



DEFINITION OF ACTIVE PHARMACEUTICAL INGREDIENT

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached revision, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mails: kopps@who.int with a copy to Ms Marie Gaspard (gaspardm@who.int) by 10 September 2011.

We will now send out our working documents electronically and they will also be placed on the Medicines web site for comment. If you do not already receive our draft specifications please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/11.426

Definition of active pharmaceutical ingredient

	Date
First draft prepared by Professor T.G. Dekker for the Prequalification Programme	June 2011
Discussion held during the Informal WHO Consultation on Specifications for The International Pharmacopoeia and quality control laboratory issues	12-14 July 2011
Revised draft circulated for comments to the WHO Expert Advisory Panel on the International Pharmacopoeia	August 2011
Consolidation of comments	September 2011
Discussion at forty-sixth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	10-14 October 2011
Further follow-up action as required	

DEFINITION OF ACTIVE PHARMACEUTICAL INGREDIENT

Background

In many WHO guidelines the following definition for an active pharmaceutical ingredient (API) (in the singular) is found under the Glossary (for instance it appears three times in the recently published WHO Technical Report Series, No. 961):

"active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings."

This definition implies, for example, that commercially available premixes of APIs (such as the popular amoxicillin + clavulanic acid premix) can be regarded as an API, which is not correct. This definition thus may lead to misinterpretation.

Proposal

It is proposed that the above definition be changed **by deleting "or mixture of substances"**, in accordance with the definition already appearing in WHO Technical Report Series, No. 961, Annex 10 (*Procedure for prequalification of pharmaceutical products*):

"active pharmaceutical ingredient (API)

A substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings."

If this is agreed to, it should be applicable to future WHO documentation or any current documentation whenever revised.

Motivation

The moment an API is mixed with another API, or with an excipient, it is no more considered an API. This is best illustrated by the guidelines mentioned below.

The current draft *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* (QAS/10.373/Rev.1), line 1944, reads:

"For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the first step in the manufacture of the final product and, **therefore, the mixture does not fall under the definition of an API.** The

only exceptions are in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section."

Exceptions referred to in the above paragraph are rare and only a few are found in the PhEur, for instance Moxidectin and Streptomycin Sulphate ("stabilizers may be added").

EMA's *Note for guidance on start of shelf-life of the finished dosage form* (CPMP/QWP/072/96) states (biologicals excluded):

"The date of production of a batch is defined as the date that the first step is performed involving combination of the active ingredient with other ingredients. For medicinal products consisting of a single active ingredient filled into a container, the initial date of the filling operation is taken as the date of production."

It is clear from the above that the definition of the API should only be with respect to a single substance and should exclude "combination of substances".

[Note from the secretariat: The proposed change was supported during the informal consultation on specifications for medicines and quality control laboratory issues held on 12-13 July 2011.]
