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COMMUNICATION TO STAKEHOLDERS

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Frequently asked questions (FAQs) on Active Pharmaceutical Ingredient

1. INTRODUCTION

This document is intended to provide communication to the API suppliers to assist them with adequately addressing the most common queries raised by SAHPRA.

What information should be provided for the recovered solvents used in the manufacturing process of the API?

- Describe the recovery process in detail including the exact step(s) that they are re-introduced.
- State what ratio (or range of mixtures) of fresh and recovered solvents will be used.
- State whether the solvents were recovered from the same manufacturing process of the same API or whether it comes from another source.
- Specifications and CoAs for each recovered solvent.

What information should be provided for the API starting material (API SM) in section 3.2.S.2.3?

- The name and address of each manufacturer(s) of the API SM or reaction intermediate supplier.
- Justification of the proposed starting material(s) according to ICH Q11.
- The name, chemical structure, flow diagram of the synthetic route of the API starting material (including reagents, solvents and catalysts (if applicable)), and specification.

- Materials used in the manufacture of the API (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. State if specifications have been provided for all other materials used in the preparation of the drug substance (i.e., raw materials, solvents, reagents, catalysts, recovered materials, seed crystals) and comment on their acceptability.
- Specifications for starting materials should include tests and acceptance criteria for appearance, identity, purity, and potency, where applicable. Well-defined controls of potential impurities should be included. Special consideration should be given to potential isomeric impurities and genotoxic impurities, particularly those that could be carried through the synthesis to the API.
- For API, or API manufactured with reagents obtained from sources that have potential of transmitting Bovine Spongiform Encephalopathy (BSE)/ Transmissible Spongiform Encephalopathy (TSE) agents (e.g. ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/ TSE affected country/ area, or data should be provided demonstrating that the material is not at risk of transmitting BSE/ TSE (e.g. an EDQM Certificate of Suitability).
- The Certificate of analysis for batches of API SM issued by each proposed API SM manufacturer should be provided. The corresponding certificates of analysis issued by the API manufacturer upon receipt for each of these batches.

What information should be provided for an API intermediate when the intermediate is obtained from external supplier?

- The API intermediate are increasingly common in submitted APIMFs, or arise because of the request for redefinition of the API SM. The introduction of such a supplier invariably complicates the submitted APIMF and therefore attention must be given to presenting information on the intermediate in a clear and logical manner.
- Two considerations include:

  (a) The API manufacturer is responsible for all steps undertaken in the manufacturing process, from the introduction of the API SM(s), and this should be reflected in the APIMF.

  (b) It needs to be ensured that an API intermediate is of the same quality and controlled in a consistent manner whether supplied internally or externally.
- With respect the first point above, the steps and controls undertaken by an external intermediate manufacturer must be integrated into the APIMF. Equally, the nomenclature of the various molecules

and manufacturing steps may need to be revised to ensure the overall process and molecules are clear and consistent. Some examples of expectations are:

- All intermediate suppliers are listed in section 3.2.S.2.1.
- A complete, terminologically consistent, and detailed manufacturing process description is supplied in section 3.2.S.2.2.
- Full information on all API SM suppliers — whether these are supplying the API manufacturer directly or an external intermediate manufacturer — is provided and discussed in 3.2.S.2.3.
- All materials used in the preparation of the API, including by the intermediate supplier, should be provided in 3.2.S.2.3.
- In-process controls, critical steps and intermediate controls that are undertaken by the intermediate manufacturer are listed in section 3.2.S.2.4.

- With respect to point (b), when an intermediate is sourced from an external supplier, information should be supplied in section 3.2.S.2.4 to illustrate that internally and externally sourced intermediate are of comparable quality and held to the same quality standards. Some examples of expectations are:
  - The specification applied by the API manufacturer to batches of the intermediate is provided, together with a statement clearly stating that all batches of intermediate (both internally and externally sourced) are tested to this standard.
  - The specifications applied by the intermediate suppliers at release are provided.
  - A justification for the suitability of the API manufacturer's intermediate specifications is provided that considers all sources of the intermediate.
  - Comparative batch analysis for batches of intermediate tested by the API manufacturer from all sources of the intermediate are provided.

What additional information should be provided for sterile APIs?

- Full validation data on the aseptic processing and sterilisation process where there is no further sterilisation of the FPP.
- A complete description for maintenance of sterility during storage and transportation.
- Justification for the choice of sterilisation method and comment on its acceptability.
- The following should be stated for sterilisation filtration: type of filter and its pore size (≤ 0.22 micron), pre-filtration bioburden (NMT 10 CFU/100 ml), integrity rest of the filter before and after

use, validation of the sterile filter (physical and chemical combability, adsorption, extractables, viability and bacterial challenge test), validation of the process by media fills.

What information should be provided for the impurities of the API?

- Discuss the possible carryover of impurities that may arise during the synthesis of the API from the redefined API starting materials and from the preparation of the redefined API starting materials themselves. All possible potential impurities that may arise from the starting materials, route of synthesis and possible degradation products should be listed with name, structure, origin, LOD, LOQ and ranges of results in at least 3 consecutive batches as well as the proposed limits taking into account the requirements of ICH Guideline. The methods used should be explained and validated. In addition, any impurity greater than the ICH reporting threshold should be reported.
- A specific discussion as part of the overall discussion on impurities should be provided with regard to impurities with potential genotoxicity. If, based on the discussion, a genotoxic impurity is indeed liable to be present in the substance, then compliance with current guidances (e.g. EMEA/CHMP/QWP/251344/2006 or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches, December 2008) should be demonstrated.
- The class II solvent XX is used in the preparation of YY. A test and limit for this solvent should be included in the specification for the starting material (*delete if not applicable*), the intermediate, or the final API on a routine basis at a limit of XXX in line with ICH guidance. However, and in line with the EMA CPMP/QWP/450/03 guideline, the class II solvent may be exempted from routine control if it has been demonstrated, on the starting material (*delete if not applicable*), on a suitable intermediate, or on the final API, that its content is NMT 10% of the acceptable limit (i.e. ICH) for three consecutive industrial batches or 6 consecutive pilot batches. If that is the case, a test and limit can be included in the specification, on a skip-test basis, for the starting material (*delete if not applicable*), or the intermediate, or the final API. The supportive batch analysis data should be provided, and the analytical method should be validated.
- The class I solvent or metal/genotoxic impurity XX is used/formed in the final step of the API preparation. A routine test and limit for this impurity should be therefore included in the API specification at a limit of XXXX. However please note that in line with the EMA Questions and Answers document dated June 2012, it is considered possible to apply skip testing if the level of the impurity does not exceed 30% of the limit, derived from either TTC or otherwise defined acceptable limit etc., in the API. Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production

scale batches. If this condition is fulfilled, a test and limit can be included in the API specification on a skip-test basis. The analytical method should be validated.

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