

THE ACTIVE PHARMACEUTICAL INGREDIENTS STARTING MATERIAL (APISM) AND OTHER MATERIALS IN API MANUFACTURE: SCIENTIFICALLY-BASED PRINCIPLES FOR THE COMMON TECHNICAL DOSSIER

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Until now, no clear guidance has been available from any authority on a key aspect of drug applications/marketing authorizations, namely, the determination of a suitable starting point for the description of the synthesis of the active pharmaceutical ingredient (API). This paper describes, for the first time, a fully scientifically-based proposal for such guidance. It is intended as a recommendation to the International Conference on Harmonization (ICH) expert working group developing guidance with respect to the definition of the "API Starting Material" (APISM) within the Common Technical Document (CTD) initiative. The authors recommend a similar approach to be used in the ICH to define the starting point in the API synthesis, after which full Current Good Manufacturing Practice (cGMP) principles should apply.

Key Words: API; Starting material; ICH; Dossier; GMP

INTRODUCTION

IN 1987 THE FIRST GUIDANCE was issued by an authority on how to determine what the APISM should be in drug applications. Historically, the most extensive requirements on API process descriptions ex-

isted in the United States but due to the lack of guidance, the approaches used were of a rather ad hoc nature. In Europe, the description of the API process was usually very limited and lacked detail. For compendial APIs a reference to the pharmacopoeia was sufficient. This situation remained unchanged in Europe until the early 1990s. A similar situation exists in Japan to this day.

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DISCUSSION

The First Guidance

In the United States, the situation changed with the issuance in February 1987 of a Food

and Drug Administration (FDA) guideline entitled "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances." This contained the following guidance:

"While a definition of starting material applicable to all situations cannot be given, the following criteria for defining a starting material may be helpful:

- It is incorporated into the new drug substance as an important structural element.
- It is commercially available.
- It is a compound whose name, chemical structure, chemical and physical characteristics and properties and impurity profile are well defined in the chemical literature (see glossary).
- It is obtained by commonly known procedures (this applies principally to starting materials extracted from plants and animals and to semi-synthetic antibiotics).

Frequently, the starting material will meet several of these criteria. If it does not meet any, it is probably not the starting material. When an applicant wishes to use a starting material that is not commercially available, the material should meet criterion c. In addition, for material that is not commercially available, it may be necessary to carry out more testing for impurities than would be needed for a commercially available product.

The starting material may be the subject of a DMF (e.g. some starting materials for semi-synthetic antibiotics). When the starting material is itself a drug substance, the synthesis of this material should be provided either in full or by authorized reference to an NDA or DMF. Generally, the decision about what is the starting material has been reached by agreement between the applicant and the FDA chemist before submission of the NDA (e.g. during an IND end-of-phase 2 meeting or a pre-NDA meeting)."

In practice, the above guidance seemed to give rise to many different interpretations. This resulted, for example, in different APISMs for identical products and processes being submitted by different applicants. Furthermore, this guidance was regarded as an approach that largely lacked a scientific basis.

ICH: Common Technical Document

In the recent ICH M4 initiative on the Common Technical Document and in the ICH Q7A ("GMP for APIs"), discussions have been initiated regarding the development of a more appropriate guidance for the definition of APISM. A preliminary proposal was formulated during the expert group meetings in Tokyo in August 1998:

- A material used in the manufacture of an API which is incorporated as a significant fragment into the structure of an intermediate and/or the API,
- An article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or it may be manufactured in-house, and
- The APISM is of defined chemical properties and structure.

It is the opinion of the authors of this article that this approach lacks a scientific basis and will lead to divergent interpretations. While this approach may lead to an APISM only one or two steps removed from the API, the APISM may also be up to 20 steps removed from the API. Examples of each case are given in Figures 1 and 2, where the manufacturing process of acetylsalicylic acid is two

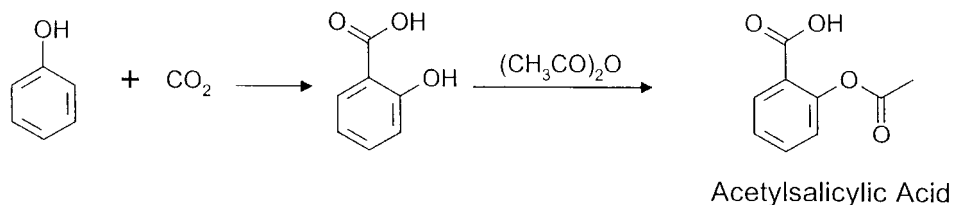


FIGURE 1. The manufacturing process of acetylsalicylic acid: two steps.

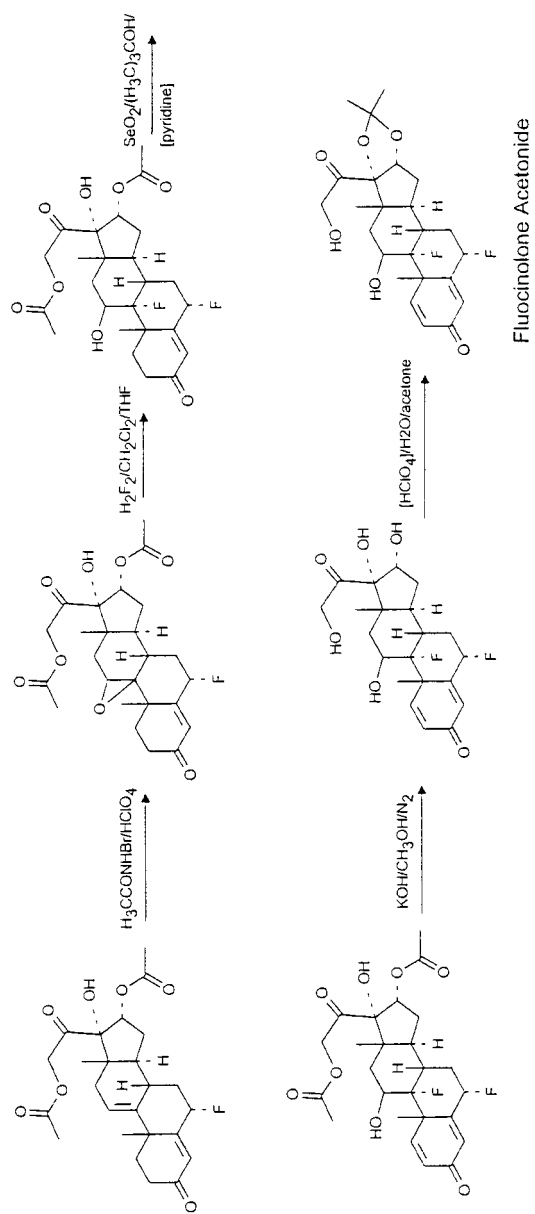


FIGURE 2. Continued.

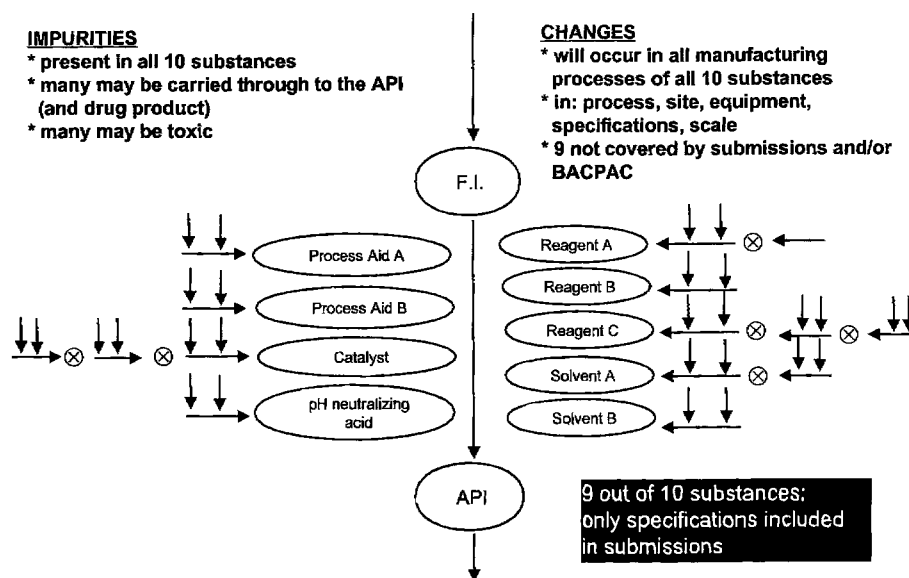


FIGURE 3. Demonstrating full analytical control.

steps and the manufacturing process of fluocinolone acetonide is 16 steps.

Proposal for a Scientifically-Based, Unambiguous Approach

The APISM definition was one of the subjects discussed by the International Pharmaceutical Federation (FIP) Special Interest Group's Working Group "Drug Substance" during meetings in 1997 and 1998. This resulted in a proposal for a fully scientifically-based and clear and consistent approach. The authors have further elaborated this preliminary proposal in the form of a decision tree. For the development of the approach, the following starting points were used:

1. The key issue in defining the APISM concerns *impurities* that may be carried through to the API,
2. A key criterion for assessing the potential that an impurity is carried through to the API is *the number of process steps* that a reaction step is removed from the API,
3. *Full analytical control* over substances used in the manufacture of an API should

be a key criterion in the definition of the APISM,

4. Since the proximity of a substance and its impurities in the synthetic route to the API itself is a key factor (see 2), there should be adequate *balance* between the amount of information submitted on the manufacture of *intermediates* (either late or early in the synthesis scheme) and on the manufacture of any *reagents, solvents, catalysts, processing aids*, and so forth, some of which are actually used in the final API manufacturing step,
5. Similar balance should exist between the *API* and any *excipients* that will become constituents of the final drug product,
6. Therefore, it is not considered suitable to submit extensive manufacturing information for early steps in the API synthesis, while *specifications only* are submitted for reagents, catalysts, solvents, processing aids, and excipients, even those used in the last step of the synthesis. In order to be consistent, extensive information on earlier manufacturing steps should not be required, provided that full analytical control is present for the molecule chosen as the APISM (Figure 3),

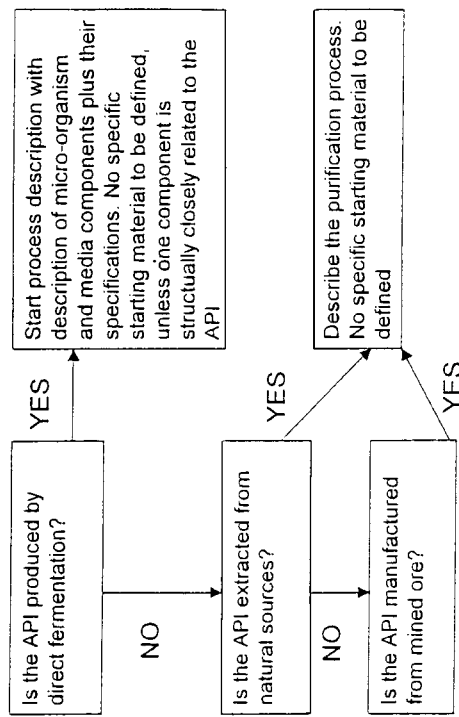
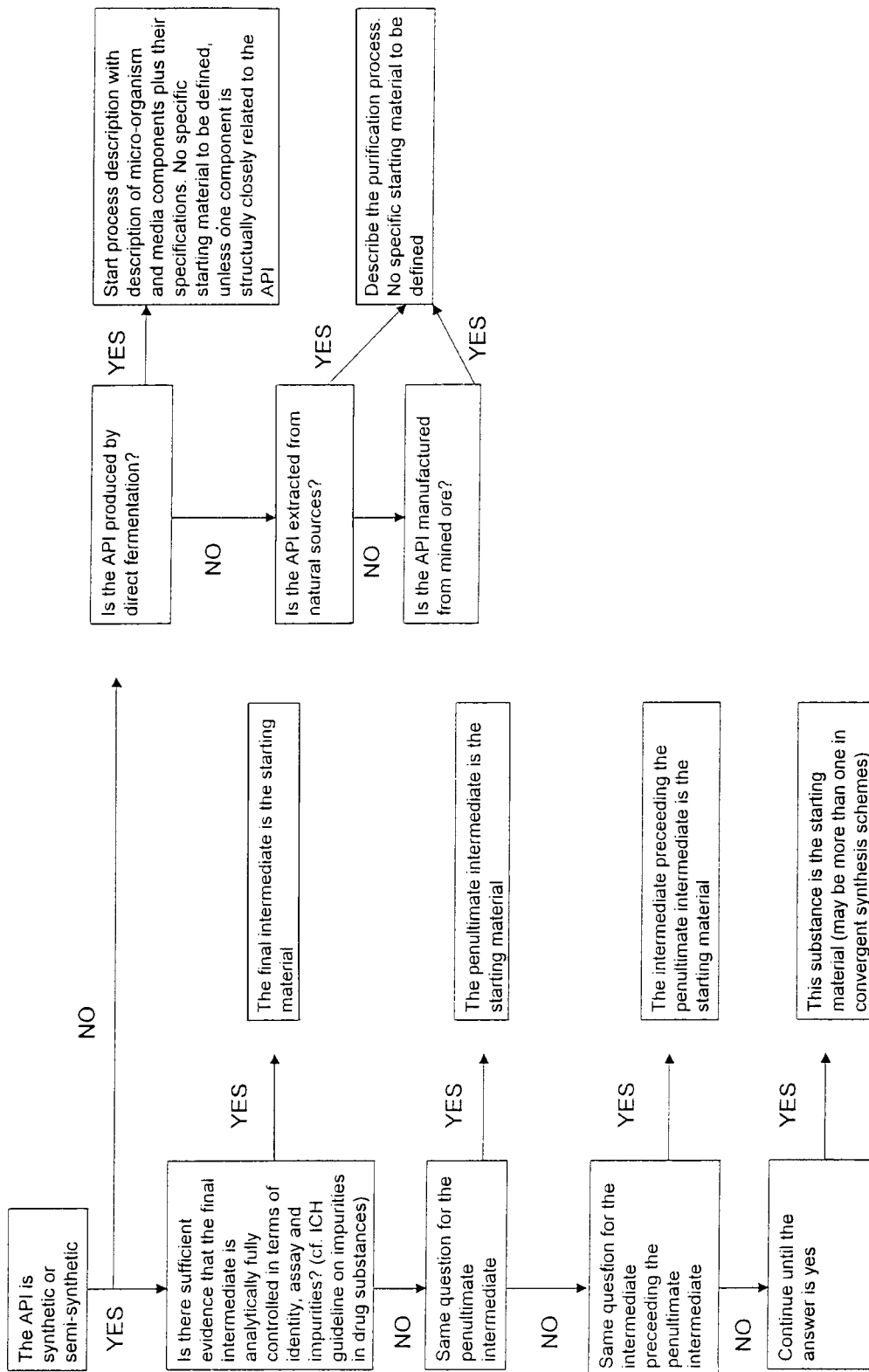


FIGURE 4. The APISM decision tree.

7. The proper way of making “full analytical control” into a powerful tool will be to adhere to the requirements of the ICH guidance on impurities in drug substances also at the level of the APISM.

Based on the above reasoning, an APISM decision tree is proposed as depicted in Figure 4. For definitions of terms used therein, please see the Appendix at the end of this paper.

Quality Controls for all Substances Involved in API Manufacture

The overall picture for the required quality control for substances involved in the manufacture of APIs, considering the approach proposed above for the APISM, would be as follows:

API. Specifications and analytical procedures should meet all the requirements laid down in ICH guidelines Q2A, Q2B, Q3A, Q3C, and Q6A.

APISM. Specifications should include appropriate limits for all impurities as defined in ICH guideline Q3A (the principles defined for the API should equally apply to the APISM) plus any additional specifications that are critical to ensuring the API will meet all its specifications.

- *Intermediates:* For any isolated intermediates an appropriate set of specifications should be defined which will ensure that the API will meet all its specifications, and
- *Raw materials:* Raw materials should be of a quality that will ensure that the API will meet all its specifications. The specifications for raw materials should be set accordingly. These will normally include as a minimum identity, assay, and impurity limits. Impurity limits for raw materials used in the final API synthesis step should be included in the raw materials section of the submission.

CONCLUSION

The decision tree approach provides, for the first time, a scientifically-based approach to

defining the APISM, which should be the starting point for the description of the API manufacturing process in drug applications or Drug Master Files. The adoption of the same science-based approach to determine the point in the API synthesis after which full GMP principles should apply would also be sound policy and is, therefore, recommended as well. It is the opinion of the authors that these recommendations for the required quality controls for substances involved in the manufacture of APIs ensure that the quality of APIs will be of a consistently high standard.

APPENDIX: GLOSSARY

Convergent synthesis: A synthesis route in which two separate synthesis paths converge, ultimately leading to the API.

Direct fermentation: Fermentation leading directly to formation of the API.

Final intermediate: A substance transformed into the API by the final conversion step (which should not be salt formation or esterification).

Full analytical control over the APISM: All requirements included in the ICH guideline on qualification of impurities in drug substances (but applied to an intermediate instead of to an API) are being met.

Natural sources: Plants, animals, humans.

Mined ore: Ore recovered from mines, already containing the API.

Raw material: A material used in the production of APIs and which is not the synthesis starting material or an intermediate. These include process aids: solvents, reagents, catalysts, etc.

Synthetic: Manufactured through chemical and/or enzymatic process steps.

Semi-synthetic: Manufactured through chemical and/or enzymatic process steps and containing one or more fermentation steps, the latter not being the final process step.

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