

## APIC POSITION PAPER API STARTING MATERIALS

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### 1. Summary

The following principles should be applied when considering API SMs:

- Definition of the SM should be based on scientific knowledge.
- Risk management principles should be applied.
- Manufacture of the API from the SM is covered by GMP, which should include appropriate supplier qualification.
- Manufacture of the SM is not necessarily covered by GMP but should be covered by an appropriate quality management system.
- Any information provided on how the SM is manufactured in order to justify the SM definition (“pre-SM information”) should not be subject to post-approval change requirements.

These principles should be applied globally. They should be applied to new submissions<sup>1</sup> that have not previously been assessed in support of a product licence application<sup>2</sup>. They should not be applied retrospectively.

Within Europe, the API SM should be assessed only once, at the first submission of the API documentation. Thereafter the agreed SM should be accepted for subsequent applications, i.e.:

- If first included in an Active Substance Master File (ASMF), new marketing authorisation applications (MAAs), in any member state, referring to the same ASMF, should not trigger re-assessment of the SM.
- When a CEP application is submitted, if an ASMF has been submitted previously and the SM accepted, this decision should be upheld by EDQM.
- If a company includes the API documentation in the MAA and then decides to submit an ASMF or CEP application at a later date, or another MAA including the same API documentation, the same should apply.

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<sup>1</sup> Includes DMFs, ASMFs, CEP applications and API documentation integrated in the product licence application dossier.

<sup>2</sup> Includes MAA, NDA, ANDA, NADA, ANADA and related applications to health authorities.

Similarly, outside Europe, the health authority should assess the API SM when the DMF / API documentation is first submitted. Once the proposed SM has been accepted, this should be upheld for all subsequent applications referencing that DMF / API documentation.

## 2. Introduction

Health authorities have noted:

- A trend to describing shorter synthetic routes starting from complex SMs.
- A general lack of information when the SM manufacture is outsourced.
- Insufficient discussion regarding the carry-over of potential impurities.

This has often resulted in assessors challenging the proposed SM and, in the last few years, the definition of API SM has been one of the top deficiencies in CEP applications.

One of the reasons given by assessors for requesting the re-definition of SMs further back in the synthetic route is the management of the lifecycle of the dossier. Originally a company may manufacture a SM in-house with full information and adequate control but later this material may be purchased with less information and control. Another reason why short synthetic routes are usually rejected by assessors is the implementation of GMP. Manufacture of SMs is not covered by GMP and often inspectors face poor supplier qualification.

Industry, in turn, is faced with inconsistencies in evaluations and a lack of clear and unambiguous guidance.

Requests from the authorities to re-define a SM further back in the synthetic route can have a major impact on the API manufacturer. When the SM is re-defined, this re-classifies the SM manufacturer as an intermediate manufacturer. This means that:

- Full information on the manufacture of the intermediate is required.

A common problem faced by API manufacturers is the reluctance of some suppliers to disclose proprietary information on their syntheses to the API manufacturer, due to the lack of a system to protect their confidentiality.

- The material must be manufactured under GMP.

This is not required for SMs therefore the manufacturer may not be in a position to comply. In addition, the manufacturer of the originally defined SM may not produce the re-defined SM himself so his systems must now cover qualification of the SM supplier.

- New quality agreements / contracts need to be drawn up.

In the case that the originally defined SM was not produced in-house, the API manufacturer may no longer have direct contact with the re-defined SM manufacturer; yet he must ensure that he is notified of changes in the manufacture of the SM to enable him to assess potential impact on the API. The SM may have other, larger, non-pharmaceutical uses in which case the supplier may be unwilling / unable to comply with the API manufacturer's requirements.

- Existing customers of the API must submit variations / change applications.

If the API is already on the market, companies referencing the ASMF / DMF must submit variations / change applications when the dossier is updated. The increase in workload for both industry and the health authorities can lead to difficult situations when multiple stakeholders – customers and health authorities – are involved.

Clearly, it is in the interest of all concerned parties that requests for re-definition of the SM further back in the synthetic route are avoided. A common policy and harmonised approach is needed, with transparency between the API manufacturer and the health authorities. Once an authority has accepted a SM in a new API submission<sup>1</sup>, this decision should be upheld in all subsequent applications involving that submission. Requests to re-define the SM should be rare and result only from a serious concern for patient safety. The reasons for the request should be fully explained to the API manufacturer.

### 3. Definition of the API SM

The criteria used to define the API SM should be scientifically justified. A risk-based control strategy should be developed that includes not only SM specifications but also downstream GMP controls, in-process tests, operating conditions and validation of the API manufacturing process.

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. The SM specifications and overall control strategy should be based on this knowledge.

- The SM should be appropriately characterised, with a well-defined impurity profile.
- The fate of potential impurities (related substances, solvents, metals, potential genotoxic impurities) in the downstream manufacturing process should be well understood and documented.
- The capability of the downstream process to remove impurities and/or their derivatives should be established.
- Potential impurities that are critical to the quality and safety of the API should be appropriately controlled, using suitable analytical methods, depending on whether they are carried through to the API or reliably removed during processing.

In some cases, a late stage intermediate may be appropriate as SM; in other cases it may be necessary to go further back in the synthetic route. The focus should be on the level of understanding and control.

Non-science-based criteria should not be applied in the definition of the SM. These include:

- Number of synthetic steps
- Structural complexity
- Commercial availability
- Significant structural fragment

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<sup>1</sup> Includes DMFs, ASMFs, CEP applications and API documentation integrated in the product licence application dossier.

The term “significant structural fragment” should be used as stated in ICH Q11, i.e. to distinguish SMs from reagents, solvents and other raw materials. It should not trigger a search for the earliest possible substance that is a structural fragment. A commercially available material may be classified as a SM but only if it meets the scientific criteria.

Regarding the introduction of stereochemistry into the synthesis, this may occur before the designated SM if justified (as in example 4 in section 10.4 of ICH Q11).

#### 4. Manufacture of the API SM

In accordance with ICH Q7 and Q11, GMP begins with the first use of an API SM. Manufacture of the SM itself is not subject to GMP requirements.

Under GMP, the API manufacturer is required to have systems in place to cover supplier qualification. GMP compliance of the API manufacturer, including their supplier qualification programme, should be enforced during site inspection by the authorities.

Industry’s quality management of the SM manufacture should incorporate risk assessment. The qualification process should include a quality agreement / contract between the API manufacturer and SM manufacturer to ensure that the impact of changes in the manufacture of the SM can be adequately assessed by the API manufacturer. The SM manufacturer should have an appropriate quality system in place and on-going monitoring / evaluation should be performed by the API manufacturer.

The name and address of the SM manufacturer and qualification documentation should be available for review during site inspections. In APIC’s opinion, they should not be provided in the dossier as they do not contribute to the science-based approach.

#### 5. Pre-SM information

Many health authorities require the submission of information on how the SM is manufactured in order to assess the suitability of the SM specifications. In their policy for defining API SM, EDQM states that “this should include a flow diagram outlining enough steps of the synthesis [of the SM] and information on the solvents, reagents and catalysts used during its synthesis”.

ICH Q11 states, in section 5.2.1, that “changes to the SM specification and to the synthetic route from the SM to final drug substance are subject to regional, post-approval change requirements”. EDQM’s policy is concordant with this, stating that “the approved SM is the starting point for GMP and variations”.

While APIC recognises that it may be helpful to provide information on SM manufacture, it should not be a prerequisite. In APIC’s opinion, if the information is provided, post-approval change requirements should apply only from the SM onwards and any pre-SM information provided to justify the SM definition should be exempt from these requirements.

APIC proposes that the submission of pre-SM information is handled as follows:

- The flow chart, including solvents, reagents and catalysts, showing the manufacture of the SM may be provided if necessary.
- The definition of the SM is assessed only once therefore this pre-SM information is provided with the initial submission only, as a stand-alone document ( i.e. separate from the dossier). It is clearly marked as *regulatory non-binding* and it is understood and accepted that this information will not be updated.
- During the lifecycle of the dossier, any change to the pre-SM information is assessed by the API manufacturer.
- If the change to the pre-SM information impacts the dossier, i.e. if the SM specification or subsequent control strategy has to change, a variation / change application is submitted in the usual way to update the dossier.
- If the change to the pre-SM information does not impact the dossier, i.e. no change is required to the SM specification and/or subsequent control strategy, no action is needed.

This avoids increased regulatory burden to both industry and health authorities by focusing only on changes that potentially impact the final API.

## 6. Conclusion

APIC proposes a balanced approach to definition of the API SM, based on scientific knowledge and risk management principles. Furthermore, a thoroughly documented and justified SM definition should be acceptable globally as API manufacturers often supply their products for use in many different drug products / markets.

In conclusion:

- A risk-based control strategy is key.
  - The SM is not the only substance contributing to impurities in the API.
  - The API is not the only substance contributing to impurities in the drug product.
- There should be an appropriate balance between assessment of the SM and other process risks, e.g. other raw materials, design of the manufacturing process.
- Manufacture of APIs under GMP is a critical part of the control strategy and this includes supplier qualification. Adequate supplier qualification is a GMP requirement that must be managed by the API manufacturer and verified by inspection. More paper work is not a solution. Describing an excessive number of steps in the dossier is no guarantee of a safe API.
- The provision of information on SM manufacture should not be a prerequisite.
- Post-approval change requirements should apply only from the SM onwards.

## 7. References

*Meeting minutes from the Working Group on API Starting Materials, EDQM, 21 June 2011.*

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*ICH Q11 Development and Manufacture of Drug Substances, Step 4, May 2012.*

*ICH Q7A GMP Guide for APIs, Step 4, November 2000.*

*Top Ten Deficiencies in New Applications for Certificates of Suitability (2011), PA/PH/CEP (12) 15, June 2012.*

*Content of the Dossier for Chemical Purity and Microbiological Quality, PA/PH/CEP (04) 1 4R, February 2007.*

*Guideline on the Chemistry of New Active Substances CPMP/QWP/130/96 Rev 1, December 2003.*

*Guidance on Frequent Changes to Applications for Certificates of Suitability, PA/PH/CEP (11) 76, July 2012.*

*Draft Guidance for Industry Initial Completeness Assessment for Type II API DMFs under GDUFA, FDA, October 2012.*

*The API Starting Material and Other Materials in API Manufacture: Scientifically-Based Principles for the Common Technical Dossier, Drug Information Journal, Vol 33, 755-761, 1999, Helga Möller and Chris Oldenhof.*

## 8. Abbreviations

ANADA	Abbreviated New Animal Drug Application
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
APIC	Active Pharmaceutical Ingredient Committee
ASMF	Active Substance Master File
CEP	Certificate of Suitability of the monograph of the European Pharmacopoeia
DMF	Drug Master File
EDQM	European Directorate for the Quality of Medicines
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
MAA	Marketing Authorisation Application
NADA	New Animal Drug Application
NDA	New Drug Application
SM	Starting Material