Swissmedic training
Locarno, 21-22 May 2019

API STARTING MATERIALS AND THEIR MANAGEMENT

Michel Keller, former Swissmedic inspector
The heparin contamination crisis in 2008

• Some batches of Heparin injection of different manufacturers have been associated with anaphylactoid type reactions with thousands of patients affected, some leading to hypotension and to nearly 100 deaths


  Heparin appeared to be intentionally contaminated with OSCS to reduce the cost of production (<10% of the cost of heparin)

• Method used for the commercial preparation of porcine intestinal heparin API involved five basic steps:
  1) preparation of tissue; 2) extraction of crude heparin from tissue;
  3) recovery of raw (crude) heparin (= starting material);
  4) purification of heparin; 5) recovery of purified heparin. (“GMP steps”)


New definition of SM for Heparin

• “Hence, pooled porcine intestinal mucosae are defined as the starting material for any heparin”

Ref: Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products (EMA/CHMP/BWP/429241/2013)

“GMP steps”:
1) preparation of tissue; 2) extraction of crude heparin from tissue;
3) recovery of raw (crude) heparin (= starting material);
4) purification of heparin; 5) recovery of purified heparin.

• EP and USP monographs for Heparin sodium revised: addition of a test for absence of oversulfated chondroitin sulfate (OSCS)
GMP definitions (Glossary)

• API STARTING MATERIAL (API SM)
  A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

• RAW MATERIALS
  A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

  THIS DEFINITION OF API SM EXCLUDES SOLVENTS AND REAGENTS
Pre-SM → Pre-SM → SM-1

Custom synthesis

Application of change control and cGMP

SM-2 → STEP 1

Intermediate 2 ← Intermediate 1

STEP 2

Commodity reagent

SM-3 ← STEP 3

Intermediate 3
Final intermediate

STEP 4

Crude drug substance

Formation of a simple ester/reccrystallization

Drug substance
### Table 1: Application of this Guide to API Manufacturing

<table>
<thead>
<tr>
<th>Type of Manufacturing</th>
<th>Application of this Guide to steps (shown in grey) used in this type of manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical Manufacturing</strong></td>
<td>Production of the API Starting Material</td>
</tr>
<tr>
<td>API derived from animal sources</td>
<td>Collection of organ, fluid, or tissue</td>
</tr>
<tr>
<td>API extracted from plant sources</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>Herbal extracts used as API</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>API consisting of comminuted or powdered herbs</td>
<td>Collection of plants and/or cultivation and harvesting</td>
</tr>
<tr>
<td>Biotechnology: fermentation/ cell culture</td>
<td>Establishment of master cell bank and working cell bank</td>
</tr>
<tr>
<td>“Classical” Fermentation to produce an API</td>
<td>Establishment of cell bank</td>
</tr>
</tbody>
</table>

**Increasing GMP requirements**
Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2.

<table>
<thead>
<tr>
<th>Type and source of material</th>
<th>Example product</th>
<th>Application of this guide to manufacturing steps shown in grey</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Animal or plant sources:</td>
<td>Heparins, insulin,</td>
<td>Collection of plant, organ, Cutting, mixing, and /or initial, Isolation and purification, Formulation, filling</td>
</tr>
<tr>
<td>5. Plant sources: transgenic</td>
<td>Recombinant proteins, vaccines, allergen</td>
<td>Master and working transgenic bank, Growing, harvesting(^9), Initial extraction, isolation, purification, modification, Formulation, filling</td>
</tr>
<tr>
<td>6. Human sources</td>
<td>Urine derived enzymes, hormones</td>
<td>Collection of fluid(^{10}), Mixing, and/or initial processing, Isolation and purification, Formulation, filling</td>
</tr>
<tr>
<td>7. Human sources</td>
<td>Products from cells tissues</td>
<td>Donation, procurement and testing of starting tissue / cells(^{11}), Initial processing, isolation and purification, Cell isolation, culture, purification, combination with non-cellular components, Formulation, combination, filling</td>
</tr>
</tbody>
</table>

Increasing GMP requirements
**Table illustrating the application of Good Practices to the manufacture of herbal medicinal products**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Good Agricultural and Collection Practice (GACP)</th>
<th>Part II of the GMP Guide</th>
<th>Part I of the GMP Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutting, and drying of plants, algae, fungi, lichens and exudates *</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Expression from plants and distillation **</td>
<td></td>
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<td></td>
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<tr>
<td>Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances</td>
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<tr>
<td>Further processing into a dosage form including packaging as a medicinal product</td>
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</tr>
</tbody>
</table>
Clarification

• This workshop is not about the selection of API starting materials (API SMs) and source materials (i.e. where the drug substance manufacturing process begins): this is ruled by ICH Q11.

• Actually, ICH Q7 provides guidance regarding good manufacturing practices for the drug substance, but does not provide specific guidance on the selection and justification of starting materials. (Q&A on Q11; 5.2)

• However, as inspector you may have to challenge the way the API manufacturer defines one specific API SM vs. API intermediate («downgrading» of API intermediate to API SM).
Question 1

• “No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).” (ICH Q7, 2.17)

• «The applicant should set appropriate controls and should justify the proposed specification for the actual and potential impurities that are reasonably expected in a proposed starting material, based on the scientific knowledge and available information“ (ICH Q&A on Q11, 5.13)

• “The API manufacturer should demonstrate a thorough knowledge of the quality of the SM and its impact on the quality and safety of the final API.” (APIC Position paper on API SM, 2014)

QUESTION

What would you as inspector expect to see in order to demonstrate a thorough knowledge of the quality of both SMs and their impact on the quality of the final API?

You may list and describe the elements of a system likely to ensure this thorough knowledge.
Question 2

• Q: Can the Lifecycle Management section of ICH Q11 (Section 9) apply to starting materials?

• A: Yes. Changes in earlier synthesis steps (upstream) must be made in accordance with the quality assurance system of the applicant. Residual risks in regards to the drug substance quality are to be assessed. The corresponding regulations of ICH Q7 and ICH Q7 Q&A document (Chap. 7 and 13, respectively), Q9 and Q10 (Chap. 2.7) must thereby be applied to starting materials as well. (ICH Q&A on Q11)

QUESTION
Change control of SMs suppliers: what should be considered by the API manufacturer/ how to do it appropriately?
Question 3

• “An on-site audit (of suppliers of materials) is not required; however, an on-site audit could be a useful tool in the evaluation of a supplier.” (ICH Q&A on Q7, 7.4)

• 5. Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. (GMP, annex 2)

• “Audits are not mandatory as per current GMP and should be considered on a case by case basis.” (APIC “How to do” Document, 2018)

QUESTION
Assuming that the API manufacturer audits suppliers of one API starting material, what would you ask for and check in terms of evaluation of suppliers?
Question 4

• “Companies should consider redefining the API Starting Material for well-established products. This offers the opportunity to reduce the overall GMP requirements for early manufacturing steps and to shift the focus to be on the control of the critical synthetic steps starting from the redefined API Starting Materials. [...]”
(APIC: “How to do” document, 2018)

**QUESTION**

During your inspection you observe/discover/take notice that the company is in process of “redefining” one of its intermediates (Px) to an API starting material. I.e. some batches have already been produced with this “redefined” product.

How would you handle this situation?
References

Regulatory
• GMP part II (ICH Q7)
• GMP annexes 2, 7
• ICH: Q9 (QRM); Q10 (PQS); Q11 (PD); Q&A on Q7; Q&A on Q11
• Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products, EMA/CHMP/BWP/429241/2013

Literature
• Graham T. Illing, Robert J. Timko, Linda Billett: Drug Substance Starting Material Selection, Pharmaceutical Technology, Volume 32, Issue 12, Dec 02, 2008 (slide 5 of this presentation)
Time frame (90’)

• Introduction 15’
• Sub-groups (4) work on questions 1-4 55’
  Including consolidation of 2x2 sub-groups to 2x1 groups
• Groups (2) results presentations 20’ (2x10’)
