Sharing Drug Substance M7 information to HA and MAH:

"How to do" document

Interpretation of the ICH M7 guideline and other relevant guidelines with regard to M7 data sharing

Version 1

(March 2023)

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1. Introduction

BACKGROUND

Impurities, originating from chemical synthesis and/or degradation, reside in all drug substances. In order to assure safety of the drug substance, levels of impurities in drug substances need to be qualified and controlled. Furthermore, some impurities have the potential to be DNA-reactive and therefore cause mutations with carcinogenic risk to the patients; these impurities are referred to as (potentially) mutagenic impurities.

Based on the latter, it is important for drug substance (DS) manufacturers to assess the mutagenic potential of impurities, and share relevant data regarding the assessment with health authorities (HAs) and marketing authorization holders (MAHs) to review and assure safety of the drug product (DP). The assessment of impurities to assure safety is crucial throughout the development process and life-cycle management of a DS/ DP.

ICH M7 guideline, which describes recommendation on how to perform assessment of mutagenic potential of impurities residing in drug substances, was first published in year 2013, and is required to be implemented since January 2016.

The guideline briefly states what data regarding performed mutagenic impurities (MIs) assessment the DS manufacturer should include in regulatory documentation. However, it seems that different DS manufacturers have different approaches to data sharing to both HAs and MAHs.

The question on what data DS manufacturers should share, especially with MAH, gained additional importance with the Valsartan issue and newly published Nitrosamine guidelines, which require detailed data to be shared with MAH. Furthermore, in the EU, MAH is responsible for DS quality as per the legislation.

Therefore, the Industry should discuss and define what data regarding MIs assessment should be shared with HAs and MAHs.

THE OBJECTIVE OF THE DOCUMENT

The objective of the document is to present APIC recommendations on what data regarding MIs assessment of the DS should be shared with HAs and MAHs.

The document describes the APIC M7 Taskforce current thinking on the topic and should be viewed as recommendations, unless specific regulatory requirements are cited.

SCOPE OF THE DOCUMENT

Scope of the document is data sharing for all DS that require MIs assessment in line with ICH M7 for submission in countries that are ICH Members/Observers. Details on the type of DS and submissions that require ICH M7 assessment is presented in chapter *2. ICH M7 Guideline requirements regarding information sharing of this document.*

Nitrosamines are part of the Cohort of Concern (CoC) compounds defined by the ICH M7 guideline. Regarding data sharing on the risk of Nitrosamines in API with MAH, the APIC template is recommended to be used. Data sharing regarding Nitrosamines is not in scope of this document.

2. ICH M7 Guideline requirements regarding Information sharing

1. Guideline implementation for new / existing drug substances

The ICH M7 guideline *“ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK M7(R1)*” provides guidance on how to assess mutagenic potential of impurities in drug substances. The assessment of (potentially) mutagenic impurities as per the guideline is required for:

- new drug substances / drug products

- post-approval changes to marketed products

- new marketing applications for products with a drug substance that is present in previously approved product.

Furthermore, the guideline describes the type of DS/DP that are out of scope of the guideline; “Assessment of the mutagenic potential of impurities as described in this guideline is not intended for the following types of drug substances and drug products: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin.”

However, if the manufacturing of above type of DS/DP includes a synthesis step, the assessment as per the guideline might need to be performed.

The guideline contains recommendations about implementation of the guideline in chapter *2. Scope of the guideline, 4. Considerations for marketed products, Appendix 1* and *Appendix 2* (Implementation of guideline), which are implemented in EU as well (EMA/CHMP/ICH/83812/2013).

Further guidance on the type of submissions that require an ICH M7 assessment of the API, based on the ICH M7 guideline, can be found in documents prepared by APIC M7 Taskforce; please refer to Appendix of this document.

In submissions where ICH M7 assessment of the DS is required, the Drug Master File (DMF) holder is expected to include information on the performed assessment within the DMF submission.

2. What data to be included in DMF

The ICH M7 guideline chapter *9.2. Common technical document* provides general recommendations on what data regarding performed assessment to include in the DMF / dossier:

“For actual and potential process related impurities and degradation products* where assessments according to this guideline are conducted, the mutagenic impurity classification and rationale for this classification should be provided:

- This would include the **results and description of in silico (Q)SAR systems used**, and as appropriate, supporting information to arrive at the overall conclusion for Class 4 and 5 impurities.
- When bacterial mutagenicity assays were performed on impurities, **study reports** should be provided for **bacterial mutagenicity assays** on impurities.
- **Justification for the proposed specification and the approach to control should be provided** (e.g., ICH Q11 example 5b, Ref. 12). For example, this information could include the acceptable intake, the location and sensitivity of relevant routine monitoring. For Option 3 and Option 4 control approaches, a summary of knowledge of the purge factor, and identification of factors providing control (e.g., process steps, solubility in wash solutions, etc.) is important.”

As stated above, both actual and potential process related impurities and degradation products need to be included in the assessment of (potentially) mutagenic impurities. For additional clarity, definitions of “actual impurities” and “potential impurities” are described below.

Actual Impurities:

According to the ICH M7 guideline, “actual impurities include those impurities that are observed in the drug substance above the ICH Q3A reporting threshold”.

Potential Impurities:

According to the ICH M7 guideline, potential impurities are components that can be starting materials, reagents and intermediates or impurities that form under storage. Therefore, these impurities are obvious from the reaction scheme or result from theoretical considerations, but are not present in the final DS/DP above the ICH Q3A reporting threshold.

The impurities can be divided into two different types:

- Process related impurities (actual and potential)
- Degradation products (actual and potential)

All of these impurities should be considered in the ICH M7 assessment, as recommended by the ICH M7 guideline. The impurities should be discussed and listed. Each impurity should be evaluated separately.

It is important to notice that impurities which are appearing in raw materials, solvents, catalysts, etc. shall be included in the assessment as well.

The ICH M7 Q&A of 29 June 2020 (status Step 3) addresses some aspects regarding information expected in the CTD (Question 9.2):

Module 2: brief summary of the ICH M7 risk assessment and control strategy

Module 3 (typically section 3.2.S.3.2 Impurities): details of ICH M7 risk assessment and control strategy:

Hazard assessment*: provide table with:

- impurity chemical structure
- (Q)SAR results (pos/neg predictions, out-of-domain)
- bacterial reverse mutagenicity assay results (pos/neg, if available)
- ICH M7 impurity class (1-5) assignment
- supporting information (e.g., information/links for bacterial reverse mutagenicity assays, literature reports, (Q)SAR expert analysis, etc.)
- The in-silico systems used (name, version, endpoint) can also be noted*

ICH M7 impurity control strategy: provide table with:

- impurity origin (e.g., synthetic step introduced, degradant, etc.)
- ICH M7 class, purge factors (e.g., measured or predicted)
- ICH M7 control Option (1-4)
- control strategy (i.e., including in-process or compound testing rationale)
- supporting information (e.g., information/links for justifications, calculations)
- The maximum daily dose, TTC, and proposed duration of treatment can also be noted

*According to M7 Taskforce member's experience, detailed safety study information can be presented in Module 1 (Additional data or Literature folder) or Module 3 RP DMF (e.g. 3.2.S.2.6, 3.2.S.2.5).

Note: Question **9.1 is addressing the necessity to repeat** ICH M7 **(Q)SAR predictions** made during **development** before MA application – no need to repeat the in-silico predictions; predictions made during development are still valid.

3. New submission (DMF/ASMF & CEP) - Sharing M7 information to HA

Markets: countries that are ICH Members/Observers

Guideline requirements examples (ICH M7, EU, EDQM, Ph.Eur)

1. ICH M7 guideline

ICH M7 guideline (EC, Europe - Implemented; Date: 1 March 2018; Reference: CHMP/ICH/83812/2013) requirements regarding sharing M7 information are described within the chapter *ICH M7 Guideline requirements regarding Information sharing* of this document.

The requirements apply to new submissions of new and existing active substances (post-approval changes with impact on the risk of (potentially) mutagenic impurities or new marketing applications with drug substance previously approved in marketed product).

2. EU: EMA Guideline on the chemistry of active substances (EMA/454576/2016)

The EMA guideline describes requirements for data to be included in DMFs for new submissions of new and existing active substances.

Regarding mutagenicity assessment of impurities, the guideline refers to ICH M7 guideline and further states:

"...Information on impurities and their carry-over should be provided. This includes related substances, residual solvents, elemental impurities, reagents and those derived from reagents. The related substances considered as potential impurities arising from the synthesis and degradation products should be discussed and described briefly including an indication of their origin. The mutagenic potential of impurities should be addressed."

The guideline includes very general requirement describing the need for MIs assessment, and includes reference to the ICH M7 Guideline. There is no guidance on what data to be included in the DMF, which results in different approaches to data sharing by different DS manufacturers.

3. EU: Concept paper on the revision of the guideline on the chemistry of active substances (EMA/CHMP/600383/2022, July 2022)

The Concept paper describes the need to update above EMA guideline to include additional requirements on what data regarding MIs and Nitrosamines should be included in the DMF.

4. Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier (CHMP/QWP/297/97 Rev 1/Corr, February 2005)

The guideline states in section 2.2 of ASMF that “The toxicological implications of impurities not included by the monograph should be addressed. That means that the specificity of the method to these additional impurities must always be investigated, but the discussion of the toxicological implications (qualification) is only required if defined thresholds are exceeded, cf. Note for Guidance “Impurities in New Veterinary Drug Substances (CVMP/VICH/837/99), Note for Guidance “Impurities in new Drug Substances (CPMP/ICH/2737/99) or Ph. Eur. General Monographs “Substances for Pharmaceutical use”.

5. CEP: EDQM guideline Content of the dossier for chemical purity and microbiological quality (PA/PH/CEP (04)1, 6R)

The EDQM guideline describes requirements for data to be included in applications for a new CEP submissions for new and existing active substances.

Regarding mutagenicity assessment of impurities, the guideline refers to ICH M7 guideline and further states:

“...*In line with current EU guidance on potential mutagenic impurities (ICH M7) a specific discussion as part of the overall discussion on impurities should be provided with regard to impurities with potential /mutagenicity. If a mutagenic impurity is liable to be present in the substance then the control strategy should be demonstrated to be in compliance with current EU guidance. Justified control limit should be proposed together with a validated method for determining the content of the mutagenic impurity....”*

The guideline gives general guidance on what information regarding MIs assessment needs to be included in the DMF, however does not give detailed instructions and leaves room for interpretation, which results in different approaches to data sharing by different DS Manufacturers.

6. Ph. Eur. General Notice “Substances for pharmaceutical use (2034)”

This General Notice requires active substances (within scope) to comply with ICH M7.

7. Ph. Eur. General Notice “Pharmaceutical Preparations (2619)”

A proposal for revision of this general notice was published in Pharmeuropa 33.2 (April 2021). It refers to Ph. Eur.

What data to provide & where to include the data

Considering the existing guidelines requirements and based on practical experience of APIC Members, the following information on MIs Assessment for DS should be shared within the DMF to HAs from Regulatory perspective, in cases where ICH M7 assessment is required:

- Risk for presence of (potentially) mutagenic impurities should be addressed in line with the ICH M7 guideline, including Cohort of concern compounds

- Section 3.2.S.2.2 should include enough process information (e.g. all materials used, process conditions) to reveal potential risks of MIs formation.

- Mutagenic potential of impurities is typically addressed within the section *3.2.S.3.2 Impurities* of the DMF

AP DMF section 3.2.S.2.1 Manufacturers

Section should include the following information (if mutagenic impurities controlled on release specification):

- Contract laboratories that are used for (release) testing of identified mutagenic impurities or for validation of analytical method for release

Section 3.2.S.3.2 Impurities

Section should include information of the MIs assessment including:

- list of all actual and potential impurities (typically including starting material synthesis*)
- impurity classification for each impurity (including summary of results of two in-silico tools**)
- list of identified (potentially) mutagenic impurities, including CoC compounds
- information on overall control strategy for each MI and appropriate justification & data in line with the ICH M7 guideline

*According to the ICH M7, risk-based approach should be used for deciding the point in the synthesis after which the impurities should be evaluated for their mutagenic potential.

**According to M7 Taskforce member’s experience, detailed safety study information can be presented in Module 1 (Additional data or Literature folder) or Module 3 RP DMF (e.g. 3.2.S.2.6, 3.2.S.2.5).

Regarding control strategies, the following information should be shared:

Option 1 control strategy

The following information is recommended to be provided to HAs to support the control strategy:

- origin of the impurity and its fate in the process
- calculated acceptable concentration limit
- established specification limit in the API
- analytical method description and validation (reference to section 3.2.S.4.2 and 3.2.S.4.3)
- batch data to support established specification limit
- in case of skip testing: batch data to support (6 consecutive pilot-scale or 3 consecutive commercial-scale batches), levels < 30 % of the acceptable limit

Option 2 control strategy

The following information is recommended to be provided to HAs to support the control strategy:

- origin of the impurity and its fate in the process
- calculated acceptable concentration limit
- where it is controlled (raw material, intermediate etc.) and justification
- established specification limit in the raw material/intermediate etc.
- description of analytical method, validation report – reference to RP DMF
- batch data to support established specification limit

Option 3 control strategy

The following information is recommended to be provided to HAs to support the control strategy:

- origin of the impurity and its fate in the process
- information on calculated acceptable concentration limit
- where it is controlled (raw material, intermediate etc.) and justification
- specification acceptance criteria
- description of analytical method, validation report
- describe fate and purge of impurity
- batch data to support established limit (spiking experiments demonstrating levels < 30 % of acceptable limit in the DS)

Option 4 control strategy

The following information is recommended to be provided to support the control strategy:

- origin of the impurity and its fate in the process

- justification that the process is capable to purge the impurity (e.g. purge factor calculation)

Established control strategies for MIs should be reflected throughout the DMF, if applicable (e.g. if Option 1 established for a certain MI, the control should be reflected in section 3.2.S.4.1 Specification, 3.2.S.4.4. Batch data etc.)

4. New submission (DMF/ASMF, CEP) - Sharing M7 information to MAH

Markets: countries that are ICH Members/Observers

Guideline requirements examples (EU, EDQM)

1. EMA Guideline on Active Substance Master File Procedure (CHMP/QWP/227/02 Rev 3/Corr, May 2013)

The guideline provides general recommendations on the use of ASMF procedure in support of MA, including instructions on ASMF procedure and briefly describes the principles of the data sharing to MAH when ASMF procedure is used.

The guideline states that “The main objective of the Active Substance Master File (ASMF) procedure, formerly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the active substance manufacturer (ASM) to be protected, while at the same time allowing the Applicant or Marketing Authorisation (MA) holder (MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance.”

The guideline describes general principles of data sharing with MAH if the ASMF procedure is used for DS. However, it does not give detailed instructions on what data to be shared and leaves room for interpretation, which results in different approaches to data sharing by different DS Manufacturers. At the same time, the guideline states that the ASMF Applicant’s Part (AP) should contain sufficient information to enable the Applicant/MA holder to take full responsibility for an evaluation of the suitability of the specification for the active substance to control the quality of this active substance for use in the manufacture of a specified medicinal product.

2. Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier (CHMP/QWP/297/97 Rev 1/Corr, February 2005)

The guideline states in section 2.2 on ASMF that "The toxicological implications of impurities not included by the monograph should be addressed. That means that the specificity of the method to these additional impurities must always be investigated, but the discussion of the toxicological implications (qualification) is only required if defined thresholds are exceeded, cf. Note for Guidance "Impurities in New Veterinary Drug Substances (CVMP/VICH/837/99), Note for Guidance "Impurities in new Drug Substances (CPMP/ICH/2737/99) or Ph. Eur. General Monographs "Substances for Pharmaceutical use".

3. EDQM "CEP holders responsibilities towards their customers" (PA/PH/CEP(21)57

The EDQM has provided guidance on the CEP Holders responsibilities toward their customers. In addition to information on latest CEP Revision and CEP status the following is stated:

In addition to the CEP itself, CEP holders should provide the MAH with any necessary information that is needed to guarantee the quality, safety and efficacy of the medicines e.g. information on the route of synthesis of the API, details of risk evaluations for impurities that CEP holders have performed (nitrosamines, elemental impurities, etc.).

What data to provide & where to include the data

Considering the existing guidelines requirements and based on practical experience of APIC Members, the following information on MIs Assessment for DS should be shared within the DMF to MAH from Regulatory perspective in cases where ICH M7 assessment is required:

- Risk for presence of (potentially) mutagenic impurities should be addressed in line with the ICH M7 guideline, including Cohort of Concern compounds.

- Section 3.2.S.2.2 AP should include enough process information (e.g. relevant materials used from SM to API, process conditions) to reveal potential risks of MIs formation.

- Mutagenic potential of impurities should be addressed within the AP section 3.2.S.3.2 Impurities of the DMF, shared with MAH.

AP DMF section 3.2.S.2.1 Manufacturers

Section should include the following information (if mutagenic impurities controlled on release specification):

- Contract laboratories that are used for (release) testing of identified mutagenic impurities or for validation of analytical method for release

AP DMF section 3.2.S.3.2 Impurities

Section should include the following information:

- list of actual and potential impurities* (name, structure, origin, limit, classification, summary of control)
- list of identified (potentially) mutagenic impurities, including CoC compounds
- TTC limit, MDD used for acceptable limits calculation
- information on overall control strategy for each MI and appropriate justification & data in line with the ICH M7 guideline

* Impurities that have been concluded to be theoretical during R&D do not need to be listed

Note: Sharing information on impurities originating from regulatory starting material (SM) synthesis with MAH should be based on risk-based approach and the length of the synthesis after introduction of designated regulatory SM (e.g. the risk of carry-over of SM impurities to the DS).

Option 1 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- information on calculated acceptable limit

- DS specification acceptance criteria

- batch data to support established limit

- in case of skip testing: batch data to support (6 consecutive pilot-scale or 3 consecutive commercial-scale batches, levels < 30 % of the acceptable limit)

Option 2 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- information on calculated acceptable limit

- where it is controlled (raw material, intermediate etc.) and justification

- specification acceptance criteria

- optional: batch data to support established limit

Option 3 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- information on calculated acceptable limit

- where it is controlled (raw material, intermediate etc.) and justification

- specification acceptance criteria

- optional: fate and purge of impurity, batch data to support established limit (spiking experiments demonstrating levels < 30 % of acceptable limit in the API)

Option 4 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- justification of control strategy (justification based on physico-chemical properties and/or purge factor calculation*)

*In case of purge factor calculation, the following data might be shared: starting levels, required purge, calculated purge.

Above listed documentation should be shared for MAH to assess DS quality and its impact on DP quality and appropriateness of DS to be incorporated in DP.

For both DMF & CEP submissions, the extent of data shared with MAH should be the same.

Additionally for CEP:

The following information should be additionally shared to MAH:

-The Applicant should include a written assurance that no significant changes in the manufacturing method have taken place following the granting of the certificate or its last revision. This assures that the “Customer Information / Statement” is still valid.

-Along with the CEP, the Applicant should supply results of batch analysis demonstrating compliance with the Ph.Eur. monograph and including any additional tests/limits listed on the CEP (e.g. residual solvents, additional impurity tests).

CHMP/QWP/297/97 Rev 1 corr: Guideline on summary of requirements for active substances in the quality part of the dossier - Section could include the following information:

- a) information as to the length of time that the active substance from the particular named source has been on sale in the European Union and elsewhere, including the types of dosage forms (and the target species) involved;
- b) a statement that, in the above period, there had been no significant change in the method of manufacture leading to a change in the impurity profile of the active substance;

- c) if possible, evidence that samples of the active substance from the named source had been supplied to the Ph.Eur. Commission or a national Pharmacopoeia Commission and have been taken into account in the development of the monograph.

How to submit

A copy of the latest version of the AP ASMF/DMF, together with other documentation (e.g. LoA, QoS,..) should be sent to MAH.

Additionally for CEP:

- if any (potentially) mutagenic impurity is controlled in release specification, the CEP will have necessary analytical methods to control DNA-reactive impurities appended.

- A written assurance for the MAH is not part of the DMF, but can be provided as “Customer Information / Statement” on company letterhead.

Quality aspect

In case of new findings (e.g. adoption of new limits, change in M7 assessment or risk factors), the API Manufacturer might need to share additional data than what is defined within chapter Regulatory aspect to MAH.

5. Post-approval change (DMF/ASMF & CEP) - Sharing M7 information to HA

Markets: countries that are ICH Members/Observers

Focus: changes that impact impurity profile of the DS

Guideline requirements (ICH, EU, EDQM)

1. ICH M7 guideline

Regarding the ICH M7 assessment of post-approval changes, the guideline states the following:

"Assessment as per ICH M7 guideline "applies to post-approval submissions of marketed products, and to new marketing applications for products with a drug substance that is present in a previously approved product, in both cases only where:

- Changes to the drug substance synthesis result in new impurities or increased acceptance criteria for existing impurities;
- Changes in the formulation, composition or manufacturing process result in new degradation products or increased acceptance criteria for existing degradation products;
- Changes in indication or dosing regimen are made which significantly affect the acceptable cancer risk level."

"Post approval submissions involving the drug substance chemistry, manufacturing, and controls should include an evaluation of the potential risk impact associated with mutagenic impurities from changes to the route of synthesis, reagents, solvents, or process conditions after the starting material. Specifically, changes should be evaluated to determine if the changes result in any new mutagenic impurities or higher acceptance criteria for existing mutagenic impurities. Reevaluation of impurities not impacted by changes is not recommended."

2. Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01)

The guideline describes recommendations for classification and submission of post-approval changes for ASMFs.

3. EDQM: Guideline on Requirements for Revision/Renewal of Certificates of Suitability to the European Pharmacopoeia Monographs (PA/PH/CEP (04) 2)

The guideline describes recommendations for classification and submission of post-approval changes for CEPs.

What data to provide

DMF holders and Holders of a CEP must inform the HAS of change(s) to the information provided in the initial application.

Information to be provided to justify the post-approval changes should follow requirements of above listed guidelines.

a) In case the change results in a new impurity:

In case of changes in the DS impurity profile that result in a new impurity being formed, the impurity needs to be assessed in line with ICH M7 guideline.

Existing ICH M7 assessment should be revised to include the new impurity.

The following data for the new impurity should be included in the variation package and revised assessment:

- Origin of the impurity
- Impurity classification (including summary of results of two in-silico tools*)
- In case impurity is identified as (potentially) mutagenic, information on overall control strategy and appropriate justification & data in line with the ICH M7 guideline

b) In case the change impacts levels of existing impurities:

Impact on performed ICH M7 assessment should be evaluated. Depending on the type of change and the impacted impurity, the assessment report might need to be revised (i.e. if change results in higher levels of identified (potentially) mutagenic impurities).

6. Post-approval change (DMF/ASMF, CEP) - Sharing M7 information to MAH

Markets: countries that are ICH Members/Observers

Focus: changes that impact impurity profile of the DS

Guideline requirements

1. ICH M7 guideline

ICH M7 guideline requirements regarding sharing M7 information are described within the chapter *ICH M7 Guideline requirements regarding Information sharing* of this document.

The requirements apply to post-approval changes with impact on the DS impurity profile and the risk of (potentially) mutagenic impurities (and new submissions of new and existing active substances).

2. EMA Guideline on Active Substance Master File Procedure (CHMP/QWP/227/02 Rev 3/Corr, May 2013)

“As for medicinal products, ASMF holders should keep the content of their ASMFs updated with respect to the actual synthesis/manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements. ASMF holders shall not modify the contents of their ASMF (e.g. manufacturing process or specifications) without informing each Applicant/MA holder and each National Competent Authority/EMA. This obligation remains valid until the Letter of Access has been withdrawn by the ASMF holder, see Annex 4. ASMF holders should provide the updated ASMF to all interested parties with reference to the revised version number.

Any change to the ASMF should be reported by every MA holder to the relevant National Competent Authority/EMA by means of an appropriate variation procedure. A Submission Letter should be provided (Annex 3)”

3. CEP holders responsibilities towards their customers (PA/PH/CEP (21) 57)

Variations / CEP revisions

“To allow the MAH to evaluate the impact of any change introduced by the API manufacturer/CEP holder, regardless of whether it leads to a revision of the CEP and to update the marketing authorisation information, it is of utmost importance that the CEP holder provides the necessary information to their customers. Depending on the criticality of the change, the quality agreements in place should specify whether the implementation needs pre-approval by the MAH.”

What data to provide & where to include the data

DMF: DMF holder/ CEP holder is required to inform MAH of change(s) to the information provided in the initial application that has been/will be reported to HAs:

- Changes to the Applicant's part should be described and justified.

- Restricted part changes should be briefly summarized.

- Any change that impacts actual / potential impurities in the DS should be reported to MAH.

a) In case the change results in a new impurity:

In case of changes in the DS impurity profile that result in a new impurity being formed, the impurity needs to be assessed in line with ICH M7 guideline. Assessment data should be provided within the variation package:

- Origin of the impurity
- Impurity classification
- In case impurity is identified as (potentially) mutagenic, information on overall control strategy and appropriate justification & data in line with the ICH M7 guideline

For details on the data to be provided, please refer to chapter *3. New submission (DMF/ASMF & CEP) - Sharing M7 information to HA* within this document.

b) In case the change impacts levels of existing impurities:

In case the change impacts levels of existing impurities in the DS, impact on performed ICH M7 assessment should be evaluated and the assessment revised if needed (i.e. if change results in higher levels of identified (potentially) mutagenic impurities).

7. Data sharing for Fermentation Products – to HA & MAH

Guideline requirements

1. ICH M7 guideline

Regarding the fermentation products, the guideline states:

"Assessment of the mutagenic potential of impurities as described in this guideline **is not intended** for the following types of drug substances and drug products: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, **fermentation products**, herbal products, and crude products of animal or plant origin."

The guideline states that the ICH M7 assessment is not intended for fermentation products. However, the guideline also states that structural classes of mutagens that can display extremely

high carcinogenic potency (Cohort of Concern - Coc), i.e., aflatoxin-like-, N-nitroso-, and alkyl-azoxy structures should be evaluated.

Since it is known that fermentation products can be a source of aflatoxin contamination**,** and based on practical experience of the APIC members, **the fermentation products should be evaluated for the risk of presence of Cohort of Concern compounds.**

What data to provide & where to include the data

Based on the above and practical experience of APIC Members, for fermentation products, assessment of the Cohort of Concern (Coc) type impurities should be performed.

Submissions to HA should include information on the CoC assessment:

-evaluate the risk of aflatoxin presence (origin, literature/batch data to justify absence/ established control strategy and justification).

- evaluate the risk of alkyl azoxy presence

- evaluate the risk of Nitrosamines* as per the relevant guidelines

Performed CoC assessment should be summarized in a report, which is recommended to be included in the DMF (section 3.2.S.3.2 Impurities or other)

* Nitrosamines are part of the Cohort of Concern compounds defined by the ICH M7 guideline. Regarding data sharing on the risk of Nitrosamines in API with MAH, the APIC template is recommended to be used. Data sharing regarding Nitrosamines is not in scope of this document.

8. Data sharing for Semi-synthetic products

Guideline requirements

Semi-synthetic drug substance is substance derived from natural product (e.g. fermentation), which is further modified by chemical synthesis.

1. ICH M7 Q&A guideline (EMA/CHMP/ICH/321999/2020)

Are semi-synthetic drug substances and drug products included in the scope of ICH M7?

Yes, for certain cases. **If a semi-synthetic drug substance is manufactured using steps that could introduce mutagenic impurities or degradants** (e.g., post-modification of a fermentation product or late-stage introduction of a linker) **a risk assessment is warranted.** The following compounds used in the manufacturing process of semi-synthetic drug substances and drug products should be considered within the scope of the application of ICH M7:

- chemically-synthesized intermediates and actual impurities therein
- reagents

What data to provide & where to include the data

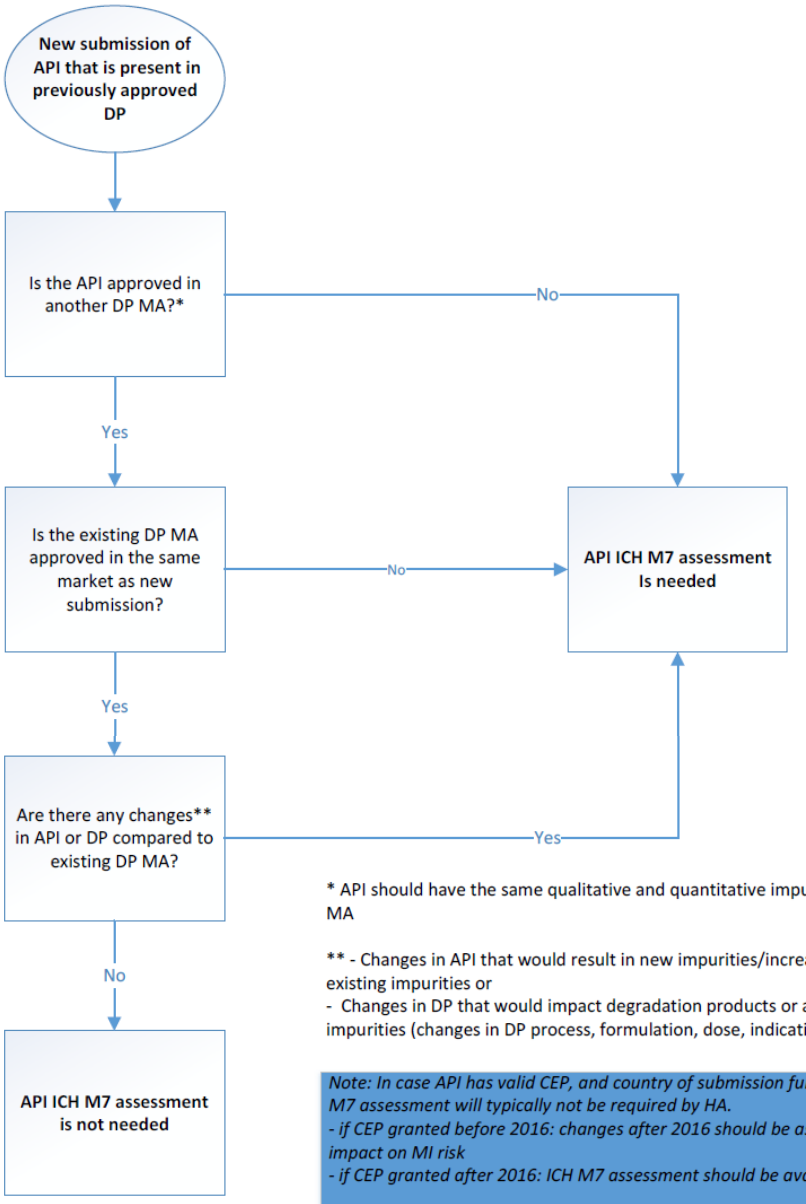
1. Assessment of synthetic steps

Compounds originating from the synthetic steps should be evaluated in line with ICH M7 guideline. For information on the data to be shared please refer to chapters *3. New submission (DMF/ASMF, CEP) - Sharing M7 information to MAH* and 4. *New submission (DMF/ASMF, CEP) - Sharing M7 information to HA.*

Appendix – Decision tree on Retrospective M7 Assessment (prepared in Step 1 of APIC M7 TF)

Decision trees regarding submissions where Retrospective ICH M7 assessment is required are provided on the following pages.

1. New marketing application for products with a drug substance that is present in a previously approved product



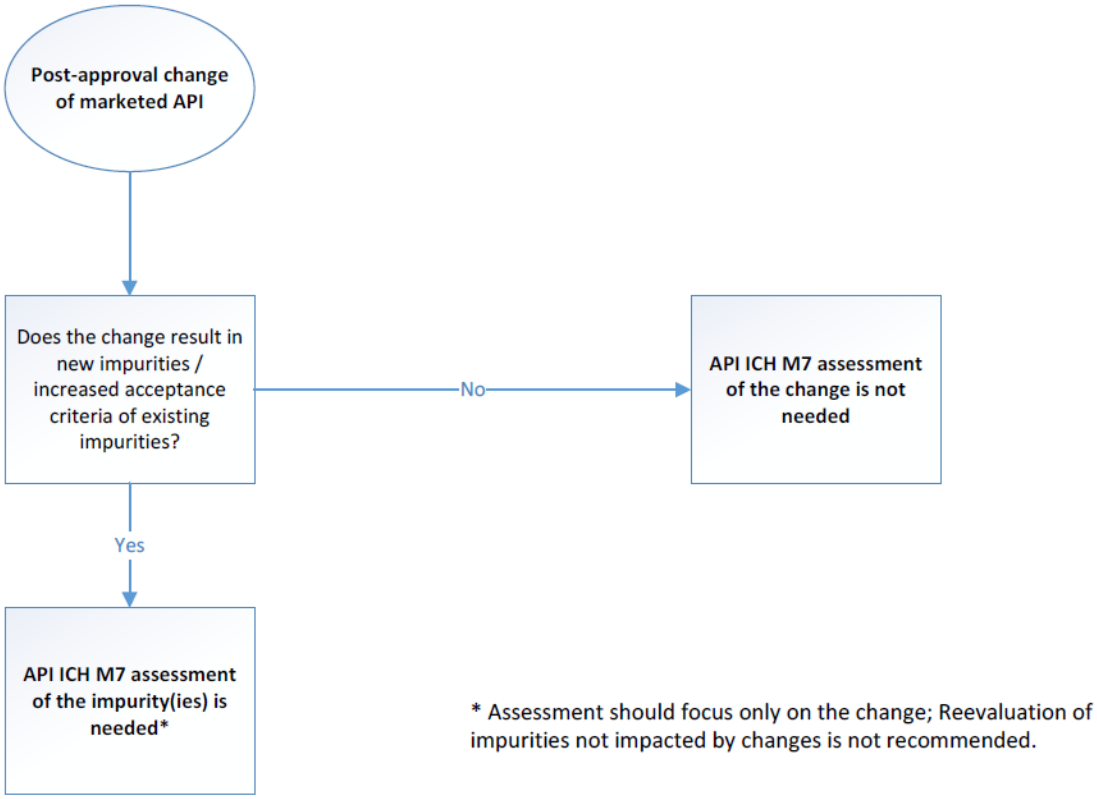
* API should have the same qualitative and quantitative impurity profile as in approved MA

** - Changes in API that would result in new impurities/increased acceptance limits for existing impurities or
- Changes in DP that would impact degradation products or acceptance criteria for impurities (changes in DP process, formulation, dose, indication, treatment duration,..)

Note: In case API has valid CEP, and country of submission fully recognizes CEP, ICH M7 assessment will typically not be required by HA.
- if CEP granted before 2016: changes after 2016 should be assessed as per ICH M7 if impact on MI risk
- if CEP granted after 2016: ICH M7 assessment should be available

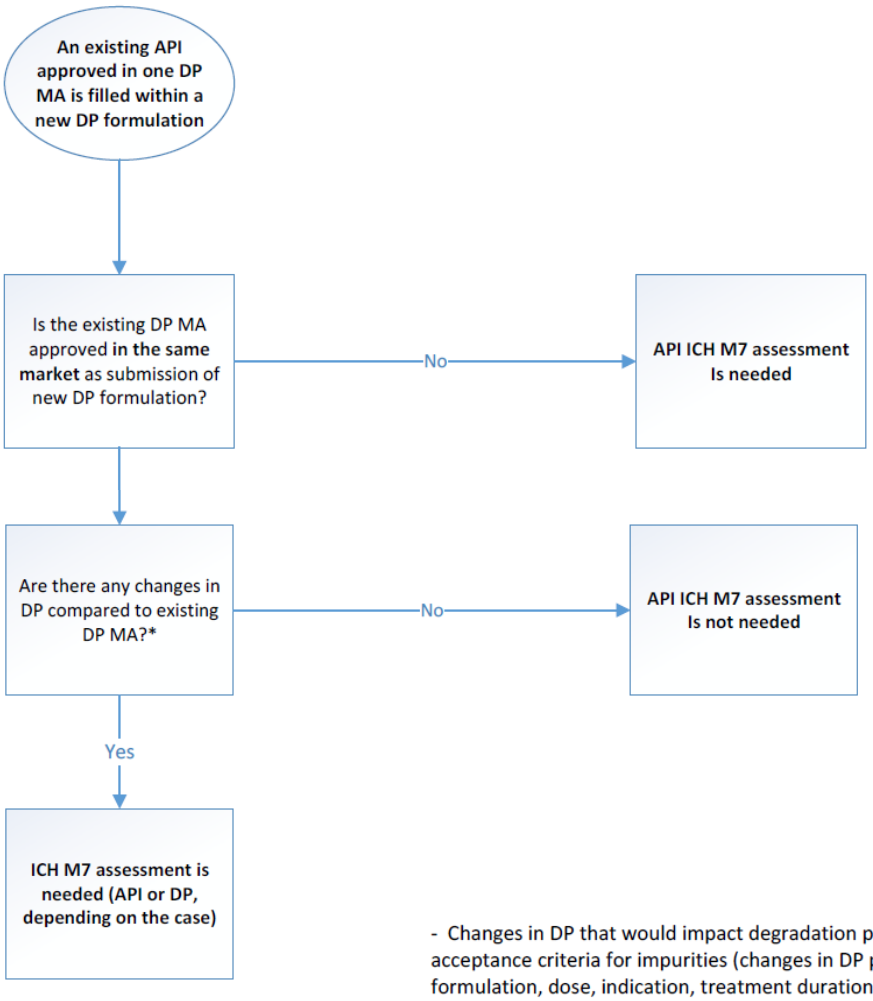
However, it is important to consider changes in DP with regard to MI risk coming from API. Even in case of CEP, MAH might request outcome of the ICH M7 assessment to be shared to consider impact of DP formulation on the MI risk, and to take responsibility for the quality of the API.

2. Post-approval change of marketed API



* Assessment should focus only on the change; Reevaluation of impurities not impacted by changes is not recommended.

3. A new formulation of an approved API is filed (the same MAH)

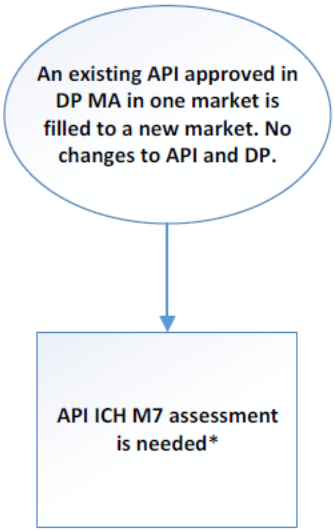


- Changes in DP that would impact degradation products or acceptance criteria for impurities (changes in DP process, formulation, dose, indication, treatment duration,..)

Note: In case API has valid CEP, and country of submission fully recognizes CEP, ICH M7 assessment will not be required by HA.
- if CEP granted before 2016: changes after 2016 should be assessed as per ICH M7 if impact on MI risk
- if CEP granted after 2016: ICH M7 assessment should be available

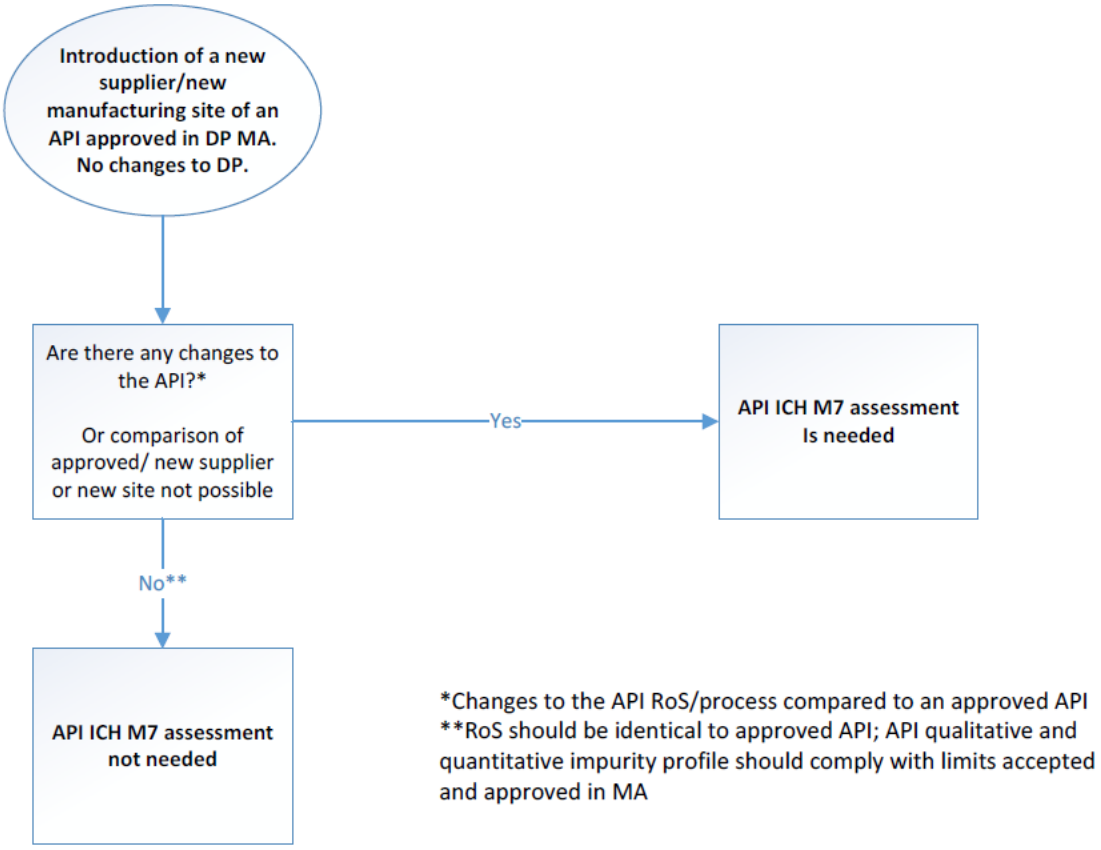
However, it is important to consider changes in DP with regard to MI risk coming from API. MAH might still request outcome of the ICH M7 assessment to be shared to consider impact of DP formulation on the MI risk, and to take responsibility for the quality of the API.

4. A product that is previously approved in a market is filled for the first time in a different market. The product is unchanged.



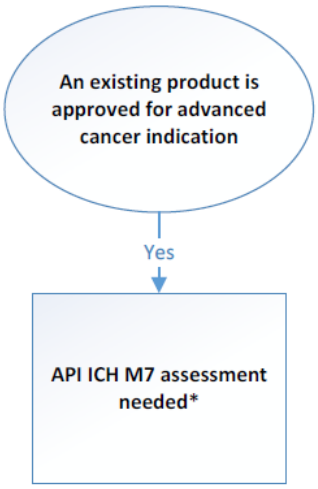
Note: In case API has valid CEP, and country of submission fully recognizes CEP, ICH M7 assessment will not be required by HA.

5. A new supplier or new site of the API is registered



*Changes to the API RoS/process compared to an approved API
**RoS should be identical to approved API; API qualitative and quantitative impurity profile should comply with limits accepted and approved in MA

6. An existing product associated with an advanced cancer indication is now registered for use in non-life threathening indication



*Since the patient population and acceptable cancer risk have changed, the previously approved impurity control strategy and limits will require reevaluation.

7. New combination product is filed that contains one new drug substance and an existing drug substance