APIC Active Pharmaceutical Ingredients Committee

Q11, practical aspects of implementation- an Industry perspective

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APIC Active Pharmaceutical Ingredients Committee

Q11, practical aspects of implementation- an Industry perspective

- Introduction
- Background on the discussion on RSMs
- Guidelines; global and regional
- Interpretation of the guidelines
- Practical consequences of redefinition
- Personal experience
- New developments
- Conclusion

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Introduction

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30+ years of experience in the regulatory (API-) field.

Board member of APIC (European API Industry organization).

Lecturer for a number of ECA courses (European Compliance Academy) on regulatory topics.

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Background on the discussion of RSMs

- As dictated in ICH Q7, GMP starts at the Regulatory Starting Material (the RSM).
- Thus, no legal basis for GMP before the RSM.
- Health Authorities fear that sub standard APIs can enter the market since GMP is thus not guaranteed for a sufficient part of the synthesis (maybe including critical steps).
- Industry does not want to avoid GMP but having a short synthetic route means less regulatory burden for post approval change control.

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Background on the discussion of RSMs

Health authorities objectives

- Risk to API quality (impurities, contamination)
- Visibility of synthetic route
- MAA responsibility to provide sufficient information

Industry objectives

- Regulatory relief – fewer changes/variations
- Proprietary information

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Background on the discussion of RSMs

- Starting materials need a holistic approach. Having a sound understanding of the entire route of synthesis helps to define the appropriate RSM.
- No “cherry picking”, compliance with one or two items from the guidance is not sufficient.
- Authorities focus a lot on “fate and purge of impurities”. What is present in the RSM, and what during the process and what is present in the API and where were those impurities formed in the process.

Guidelines; global and regional

ICH Q7

- Incorporated as significant structural fragment onto the structure of the API.
- Can be an article of commerce.
- Normally has defined chemical properties and structure.
- This guideline (on GMP) does not apply to steps prior to the introduction of the defined RSM.

Guidelines; global and regional

ICH Q11 extensively addresses the justification for starting materials.

For synthetic drug substances

- Changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to impact the quality of the drug substance;
- Manufacturing steps that impact the impurity profile of the drug substance should normally be included;
- RSM should be a substance of defined chemical properties and structure.

Guidelines; global and regional

Q11 (For synthetic drug substances)

- RSM is incorporated as a significant structural fragment into the structure of the drug substance.
- Ability of the analytical procedures to detect impurities in the starting material.
- Fate and purge of those impurities and their derivatives in subsequent processing steps.
- How does the proposed starting material specification contribute to the control strategy.
- Justification of commodity RSM (commercially available) is generally not needed.

Guidelines; global and regional

Q11 for semi-synthetic drug substances

- Same principles apply as for synthetic drug substances;
  - Ability to analytically characterize the RSM of biological origin;
  - Impact of fermentation/extraction process on the impurity profile;
  - Risks from microbial and other contamination should be addressed.

Q11 for biotechnological drug substances

- Cell banks are the starting point for the manufacturing process.

Guidelines; global and regional

Important clarifying regional guidelines:

- Top Ten Deficiencies in New CEP Applications (2011), dated June 2012 (update published over 2015-2016, but please also read the old one).
- EMA Reflection paper on the requirements for selection and justification of starting materials for the manufcature of chemical active substances (published October 2014).

The EDQM document Top Ten Deficiencies provides detailed requirements. The EMA Reflection Paper gives an overview of the current way of thinking in EMA. It is quite detailed as to what the expectations are.

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Interpretation of the guidelines

- It is obvious that not the text of the guidelines, but the interpretation thereof is of the highest importance for both Industry and the Regulatory Authorities.
- At the end of the day, a common understanding of the issue leads to good quality dossiers and documents and to easier assessments (and thus quicker approvals).

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Interpretation of the guidelines

- The most important issue to tackle is the impurity profile. It is key to the authorities to see that you have knowledge in place on “what happens with the impurities that are present in the RSM” and “where are the impurities that are present in the API formed”. On top of this you need to know whether there are any impurities formed and removed during the process.
- This is called fate and purge of impurities.
- Obviously your control strategy needs to be based on this information.

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Interpretation of the guidelines

- When writing your submission (or an update of your submission) you should write the chapter on the RSM (it is in the Closed Part of your DMF, so no fear for disclosing confidential information to your customers) using terminology of the guidelines. Show the assessor that you have considered all the different elements listed in the guidelines to determine the suitability of the RSM.
- Share your knowledge. It may be obvious to you that your choice is in line with the expectations but share the information of the rationale with the assessors to make them understand it.

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Interpretation of the guidelines

- Also, provide information on the control strategy on the starting material. Confirm that there are agreements in place with the supplier(s) to ensure that the specifications you have described are guaranteed and that changes at the supplier will be assessed for their ability to effect these specifications.
- List the suppliers' name and address, and provide their flow chart.
  If you have more than one supplier for the same RSM and their flow charts are different you should address that as well.

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Practical consequences of redefinition

- For most of the generic APIs that are currently marketed, the DMFs are already in place.
- New focus points, such as the RSM, may pop up when a new MAH wants to refer to the same file, or when the file is opened for other reasons (-major- changes e.g.).
- This seems a strange position , since the patient's safety is absolutely not impacted: the first product on the market has apparently never had any safety issues, caused by the API RSM!
- Yet, we see an increasing number of questions from the HA's.

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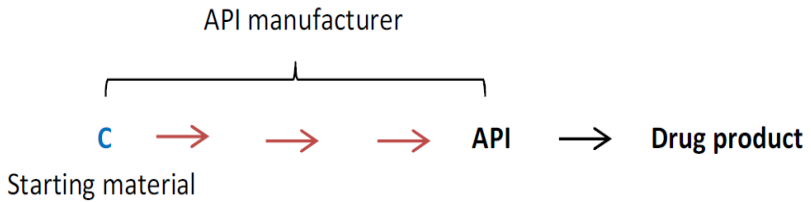
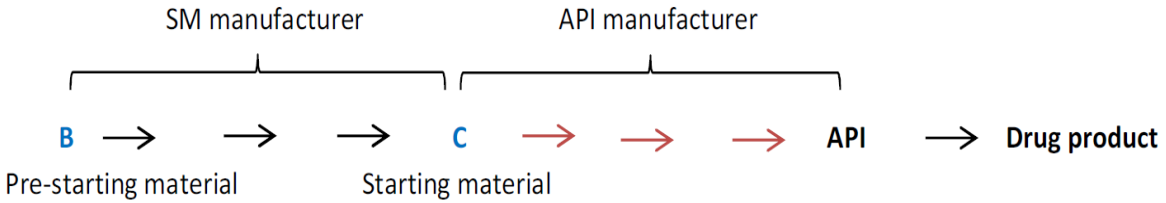
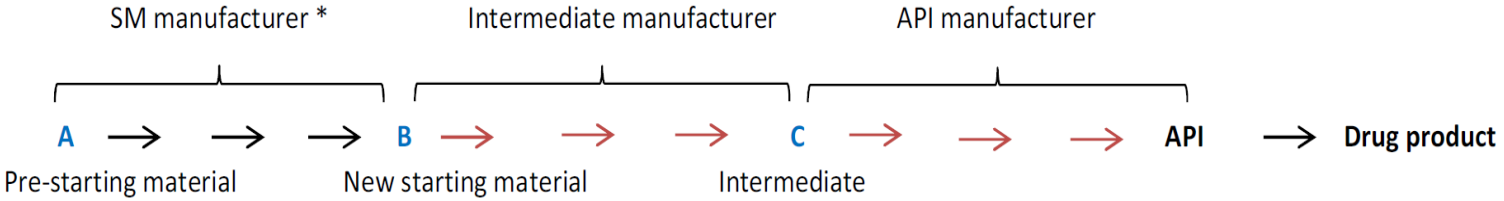
1. **API on the market for many years supported by an ASMF:**



2. **CEP application:**



3. **Re-definition of starting material:**



* API manufacturer's supplier's supplier = MA holder's supplier's supplier's supplier

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Practical consequences of redefinition

- The redefinition of a starting material may have huge consequences: suddenly your API RSM supplier becomes an intermediate supplier. If the new RSM is not fully produced by this original supplier, another supplier comes into the picture!
- You are the responsible company, so you are to ensure that GMP is applied on all the steps. This requires very specific Quality Agreements with these suppliers.
- Steps that were formerly not subject to change control are subject to change control from the redefinition onwards.

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Practical consequences of redefinition

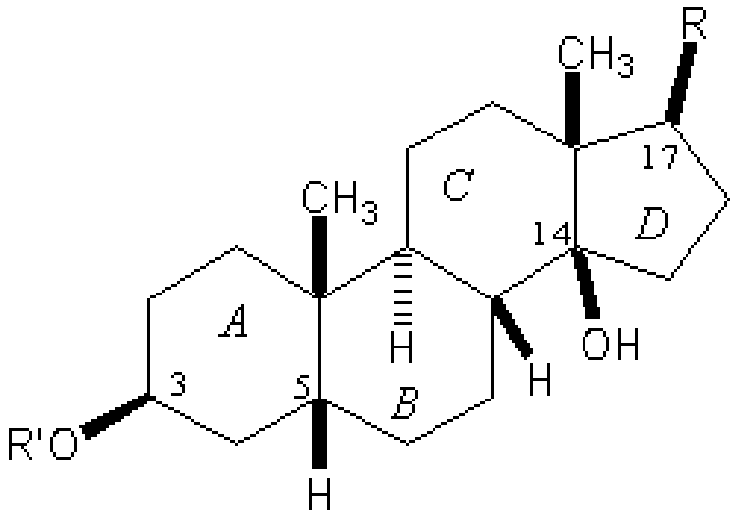
Personal experience

- I have seen many many situations where the API manufacturer was asked to redefine the RSM. In Europe this situation often arises when a CEP is requested.
- Also, in the USA, under GDUFA, the assessors have this as a specific point of interest.
- In Japan the assessors start to raise questions as well.

- As long as science is the basis, and the safety of the patient is the main concern, these questions are understandable. In the next slides I will share an example where this seemed not to be the case.

Personal experience

- ASMF (= European Drug Master File) for a steroid with 13 chemical conversion steps described.
- For steroids the chemical backbone is always the same.



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Personal experience

- It is thus difficult to fulfil the requirement that “the RSM should generally not have a structure that is very close to that of the final substance in relative size and complexity”
- The ASMF was referenced for the originator’s product. When the ASMF was first referenced for generic applications, 8 countries asked for name and address for every supplier of the Starting Material and a description of the synthesis for each supplier, starting from the natural source.
  Moreover, it was asked to provide details on origin (plants) and method used for extraction.

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Personal experience

- It seems strange that the originator's product was deemed safe for many years without this information.
- 13 (!) chemical conversion steps were described and the impurities that are potentially present in the API do not originate from the starting material.
- What does the additionally required information provide in terms of patient safety??

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Personal experience

- We have “fought” very hard to get the current RSM accepted, and finally succeeded. The fact that none of the impurities in the API originated from the RSM and none of the impurities from the RSM made it all the way to the API was the “winning” rationale.
- “Fate and purge of impurities” !

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New developments

ICH Q11 Q and A document

- The ICH Q11 Q and A document that deals exclusively with Questions and Answers on the selection of Regulatory Starting Materials has recently been published for public consultation.
- The deadline for comments has now passed and the ICH Working Group will internally discuss all the comments received.
- For some points this document gives very clear recommendations.

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New developments

ICH Q11 Q and A document

- Industry organizations are –as always- also involved in the preparation of the Q11 Q and A document.
- It can be found on the ICH website.

New developments

EDQM revision guidelines

•In the current version of the guideline PA/PH/CEP (04) 2, 6R, July 2014, for revisions, there is no difference between changes before and after the starting material. In other words, the pre-starting material information is also subject to change control.
In the industry view this is not in line with the other ICH guidelines. Change control is part of GMP, which starts at the RSM.

New developments

EDQM revision guidelines

•This has been a point of discussion for many years and recently EDQM has decided to change their point of view (in line with e.g. the European Quality Working Group). Only pre starting material changes that lead to a change in the specifications of the RSM will require a regulatory submission.

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Conclusion

- Regulatory Starting Materials are one of the hot topics in the regulatory world nowadays.
- Where Industry favours short synthetic routes to prevent changes/variations, Health Authorities fear the lack of GMP (and thus control) before the RSM.
- The combination of a good rationale for the choice of the RSM (based on Q11) and the chosen control strategy should be well explained in the regulatory documentation so the assessor can understand.
- Redefinition of RSMs has huge consequences for the API producer, which is certainly underestimated by the Health Authorities.

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