

Additional Information on *The International Pharmacopoeia*

The history of *The International Pharmacopoeia* dates back to 1874 when the need to standardize terminology and to specify dosages and composition of drugs led to attempts to produce an international pharmacopoeial compendium. The establishment of the Expert Committee responsible for the International Pharmacopoeia was approved in 1948 by the First World Health Assembly .

Whenever possible, classical procedures are used in the analytical methods so that the use of expensive equipment is minimized in the application of *The International Pharmacopoeia*. In addition, in cases where more complex methods are specified, alternative methods are also described, where possible. Information on revised concepts and perspectives was published in WHO Technical Report Series, No. 908, 2003, Annex 2 [\[please see link on the main page\]](#).

Scope and function of *The International Pharmacopoeia*

It is emphasized that pharmacopoeial specifications represent only one element of the quality assurance of medicines. Pharmaceutical substances and dosage forms for human use, as described in a monograph of *The International Pharmacopoeia*, should be manufactured according to the current requirements of Good Manufacturing Practices (GMP) [please see related web link](#). The processes, premises, equipment, and installations should also comply with the provisions of the product license or marketing authorization, relevant regulations and, in the case of products destined for export, with any binding international norms that would affect their entry onto the market. In many cases this compliance cannot be verified by analyzing a sample of the final product against a pharmacopoeial monograph. The national, regional or other competent authority will need to ensure that all relevant provisions have been met by any means at its disposal, including use of appropriate certificates, inspection of the manufacturing sites or testing of samples beyond specifications.

It should be understood that a distinction exists between pharmacopoeial standards and manufacturers' release specifications. Pharmacopoeial standards are publicly-available compliance specifications and provide the means for an independent check of the quality of a product at any time during its shelf-life. Although release specifications must be compatible with pharmacopoeial specifications, they may differ in several respects. In order to ensure compliance with the pharmacopoeia, the manufacturers' specifications may need to be more exacting than corresponding pharmacopoeial requirements. The manufacturer is entitled to use other analytical methods for routine testing and, moreover, he may assure himself that the requirements of the pharmacopoeia will be met by means other than routinely performing all of the tests in the monograph. For example, on occasions, in-process controls and manufacturing process validation studies may have already provided the necessary assurances with respect to certain aspects of the monograph.

The requirements of the monographs are not framed to detect all possible impurities. The present tests are designed to determine impurities on which attention should be focused, to fix the limits of those that are tolerable to a certain extent, and to indicate methods for ensuring the absence of those that are undesirable. It is, therefore, not to be presumed that an impurity can be tolerated because it has not been precluded by the prescribed tests. In some purity tests, limits are indicated additionally in brackets in percentage terms: as stated in the General Notices, such limits are given for information only (see under Related substances below).

The degree of protection provided by pharmacopoeial standards will depend not only on their technical content but also to a great extent on how they are used. The specified tolerances and limits allow for the inherent variations that occur during production and packaging, as well as for subsequent degradation within normal handling and storage conditions and for any acceptable variance of analytical results.

When pharmacopoeial standards are used to establish the compliance of products with regulatory requirements, the following principles apply:

- The interpretation of a monograph must be in accordance with all general requirements and testing methods, texts, or notices pertaining to it as found in the current edition of the pharmacopoeia.
- No further tolerances are to be applied to the limits prescribed.
- A product is not of pharmacopoeial quality unless it complies with all the requirements stated.

Related substances tests in *The International Pharmacopoeia*

The following explanatory notes provide guidance as to the current approach to the control of impurities in dosage form monographs in development for inclusion in the International Pharmacopoeia. [WHO Technical Report Series, No..., 2007 ([in press](#))]

Objective

For dosage form monographs the main purpose of a test for Related substances is to control degradation impurities. Wherever possible, however, the objective is also to limit impurities arising during synthesis of the API. This approach provides the means for an independent control laboratory (e.g. a small regulatory laboratory) without access to manufacturer's data to establish whether or not an API of pharmacopoeial quality has been used to manufacture the dosage form under examination. Such an approach is consistent with the aims and purpose of The International Pharmacopoeia.

General considerations

It is recognized that the limits for degradation impurities in dosage form monographs may sometimes need to be higher than the limits for the same impurities in the monograph for the corresponding API.

The limits set for degradation impurities may need to be different for different types of dosage form. For example, higher limits may need to be set for an oral solution than for tablets.

Total limits need to be interpreted with caution since the numerical limits given in parentheses for individual impurities are only approximate values given for information. In addition, the limits in any one monograph may be a mixture of "real" limits (where a solution of the impurity – either as an RS or a reagent – is used to set the limit) and nominal limits (where a dilution of the test solution is used).

In the absence of evidence that the limit for any particular impurity needs to be set on the basis of its toxicity, limits will normally be chosen based on batch data for products manufactured in accordance with GMP and will take account of factors such as the number of impurities normally present, the type of dosage form, route of administration and dose regimen. Limits in monographs for formulated preparations will also take account of the limits set in the monograph for the API.

Application

The extent to which the above objective can be met will depend on a variety of factors including the nature and availability of impurities (as RS, reagents, made in situ), the number of active ingredients and the complexity of the formulation. In applying this overall approach to individual dosage form monographs, the following cascade (decision tree) will, therefore, be followed to adapt the test to the particular circumstances:

- If a test mix RS can be established for use in the monograph for the API, the same approach as for the substance monograph will be adopted. Limits may need to be different.
- If a test mix RS cannot be obtained, the responsible laboratory will examine whether the monograph could include instructions to generate certain impurities by *in situ* degradation.
- In cases where *in situ* degradation alone or together with the use of reagents permits satisfactory peak identification, specific limits for certain impurities will be included.
- In cases where none of the above means is available to identify specific impurity peaks unequivocally, a general test with an "open" design will be used (that is, nominal limits for any secondary peaks will be set using a dilution of the test solution). Where it is known that several impurities are likely to be present at significant concentrations, a two- or three-level test allowing the area of not more than a certain number of peaks to exceed a particular level will be used and a total limit and a disregard limit will be set.
- In cases where the main degradation impurity(ies) can be identified but where the chromatogram is complicated due to the presence of excipient peaks that cannot be identified and excluded, a limit will be specified for the main degradation impurity(ies) only. This may be the case for some oral liquids. Similar considerations may apply for dosage forms containing two or more API.
- **Note** In some cases where difficulties are encountered, it may be worthwhile considering the use of thin layer chromatography (TLC) for Related substances (using, e.g. the method already specified in the monograph for identification). The use of TLC may facilitate differentiation of API(s) and impurities (spots of different colours) and certain excipients may more easily be excluded (e.g. left on line of application).