General principles for Monographs on Finished Products (FPs) containing chemically defined active substances

This document is intended to provide additional information to users on how to read and apply future individual FP monographs. It shall be read in conjunction with the Ph. Eur. General Notices, the relevant dosage form monograph and the general monograph on *Pharmaceutical Preparations* (2619).

The monograph specifications are based on currently approved medicinal products in Member States. Nevertheless, the suitability of the FP monograph specifications to adequately control the quality of the finished product needs to be demonstrated in the marketing authorisation application (MAA). Unless otherwise indicated, FP monographs cover different formulations and strengths (where possible) of the same dosage form, containing the same active substance (active pharmaceutical ingredient).

The Ph. Eur. Commission only elaborates monographs on products that have been authorised in at least one of the member states of the Ph. Eur. Convention and that contain an active substance for which a monograph has already been published in the Ph. Eur. or is on the work programme of the Ph. Eur. As with other Ph. Eur. monographs, the elaboration and revision of finished product monographs will be subject to public consultation and take into account current scientific knowledge and relevant medicinal products authorised at the time. The quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system. The quality system must assure that the articles consistently meet the requirements of the Pharmacopoeia.

The Ph. Eur. Commission has decided to start with the elaboration of monographs on products which are currently still under patent but which have a high public health interest. However, the Ph. Eur. Commission could also consider elaborating monographs on multi-source products. This would require critical assessment before adding such monographs to the Ph. Eur. work programme, paying particular attention to the following:

- the usefulness of having a Ph. Eur. monograph, for example, in the case of an interest in international harmonisation or public health related issues, and
- the impact on already registered products.

Testing procedures: Since the choice of analytical procedures may be affected by the formulation and/or the manufacturing process, it must be demonstrated that the testing procedures described in an FP monograph are suitable for the specific FP. This demonstration has to be documented in the marketing authorisation application. The assessment of these data shall be part of the marketing authorisation procedure.

Release vs. Shelf-life specifications: FP monographs provide shelf-life specifications. In addition, applicants in Europe will have to propose release specifications in the MAA in line with national or regional legislation.

Additional information on sections of FP monographs:

Title:

The title is made up of the active substance and the dosage form. Where available, a recommended INN (or an INNM derived from it) is usually used to describe the substance; if no INN or INNM exists, then a national non-proprietary name (e.g. a BAN) or another appropriate, established name may be used. The dosage form is derived from the appropriate dosage form general monograph and Standard Terms.

Related substances test:

In compliance with the ICH guidelines "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (ICH Q6A) and "Impurities in new drug products" (ICH Q3B R2), FP monographs limit degradation products arising during manufacture and shelf-life of the finished product, including those impurities of synthesis that are also degradation products. In certain circumstances, it is necessary to identify other impurities of synthesis in the finished product, e.g. when they are detected in the test for related substances at a level greater than the reporting threshold in the finished product. To this end, the FP monograph describes how to identify any such known impurities of synthesis, so that they are not reported and can be excluded from the total of impurities.

FP monographs are not designed to control impurities of synthesis that are not degradation products. However, methods provided in the FP monograph could be used to control impurities of synthesis known to be detected by the FP monograph, if validated for that purpose.

As with active substance monographs, the Ph. Eur. requirements for FPs are not framed to take account of all possible impurities. It is not to be presumed, for example, that an impurity that is not detectable by means of the prescribed tests is tolerated if common sense and good pharmaceutical practice require that it be absent. It is therefore acknowledged that additional controls may be required to monitor degradation products other than those controlled by the Ph. Eur. FP monograph (e.g. degradation products related to different excipients or containers used, or from a different manufacturing process). It is the responsibility of the marketing authorisation applicant to assess which such impurities shall be monitored. This evaluation shall be part of the MAA that will be assessed by the competent authorities.

Dissolution test:

The testing procedure (test conditions, limits and acceptance criteria), if specified in the monograph, shall be mandatory unless otherwise stated in the monograph ("unless otherwise justified and authorised"). The dissolution test and limits should be sufficiently discriminatory to assure batch-to-batch consistency and where appropriate, consistency with those batches for which satisfactory evidence of efficacy has been demonstrated.

The dissolution test as described in FP monographs is not intended to demonstrate bioequivalence or to compare dissolution profiles in the case of a biowaiver and does not replace such a demonstration or comparison versus the reference product in the MAA. The dissolution test as described in FP monographs is provided for quality control only (batch-to-batch consistency).

As outlined in the ICH Guideline Q6A, for rapidly dissolving products containing active pharmaceutical ingredients which are highly soluble throughout the physiological range, disintegration may be substituted for dissolution testing. When a disintegration test is described instead of a dissolution test in a monograph, licensing authorities may require applicants to demonstrate that the relationship between disintegration and dissolution has been established over shelf-life or that disintegration is more discriminating than dissolution testing. It is expected that development information will be provided in the MAA to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing (ref. ICH Q6A).

Impurities:

This section lists all impurities, independent of their origin, that are known to be detected by one or other of the tests in the monograph.

Impurities already listed in the monograph on the active pharmaceutical ingredient keep their name.

Impurities specific to the finished product are designated by “FP-” followed by a letter of the alphabet; this is to avoid confusion with impurities in the active substance monograph.