Note for guidance on organic impurities in active pharmaceutical ingredients and finished pharmaceutical products

2017

1. Scope

Purity is a critical attribute of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), which potentially affects their safety and efficacy. Therefore, API and FPP monographs in *The International Pharmacopoeia* (Ph.Int.) shall contain specifications for purity which include requirements for the control of impurities, wherever possible.

Impurities in APIs and FPPs may include starting materials, by-products, intermediates, degradation products, reagents, ligands, residual catalysts and residual solvents. They can be classified as either organic, inorganic or biological.

This guidance note covers requirements for controlling organic process-related impurities and degradation products in APIs and FPPs, and provides guidance on how to assess compliance with Ph.Int. requirements.

Statements in this document are applicable to monographs included in Ph.Int. after the publication of this guidance note. Compliance with monographs published before this updated guidance shall be evaluated against the previous text *Related substances in dosage form monographs*[1] unless required otherwise by the competent authority. A list of all monographs included in Ph.Int. before the publication of this guidance note is presented in the document titled *Monographs to be evaluated against the text Related substances in dosage form monographs* which can be found in *The International Pharmacopoeia* under Supplementary information.

[1] The replaced text can be found on the homepage of *The International Pharmacopoeia* under “Omitted texts”.

Excluded from this guidance note are biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, herbal products, fermentation products and semisynthetic products derived therefrom and crude products of animal and plant origin.

Further excluded are the following:

- -extraneous contaminants that should not occur in APIs and FPPs and are more appropriately addressed as good manufacturing practices (GMP) issues;
- -crystallographic modifications (“polymorphic forms”);
- -impurities that arise from printing inks or excipients (reaction products between excipients and APIs are not excluded);
- -organic impurities that are leached from container-closure systems;
- -highly toxic (e.g. genotoxic) impurities or highly toxic degradation products and residual solvents (volatile organic impurities) are addressed using separate applicable guidance.

2. Defining the purity of APIs and FPPs

To control relevant organic impurities individual monographs will contain a stability-indicating test entitled “Related substances”. This test may be supplemented by a specific test where a given impurity is not adequately controlled by the related substances test or where there are particular reasons (for example, safety reasons a genotoxic/mutagenic or an enantiomeric impurity) requiring specific control.

Monographs of APIs shall include specification limits for any impurities (i.e. process-related impurities that result from the manufacturing process and degradation products) observed at levels above the identification threshold and – when appropriate – specification limits for the total. Monographs on FPPs must include appropriate limits for degradation products and, if possible to be detected by the method, impurities from the manufacturing process. This approach provides, in conjunction with the monograph on the API, the means for an independent control laboratory without access to manufacturer’s data to establish whether or not an API of pharmacopoeial quality has been used to manufacture the FPP under examination.

It is recognized that limits for degradation impurities given in FPP monographs may need to be higher than the limits for the same impurities that appear in the monograph for the corresponding API to take into account any degradation which may occur during the manufacture and/or storage of the FPP. If the test for impurities in the FPP also limits impurities arising during the API synthesis, the reporting threshold as normally determined for the dosage form degradation products (not as for the API) will apply.

Instruction for control of impurities may also be included in the manufacture section of a monograph, for example, where the only analytical method appropriate for the control of a given impurity is to be performed by the manufacturer since the method is technically too complex for general use. The production process (including the purification steps) should be validated to give sufficient control so that the product, if tested, would comply with the specified limits using a suitable analytical method.

Under the section on “Impurities” in the monographs for APIs and FPPs, known impurities are listed (transparency list) that are able to be separated and detected by the described test method(s). In FPP monographs reference may also be made to the list in the monograph of the corresponding API if the test is able to detect these known impurities. Whenever possible, the impurities

are identified as degradation products and/or synthesis-related impurities.

Tests for related substances are intended to provide control of known potential or actual impurities rather than to control all possible impurities. The tests are not designed to detect any adventitious contaminants or adulteration. APIs or FPPs found to contain an impurity not detectable by means of the prescribed tests are not of pharmaceutical quality if the nature or amount of the impurity found is incompatible with GMP or applicable regulatory standards.

3. Setting acceptance criteria for organic impurities

Limits in Ph.Int. are usually set based on:

- -the evaluation of information, provided by manufacturers, concerning the nature of impurities, the reason for their presence, the concentrations that may be encountered in material produced under GMP, the manner in which the API or FPP may change during storage and when subjected to stress conditions (e.g. light, heat, moisture, acid, base or oxygen), and information on the toxicity of any organic impurity in relation to that of the substance itself;
- -justified limits accepted when the marketing authorization was granted or when the product was included in the WHO list of prequalified APIs or prequalified FPPs. Such acceptance includes establishing the qualification of limits by scientific principles, *inter alia*, ICH Q3 guidelines;
- -limits published by other pharmacopoeias applying good pharmacopoeial practices (GPhP);[2]
- -principles published in current regulatory guidance documents, such as those published by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

[2] Fiftieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, World Health Organization, 2016. WHO Technical Report Series, No. 996, Annex 1.

Safety considerations are of particular importance in establishing acceptance criteria for impurities.

The historical safety record, the route of administration, the type of dosage form, the maximum daily dose, the duration of treatment, the patient population, the need for and the availability of the medicine are also to be taken into consideration when setting limits for impurities.

Also, comments received on the draft monographs from Member States, stakeholders and other interested parties during the public consultation phase are reviewed and considered.

4. Claiming compliance with the requirements by a manufacturer

In the event of monographs that were published prior to the publication of this guidance note[1] which have no related substances test (or equivalent) or where the existing test does not comply with the requirements of the applicable regulatory standards the manufacturer shall nevertheless ensure that there is suitable control of organic impurities.

When an API contains impurities other than those mentioned in the Impurities section (for example, because it was manufactured using an alternative method of synthesis) the manufacturer must ascertain that these impurities can be controlled by the analytical method(s) and limits described in the monograph; otherwise a new analytical method and specifications shall be developed and submitted to the competent authority for approval, while a revision of the monograph of Ph.Int. shall be proposed by the manufacturer.

When a chromatographic peak (at a level greater than the applicable identification threshold) cannot be assigned unambiguously to an impurity in the transparency list using the means described in the monograph (e.g. by means of retention times, relative retentions or comparison to reference substances mentioned in the monograph) the manufacturer has to apply additional measures in order to identify the impurity. These measures may include, for example, ensuring that the response is not due to the chromatographic solvent system or excipients used in the formulation and the identification of potential impurities not referred to in the monograph by the use of additional analytical techniques, e.g. so-called hyphenated analytical techniques, e.g. GC- or LC-mass spectrometric methods. If identification by structure is initially not possible the impurity could be listed as an unidentified specified impurity until identification has been achieved.

When an impurity not listed in the transparency list is found in an API or in an FPP (at a level above the identification threshold) it is the responsibility of the manufacturer to demonstrate that it is identified and a qualified limit is set, in accordance with the applicable regulatory standards, and to communicate this to Ph.Int..

Glossary

degradation product. An impurity resulting from a chemical change in the active pharmaceutical ingredient (API) brought about during manufacture and/or storage of the API or the dosage form by the effect of, for example, light, oxygen, temperature, pH, water or by reaction with an excipient or another API (in fixed dose combination dosage form) and/or the immediate container-closure system.

extraneous contaminant. An impurity arising from any source extraneous to the manufacturing process.

identified impurity. An impurity for which a structural characterization has been achieved.

identification threshold. A limit above (>) which an impurity should be identified, based on the applicable regulatory standards.

impurity (API). Any component of an API that is not the chemical entity defined as the API.

impurity (FPP). Any component of the FPP that is not the API or an excipient in the FPP.

intermediate. A material produced during steps of the synthesis of an API that undergoes further chemical transformation before it becomes an API.

ligand. An agent with a strong affinity to a metal ion.

polymorphic forms. Different crystalline forms of the API. These can include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

qualification threshold. A limit above which an impurity should be qualified.

reporting threshold. A limit above which an impurity is to be reported.

specified impurity. An impurity that is individually listed and limited with a specific acceptance criterion in the monograph. A specified impurity can be either identified or unidentified.

starting material. A raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API starting materials normally have defined chemical properties and structure.

unidentified impurity. An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g. chromatographic retention time).

unspecified impurity. An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion.