APIC Active Pharmaceutical Ingredients Committee

Experience with CEPs, API manufacturer's perspective

Prague, September 2017

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APIC Active Pharmaceutical Ingredients Committee

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- Introduction
- Experience with CEPs: obtaining a CEP
- Experience with CEPs: using a CEP
- Filing of changes in the CEP dossier

- Conclusion

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Introduction

What / who is APIC?

- A Technical European Industry Association, based in Brussels
- Focused on APIs from a quality and regulatory perspective

APIC Active Pharmaceutical Ingredients Committee

Introduction

APIC‘s Mission

- To promote the use of compliant APIs in medicinal products to ensure patient safety
- To represent the interests of pharmaceutical and chemical companies producing APIs and intermediates in Europe by being recognized experts who advance and influence the global GMP and Regulatory environment

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Introduction

What / who is Marieke van Dalen

- Working for Aspen Oss B.V. in the Netherlands as Global Regulatory Specialist
- Over 30 years of experience in the regulatory field
- Board member of APIC

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Experience with CEPs: obtaining a CEP

- To obtain a CEP the procedure is not that difficult: submit a dossier that is in line with all the requirements which are published on the EDQM website and you will obtain a CEP.
- In practice there is a little more to it.
- There are few CEPs that are issued without any questions being raised.
- On the EDQM website references are found to all guidelines that should be applied.

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Experience with CEPs: obtaining a CEP

- Taking into account the “EDQM Top 10 deficiencies” when compiling the dossier certainly increases the quality of the dossier and brings the dossier more in line with what is actually expected.
- The topic leading to most discussions is the topic of the starting materials. It is quite frustrating for industry that Regulatory Starting Materials (RSM) that were approved in the corresponding ASMFs are not deemed acceptable by EDQM. In the experience of the APIC members this is the most serious and most critical deficiency.

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Experience with CEPs: obtaining a CEP

- This often leads to the situation that the RSM in the CEP is different (further back in the synthesis) from the RSM in other parts of the world.
- The consequences of redefining are huge: new players may enter the supply chain, very extensive quality agreements need to be prepared with new intermediate manufacturers (who have to comply with GMP).
- The main objection from industry is NOT that GMP is too expensive, but the fact that change control starts at the RSM, and more steps thus simply means more changes to be reported..

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Experience with CEPs: obtaining a CEP

- Obviously re-definition after a CEP has already been granted is even more frustrating. Re-opening the discussion should only take place when there are serious health concerns.
- Industry also sees the RSM discussions as a major problem in the IGDRP developments. Obviously we do not want to see assessment reports with “earlier” RSMs shared with countries where a “later” RSM has been approved.

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Experience with CEPs: obtaining a CEP

- Q3D implementation still raises some questions: EDQM has published their guidance and more than 150 CEPs with a Risk Management Summary appended have been granted since September 2016.
- APIC feels that the policy seems to have moved from being a non-testing guideline applicable to medicinal products to a testing guideline applicable to APIs and excipients. Although the component approach is a choice, as is the submission of a RMS, whenever an approach is preferred by EDQM/EMA, it becomes the only way in the eyes of the MAH.

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Experience with CEPs: obtaining a CEP

- The Drug Product manufacturers and the MAHs are expecting all their suppliers to perfom a risk evaluation, including test results.
- This is particularly strange for APIs that are really low dosed: in these cases, making the calculations using PDE's, even percentages of elements present in the API would be safe!

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Experience with CEPs: using a CEP

- In the EU, the use of a CEP is well established and runs rather smoothly.
- In some occasions questions are being raised on topics already assessed by EDQM. In those cases we try to refer the Authority to the EDQM assessment report.
- Outside of the EU, different approaches are being used..

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Experience with CEPs: using a CEP

- There are non-EU countries who actually have a system in place to accept CEPs: e.g. Switzerland, Australia, New Zealand.
- However, often there is a “CEP plus” requirement: the CEP can be submitted but on top of that Closed Part or Open Part information is needed (this is APIC experience in e.g. Saudi Arabia, Singapore, South Africa, Tunisia).

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Experience with CEPs: using a CEP

- In some countries, the CEP is accepted, but only as supporting information, e.g. in India where it can be used as proof of GMP. This could backfire, e.g. when more manufacturing steps (and more manufacturer site addresses) are listed on the CEP as compared to the dossier in that country. Thus, carefully consider if the pro’s outweigh the con’s.

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Experience with CEPs: using a CEP

The practical use of the CEP is in the hands of the Drug Product manufacturer: we still see that quite a few "frequently occurring" mistakes are made there.

- Use of a former version of the CEP (this means it is no longer valid!) in an application.
- Next to the CEP, incorporate the (often outdated) Applicants Part of the ASMF in the dossier. Extremely confusing for the assessor.
- Not filing revisions of the CEP through the Variations Scheme.

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Experience with CEPs: using a CEP

One thing often encountered is the lack of information on topics not covered by the CEP assessment in the DP dossier.

An example is the micronization process if the CEP has been assessed and granted for non micronized material. The DP manufacturer should get this information from the API supplier and incorporate it in their DP dossier.

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Filing of changes in the CEP dossier

- This is in the view of APIC one of the major advantages of the CEP system. In the Certification scheme changes with regards to the API are dealt with between the CEP holder (in most cases the API manufacturer) and the EDQM. If a revision of the CEP is issued, this is in almost all cases a Type 1A variation for the Marketing Authorization Holder (MAH).

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Filing of changes in the CEP dossier

The one remaining issue is the expectation to file “pre-starting material changes”. EDQM has announced that the revision guidleine will be revised to reflect the official EU position on pre-starting material information. This is however not yet completed and companies are struggling with what to do at present.

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Conclusion

Overall, API Industry is very much in favour of the CEP system. Obviously we do see some room for improvement, but the system works quite well.

In fact, our dream would be to have a similar system for non-Ph-Eur covered substances, as we think that centralised assessment for API's is the only truly workable solution for the European ASMF system.

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