the manufacturers.

- Assay by Size Exclusion Chromatography
  - Because degradation products like deamidated, oxidized forms are equally active.
  - By convention the specific activity was fixed at 3 IU/mg (WHO).
  - During development the specific activity must be demonstrated.

*Bristow A.F., Jeffcoate S.L. (1992) Biologicals, 20, 221-231*
Somatropin charge variants
(Replacement of IEF by CZE)

Figure 1 - Isoelectric focus

Figure 3 - Typical CZE electropherogram of somatropin sample H (somatropin CRS Batch 1) (result from Participant 1)
Implementation of CZE

- The method was developed in the context of a comparability study (P. Dupin, F. Galinou, A. Bayol, (Sanofi), J. Chromatogr. A, 1995; 707, 396-700).

- A collaborative study involving manufacturers demonstrated clearly that CZE was superior to IEF in resolving and quantifying the related substances. (E. Charton et al. Pharmeuropa Bio 2004-1, 47-58)

- One of first products in the Ph. Eur. with a CZE (the other one is EPO). Many QC laboratories were reluctant because not equipped with capillary electrophoresis.

- Implementation: January 2006 European Pharmacopoeia Supplement 5.3

### Table 2. Thioether Content Estimated by ES/MS Whole Molecule Analysis

<table>
<thead>
<tr>
<th>Product</th>
<th>Batch Code</th>
<th>% Thioether Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormotrop® (4 IU)</td>
<td>50897</td>
<td>32</td>
</tr>
<tr>
<td>Hormotrop® (4 IU)</td>
<td>50793</td>
<td>7</td>
</tr>
<tr>
<td>Hormotrop® (12 IU)</td>
<td>51026</td>
<td>6</td>
</tr>
<tr>
<td>Hormotrop® (12 IU)</td>
<td>50923</td>
<td>18</td>
</tr>
<tr>
<td>Yelit® (4 IU)</td>
<td>4684</td>
<td>10</td>
</tr>
<tr>
<td>Cryotropin® (4 IU)</td>
<td>50631</td>
<td>5</td>
</tr>
<tr>
<td>Saizen® (8 mg click.easy)</td>
<td>SC305D</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Saizen® (8 mg click.easy)</td>
<td>SC310</td>
<td>Not detectable</td>
</tr>
<tr>
<td>NIBSC r-hGH</td>
<td>98/574</td>
<td>Not detectable</td>
</tr>
<tr>
<td>NIBSC p-hGH</td>
<td>80/505</td>
<td>Not detectable</td>
</tr>
<tr>
<td>EP r-hGH CRS</td>
<td>Batch 1</td>
<td>Not detectable</td>
</tr>
</tbody>
</table>

All complies with:
- Ph. Eur and USP somatropin monographs

*M. Lippi et all, J. Pharm. Sc., Vol. 98, N° 12, 2009 Heterogeneity of Commercial Recombinant Human Growth Hormone (r-hGH) Preparations Containing a Thioether Variant*
Undoubtedly, new technological approaches, as demonstrated by Jung et al.,8 Hepner et al.,3,4 and finally by Datola et al.,11 could highlight product heterogeneity significantly better than existing compendial methods, supporting the comparability exercise and the definition of biosimilarity or dissimilarity in terms of quality profile between a comparator and an originator.”

M. Lipsi et al., J. Pharm. Sc., Vol. 98, N° 12, 2009 Heterogeneity of Commercial Recombinant Human Growth Hormone (r-hGH) Preparations Containing a Thioether Variant
None of the tests is based on higher ordered structure

Peptide mapping with a qualitative acc. crit. only: “the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution. “

Can we detect a new impurity not detected by other methods?

Process specific related substances detected but not mentioned (e.g. Gln18-hGH) or not detected at all (e.g. NorLeu-hGH or thioether variant)  

A. Bayol et al, Pharmeuropa Bio 2004-1, 3545
Questions

• Role of a Ph. Monograph for demonstration of Bio-similarity?
  • A comparison based only on Ph. Monograph is obviously limited and insufficient according to guidelines.

• Should a Ph. Eur. Monograph cover all possible related proteins?
  • Similar products are not expected to be identical
  • The control methods and acceptance criteria should be logically deducted from the product knowledge according to ICH Q6B
  • If biotech monographs are not specific enough discuss their use and misuses

• Potential misuses outside well-regulated regions
  • How to communicate more warning
Participation of manufacturers
An important point « Bio-similar are not at all generic product »

- The EDQM, does not accept any new application for CEPs for biological substances.

- “The characterization and determination of biological substances require not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control.”

*Certificate of Suitability to the monographs of the European Pharmacopoeia
Why is it important to participate to the elaboration of monographs

- The availability of a Ph. monograph should not be over-estimated in the bio-similar approval process.
- The publication of a monograph provides approved methods and reference material for the quality control of the drug substance.
- The risk for the innovator is that the methods, acceptance criteria and official reference material in the Ph. Monograph are not corresponding to its product (surprises and non-anticipation of changes).
- Note that wide acceptance criteria can authorize worst quality and concomitant higher yield and competitive advantage.
How

- Several manufacturers:
  - Open procedure: if only one manufacturer is willing to cooperate we can suppose that he will propose its own methods and acceptance criteria
  - If several manufacturers cooperate no guarantee but participation to the choice of the best method and time to verify the appropriateness of the acceptance criteria

- One manufacturer:
  - Confidentiality needed
  - In Europe P4 Bio procedure (only regulators have access to the data)
When

Product approval

Monograph proposal submitted

Official Monograph

Patent expiry

Regulatory Data Protection

2 – 5 years

N Years
Backup slides
Innovator Company (CMC)

Development → Approval → Production

Knowledge → Post approval changes

Comparability study (New versus previous)

Or more:

Routine controls + In Depth comparison + Pharmac; Clinical
Bio-similar Company (CMC)

- Patents, literature, available innovator DP
- Bio-similar Development,
- Knowledge
- Comparability study (Biosimilar versus innovator)
- Authority approved methods
- Accepted Reference material

?