EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the guideline on the chemistry of active substances

Agreed by Quality Working Party (QWP)	June 2022
Adopted by CHMP for release for consultation	11 July 2022
Start of public consultation	26 July 2022
End of consultation (deadline for comments)	31 October 2022

The proposed guideline will replace the current version of 'Guideline on the chemistry of active substances' (EMA/454576/2016).[1]

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	Active substance, drug substance, API, impurities, nitrosamines, chemistry, control, 'cohort of concern'[3]

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1. Introduction

This concept paper addresses the need to review and update the guideline on the chemistry of active substances[1]. This need was recognised in the report on "Lessons learnt from presence of N-nitrosamine impurities in sartan medicines"[2] (LLE), which made recommendations to reduce the risk of N-nitrosamines being present in human medicines and to help the European medicines regulatory network be better prepared to manage future cases of unexpected impurities. While in the last few years, experience has predominantly been gained in the management and risk mitigation of N-nitrosamines, it is foreseen that (some of) the principles covered in revised guideline will apply to other 'cohort of concern' (CoC) impurities[3] and also other potent toxins.

2. Problem statement

In 2018, the EU medicines regulatory network became aware of the presence of N-nitrosamine impurities in sartan active substances (APIs). Subsequently, N-nitrosamines have been detected in a significant number of other active substances. It appears that despite available guidance on how to assess and control mutagenic and potentially mutagenic impurities, the risk of formation of N-nitrosamine impurities was not adequately considered during development, manufacture and evaluation of active substances. The guideline 'Chemistry of active substances' has been identified in the LLE report as one of the most important guidelines to be revised to include further recommendations on prevention, risk mitigation and control of N-nitrosamines, other CoC impurities and also other potent toxins.

3. Discussion (on the problem statement)

The following aspects will be taken into account for the revision of the guideline on the chemistry of active substances to further define the requirements in regulatory submissions, with reference to the EMA/CMDh questions-and-answers document on N-nitrosamines[4] and the LLE report[2]:

- Guidance on appropriate process development in order to mitigate as much as possible the potential presence of N-nitrosamines or other CoC compounds as well as of other potent toxins (if applicable). The selected manufacturing process should be justified accordingly.
- Guidance on the need to provide clear information on all the materials used in the process (including raw materials, starting materials and intermediates) in relation to their function in the corresponding manufacturing step, their applied quantities, their potential contaminants and their overall quality.
- Guidance on the required discussion regarding presence or formation of N-nitrosamines or other CoC compounds as well as of other potent toxins. Clarify the new systematic approach suggested by ICH M7 on mutagenic impurities.[3]
- Guidance on the use of recycled materials.
- Guidance on specific control options for N-nitrosamines or other CoC compounds as well as for other potent toxins, including possible control points and acceptance criteria.
- Guidance on the need to consider formation of N-nitrosamines or other CoC compounds as well as of other potent toxins during storage.

4. Recommendation

The Quality Working Party (QWP) recommends revising the guideline on the chemistry of active substances taking into account the issues identified in the sartans LLE report[2] as well as learnings from the ongoing 'call for review'[5]. The revision will clarify the requirements for all applications regarding

active substances and will bring the guidance up to date with recent developments and knowledge gained on formation of N-nitrosamines and implementation of adequate risk mitigation measures. In addition to N-nitrosamines specifically, the updated guidance will be relevant also for other compounds belonging to the cohort of concern as well as other potent toxins more generally.

5. Proposed timetable

The concept paper will be released for 3 months of public consultation.

Following receipt of the comments on the concept paper, the draft for the revised guideline will be prepared and released for 6 months public consultation.

The draft guideline will be revised in light of comments received, finalised and published.

6. Resource requirements for preparation

The QWP has appointed two joint rapporteurs from members of QWP as well as a drafting group composed of QWP members and experts from different member states with expertise in the field. The drafting group will be supported by an observer from EDQM. The group will work closely with the QWP expert group on nitrosamines.

The revision will involve the EMA-QWP Secretariat, the Joint CHMP/CVMP Quality Working Party and the CHMP. Other Working Groups or Working Parties could be consulted, as necessary.

7. Impact assessment (anticipated)

The revised guideline is expected to provide additional and more comprehensive guidance related to the following aspects:

- Identified risk factors for formation of N-nitrosamines[4] and also other CoC compounds, if applicable.
- Strategies for avoiding or preventing as much as possible the formation and presence of N-nitrosamines specifically. Some of these strategies will also be relevant for other impurities such as the 'cohort of concern' compounds or other potent toxins more generally.
- Clarification on how the applicant should document and discuss the potential presence of these impurities in active substances in regulatory submissions.

8. Interested parties

Pharmaceutical Industry, EU Competent Authorities, GMP/GDP Inspectors Working Group, Non-Clinical Working Party

9. References to literature, guidelines, etc.

1. Chemistry of active substances (chemistry of new active substances) | European Medicines Agency (europa.eu)
2. Sartans Lessons Learnt Exercise Report (europa.eu)
3. M7_R1_Guideline.pdf (ich.org)
4. Nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders

5. Nitrosamine impurities | European Medicines Agency (europa.eu)