EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human use (CHMP)
Committee for Medicinal Products for Veterinary use (CVMP)

Quality Working Party questions and answers on API mix

Introductory note

These Q&A have been developed to provide information on how to deal with mixtures of API and excipients (called API mix), and to identify situations where it will be acceptable to use the ASMF/CEP procedure and perform manufacture under EU GMP Part II for the API mix.

1. What is the definition of an API mix?

An `API mix' is defined as a mixture of an API (active pharmaceutical ingredient) with one or more excipients. Typical examples are the addition of an antioxidant to an API, or the introduction of an API into a matrix.

The manufacture of an API mix is considered to be the first step of the manufacture of a finished product.

a) Under which circumstances can an API Mix be submitted as part of 3.2.S (or 2.C.1) or via an ASMF resp. a CEP?

In certain circumstances, i.e. stability or safety reasons, the applicant can submit data on such a mixture under part 3.2.S (or part 2.C.1 for products for veterinary use) or in the form of an ASMF or via a CEP. The API mix should comply with the same requirements as for an API with regard to GMP Part II, unless the mixture is sterile (in which case GMP Part I is mandatory for the sterilisation activities and steps after sterilisation). A re-test period for the API mix can in such cases be accepted, if justified.

In case of an API mix prepared due to workability purposes or reasons other than safety and stability, the manufacturing steps from the addition of the excipient to the API should be described in (the appropriate part of CTD 3.2P....). In addition the steps following addition of the excipient must be conducted in accordance with GMP Part I and an appropriate manufacturing authorisation.

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b) Is an API mix acceptable when it is stated in a pharmacopoeial monograph "A suitable antioxidant may be added" (under 'Definition')?

A statement in a pharmacopoeial monograph, such as "A suitable antioxidant may be added" is considered sufficient and acceptable per se as a justification for the use of an API mix.

However, additional justification on the choice and level of antioxidant needs to be provided, and a control test is required for the antioxidant in the API mix.

Particular care should be given regarding API mix acceptability in cases where different sources of API are used in the same medicinal product to avoid a medicinal product with alternative compositions

c) Are APIs in solutions (e.g. Benzalkonium chloride solution) considered as an API mix, and are ASMFs or CEP applications for solutions of APIs acceptable?

APIs in solutions are considered as API mixes. ASMFs for solutions are acceptable in certain circumstances as explained under question 1.b.

d) Is there a difference if there is a Ph. Eur. monograph that permits an API mix or not?

For an existing Ph. Eur. monograph for an API mix, an ASMF can be accepted or CEP can be granted, with the assumption that new monographs for mixtures would normally not be introduced into the Ph. Eur. if not justified by the safety or stability of the API.

If there is no Ph. Eur. monograph for an API mix then an ASMF can be accepted only for safety or stability reasons on a case by case basis.

2. An API mix is acceptable when there are safety or stability issues: What data should be submitted to justify the acceptability of an API mix for which there is no Ph. Eur. monograph?

In all cases the choice and level of excipient should be justified.

In case the originator uses no stabiliser, it is expected that the same approach as the originator is taken by any subsequent new product.

Acceptable stability reasons include both chemical and physical stability.

Documentation to be provided: A comparison of the stability data of both the stabilised and non-stabilised API under (V)ICH long term conditions for up to 6 months (in a refrigerator/freezer/inert atmosphere where relevant). Results with a stabiliser should demonstrate a relevant stability improvement.

For APIs of an explosive nature the use of an API mix may be justified, and an appropriate explanation is considered sufficient.

A justification based only on workability reasons, e.g. to ease handling when processed into final dosage form, is not acceptable.

Toxicological considerations (e.g. very potent drugs) fall under workability reasons and are not accepted as justifications.

3. If an ASMF/CEP for an API mix is accepted:

a) What data are required and how should the data be organised in the dossier/ASMF?

If an ASMF for an API mix is accepted, the open part of the ASMF/dossier should contain all relevant information on the mixing process, qualitative and quantitative composition of the mixture and control strategy. Data supporting the choice and the amount of the excipient should also be provided.

Information requested for the excipient(s) – Ref. Annex I (section 3.2.2.4) of Directive 2001/83/EC for products for human use and Annex I (section 2.C.1.2) of Directive 2001/82/EC for products for veterinary use.

b) Where should the excipient be stated?

Excipients should be stated in the composition of the drug product (Module 3.2.P.1 for products for human use or Part 2.A for products for veterinary use); in the SmPC – 6.1, 2 (in the case of antioxidants and/or preservatives or if required according to the CxMP excipients guidelines); in the PL – 6 and in the labelling (if required according to the CxMP excipients guidelines). For the PL for products for veterinary use: section 3 (i.e. composition, only antioxidants and/or preservatives). See also QRD templates.

c) What should be required as additional information in the case of a CEP?

The same principles apply as for ASMFs. The following information should be required as additional information in the case of a CEP:

- The description of the manufacturing process for preparation of the mixture should be provided by the API manufacturer to the applicant - in addition to the CEP. This information should be part of section 3.2.S.2.2 in the MA application dossier for human products or section 2.C.1.1 for veterinary products;
- Stability data of the mixture if not mentioned on the CEP;
- Information on the packaging material if not mentioned on the CEP.

If a new CEP is presented as a variation then these above mentioned elements should also be included as part of that submission.

In addition, as far as the variation submission category is concerned and whether or not a Type IA or even a variation will be possible at all, particular consideration should be given to the potential impact of the change on the currently registered specifications of both the API and the finished product (conditions 1 and 2 under variation change code B.III.1). In this instance, as far as condition 2 is concerned, it is important to note that product specific requirements also include the qualitative, and where relevant, quantitative composition of the API mix, as indicated in the CEP, which may impact the currently registered composition of the finished product (see question 1b).