Annex 1

The International Pharmacopoeia – related substances tests: dosage form monographs guidance notes

Objective

For dosage form monographs, the main purpose of a test for related substances is to control degradation impurities. Wherever possible, however, a further objective is to limit impurities arising during synthesis of the active pharmaceutical ingredient (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 given in dosage form monographs may sometimes need to be higher than the limits for the same impurities that appear in the monograph for the corresponding API.

The limits set for degradation impurities may also 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 only. In addition, the limits given in any one monograph may be a mixture of "real" limits (where a solution of the impurity – either as a reference substance (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 on the basis of batch data for products manufactured in accordance with good manufacturing practices (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 given 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 or 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 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 on generating certain impurities by in situ degradation.

• In cases where in situ degradation alone or together with the use of reagents permits satisfactory identification of peaks, 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 no 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 in which the main degradation impurity/impurities can be identified, but the chromatogram is complicated by the presence of excipient peaks that cannot be identified and excluded, a limit will be specified for the main degradation impurity/impurities only. This may be the case for some oral liquids. Similar considerations may apply for dosage forms containing two or more APIs.

• *Note*: In some cases when 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 Rf. value colours) and certain excipients may be more easily excluded (e.g. because they are left on the line of application).