



# Pushing for Purity



**Traces of impurities in pharmaceutical products can have drastic consequences; Dr Christian Zeine at LGC Standards GmbH outlines the ways in which their presence can be controlled and prevented**

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Impurities are always present in drug products in trace quantities. Limit and threshold values are specified by official bodies and legislation such as pharmacopoeias and ICH guidelines. Dedicated reference standards for impurities can help in the development and validation of analytical methods for impurity control, and are also used in the routine analysis of drug products. The use of such standards can provide an accurate assessment of products against regulatory limits and thereby ensures appropriate onward actions, be these data submission, process improvement or preclinical evaluation.

## TYPES OF IMPURITIES

According to the International Conference on Harmonization (ICH), impurities are defined as substances in the active pharmaceutical ingredient (API) that are not the API itself (1). For a pharmaceutical formulation (that is, a tablet or suppository), impurities are defined as substances in the product that are not the API itself, nor the excipient used to manufacture the relevant pharmaceutical (2). Investigations for their presence or absence are important due to their risk potential. Impurities can themselves be pharmacologically or toxicologically active and they can also reinforce or diminish the pharmacological efficacy of the API. Sometimes impurities may even be teratogenic, mutagenic or carcinogenic. Impurities can be divided into three categories: organic impurities, inorganic impurities and solvents.

### Organic Impurities

These arise during production and/or storage of the API and can be starting materials, by-products or degradation products. Organic starting materials and by-products are removed as much as possible after the production through downstream processing of the API. Degradation products, however, cannot be removed from the finished product. Stability tests must be carried out to prove that such degradation products do not exceed certain limits during the product shelf-life. Those limits must have been previously defined and justified for each degradation product.

### Inorganic Impurities

Inorganic reagents are required for the production of the API. Phosphates, for example, are commonly used as buffers during the reaction to adjust the pH, and organometallics are often used as catalysts in reaction processes. Such inorganic molecules count as impurities and have to be removed as far as possible from the end product.

### Solvents

The manufacture and work-up of APIs generally occurs in the liquid phase. Because of the nature of most APIs, water is often not a suitable solvent, and organic solvents – which are often toxic – can be necessary. Specified concentrations of such solvents should not be exceeded in the end product. The potential toxicity of the solvent and the technical feasibility of removing it from the API have to be considered as part of the specification process.

## EU-DIRECTIVE 2001/83/EU AND THE EUROPEAN PHARMACOPEIA

In the monographs of global pharmacopoeias, the impurities described above are often tested for by dedicated methods. Specified limits must not be exceeded if they are to meet the quality required by the pharmacopeia.

However, it does not suffice to simply follow the respective API or pharmaceutical formulation monographs in order to achieve the required pharmaceutical quality. A range of other conditions

have to be observed and followed, many of which are not described in one single pharmacopeia.

The 2001/83/EU Directive (3) forms the basis for approvals in the EU. It defines the (EP) as the first point of reference for generic APIs and medicine. If a monograph cannot be found in the *European Pharmacopeia*, an EU member state pharmacopeia can be consulted. Only if a monograph is not to be found in either the EP or a member state pharmacopeia can a pharmacopeia from a non-EU country (such as the *United States Pharmacopeia*) be consulted.

The EP is actually the most advanced pharmacopeia in the world with respect to impurities, with a list of impurities included at the end of many monographs. However, the publication of these lists can create the impression to the users of the EP that the pharmacopoeia can provide all these impurities as compendial standards (4). This is not the case; in fact, very few pharmacopeial standards for impurities are available. Furthermore, only a few of those impurity standards are designed for quantitative purposes. The majority are aimed at system suitability tests to verify the performance of the EP method after transfer into the user's laboratory.

Even so, the EP can only react to technical progress. Its monographs cannot predict all impurities which might arise from a novel manufacturing process. The 2001/83/EU Directive addresses this with the following statement in appendix 1:

“However, where a starting material... has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described (3).”

This issue is also addressed in the general text 5.10 (5) of the EP itself:

“Where an impurity other than a specified impurity is found in an active substance it is the responsibility of the user of the substance to check ... on its content, nature, ... in accordance with the general monograph on Substances for pharmaceutical use (2034), Related substances section.”

The general monograph “substances for pharmaceutical use (2034)” links the pharmacopeia with the demands of the ICH Guideline Q3A (R1) described later in this article. Q3A (R1) includes a table with threshold values for reporting, identification and qualification. This table is adopted without comment in the general monograph (6). In addition, the demand from the 2001/83/EU Directive, to test separately for impurities that are not included in the scope of the monograph and to provide specification limits, is reiterated.

In the monographs, the EP distinguishes between ‘specified’ impurities and so-called ‘other’ impurities. The relevance of this distinction becomes clear in general text 5.10:

“Where a general acceptance criterion for impurities... equivalent to a nominal content greater than the applicable identification threshold... is prescribed, this is valid only for specified impurities mentioned in the Impurities section”.

The other impurities of the list can be detected and controlled with the monograph method, but the EP has no data on the potential health risks of these ‘other’ impurities, therefore these are not considered to be specified impurities. It is the user's responsibility to carry out identification and, in some circumstances, qualification of these impurities in order to specify limits which can be justified to the authorities in the application dossier.

## ICH GUIDELINES

For completely new active substances and drugs that have not yet been described in pharmacopoeias, the ICH originally produced guidelines Q3A, Q3B and Q3C. These three guidelines have undergone several revisions and the current versions are known as Q3A (R1) (1), Q3B (R2) (2) and Q3C (R3) (7). As already mentioned, these guidelines are also used in the case of those active ingredients and finished medical products that have not been sufficiently described in pharmacopoeias. For example, the ICH guidelines would be referred to in a situation in which ibuprofen, in itself sufficiently well-known, was manufactured using a new – perhaps economically advantageous – process, as a result of which it would contain impurities not covered by existing pharmacopoeia monographs.

In addition to this, in its draft ‘Guidance for Industry – ANDAs: Impurities in Drug Substances’ (8), the FDA makes it clear that the principles of Q3A (R1) should generally also be applicable to generic products:

“The Q3A(R) (sic) was developed... to provide guidance on impurities in drug substances for new drug applications (NDAs). However, the Agency believes that... the recommendations provided... also apply to ANDAs.”

Abbreviated new drug applications (ANDAs) are the process by which the FDA assesses marketing applications for generics.

To look more closely at the subject of organic impurities, we shall consider only the guideline Q3A (R1) (‘Impurities in New Drug Substances’). Guideline Q3B (R2) (‘Impurities in New Drug Products’) corresponds in its mechanism almost completely to Q3A (R1), and the problem of organic impurities is not considered in the solvent guideline Q3C (R3), which only consists of four lists of solvents with limitations based on their toxicity profile.

## THRESHOLD VALUES FOR IMPURITIES

Q3A (R1) and Q3B (R2) are predominantly concerned with the wide field of organic impurities. In contrast to pharmacopoeia monographs, the ICH guidelines Q3A (R1) and Q3B (R2) do

not provide limits for impurities, but specify threshold values above which the ‘only’ requirement is that certain actions must be taken. Table 1, from guideline Q3A (R1) (‘Impurities in New Drug Substances’), lists the threshold values for individual actions. Should a particular impurity exceed its ‘reporting threshold,’ this impurity must be mentioned in the registration documentation (rounded values of the raw data are considered, for example, from peak area reports of analyses by HPLC).

The identification of an impurity becomes necessary when the second threshold (‘identification threshold’) is passed. Above the third threshold (‘qualification threshold’) comprehensive qualification of the impurity in question is required. Lower percentage threshold values apply for APIs with daily doses above two grams – see the second row in Table 1. The third threshold in particular – that is, the qualification threshold – should if possible not be exceeded, because the qualification studies that would then become obligatory are generally cost- and time-intensive. Qualification in the sense used here by the ICH is the process of acquiring and evaluating data confirming safety of the impurity in question, when it is present in a pharmaceutical product in the given concentration.

### QUALIFICATION BY ANIMAL STUDIES

The first step in qualification would involve a literature search to confirm that no harmful side effects would be likely to result from the impurity at the concentration in which it occurs in the product, taking account of the nature and route of the product’s administration, the likely patient profile, and the duration of use. Should the literature search identify health concerns, the production of the pharmaceutical product must be adjusted in such a way that the impurity concentration falls back to safe levels. If no such data can be found in the literature, and the impurity lies above the qualification threshold, measures must be taken to demonstrate that, in the amounts present, the impurity nevertheless has no harmful potential. It may be argued that the impurity in question also occurs simultaneously, in higher concentrations and without provoking any harmful effects, as a metabolic product in the organism. This might constitute sufficient qualification for the impurity substance.

As a rule, however, *in vivo* studies are undertaken (on cell cultures, but in many cases also on animals), as well as genotoxicity studies. These can easily take several months and, depending on the stage of development, can significantly delay clinical trials and marketing authorisation.

### STRATEGY FOR AVOIDING QUALIFICATION STUDIES

The ICH suggests in a footnote in its impurity guidelines that, after identification of a substance, the response factor thereof should be checked critically:

“After identification, if the response factor is determined to differ significantly... , it may be

appropriate to re-measure... the impurity present and re-evaluate it against the qualification threshold.”

It is thus perfectly possible, on correcting the response factor, to end up with a value below the qualification threshold, thus avoiding the necessity for prolonged studies.

Ibuprofen gives a good example of the use of the *European Pharmacopoeia* and ICH guidelines in practice. The general acceptance criterion of 0.3 per cent given in the monograph (9) is far above the ICH threshold laid down in Q3A(R1) for identification and qualification, and therefore applies – in accordance with General text 5.10 of the EP – only to ‘specified impurities’ A, B, C, D, and E. The other impurities F to R are only ‘other detectable impurities’. For them their own acceptance limits must be given in the specification and registration dossier, provided that these impurities are present in the product and that their contents are above the identification or qualification threshold of the ICH.

It is, nevertheless, advisable not to use the HPLC method of the EP exclusively for the quantification of other impurities present in the ibuprofen. Apart from the fact that the EP method does not allow for the identification of individual impurities, the work is carried out only on a dilute ibuprofen solution to quantify the impurities for the limit test, and any differences in analytical response at the specified wavelength are not taken into consideration at all in this method. Depending on the impurity, the analytical response can easily differ by 70 per cent or more from the response for ibuprofen itself (10). Therefore, response factors should be determined for each individual impurity substance.

All such determinations should be carried out with a sample of the impurity substance itself, which should be as pure as possible. Suppliers of reference standards offer reliable help, although the range of impurity standards available from individual suppliers can vary widely. Some suppliers offer only the pharmacopoeia standards already discussed above, while others also provide a more comprehensive product line of impurity standards. They may also custom-synthesise an impurity for a particular active substance if it does not form part of their standard product range.

### POSSIBLE USES OF IMPURITY REFERENCE STANDARDS

The usefulness of these materials is, of course, not confined to the performance of exact analyses with the aim of avoiding

**Table 1:** ICH-Guideline Q3A (R1) – impurities in new drug substances

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
≤ 2g per day	0.05%	0.10% or 1.0mg per day intake (whichever is lower)	0.15% or 1.0mg per day intake (whichever is lower)
> 2g per day	0.03%	0.05%	0.05%

costly qualification studies. The substances can also be used in those cases in which qualification studies have proved to be unavoidable, in order to test the toxicological potential of the impurity independently of the pharmaceutical product matrix.

In most cases, however, the substances are used for identification and quantification of the impurities in pharmaceutical products. This may be the case as part of the afore-mentioned qualification studies or in the course of the development and validation of stability indicating methods. An analytical certificate should be supplied together with the reference standard, specifying at the very minimum: general data, the method used to establish identity (NMR), the purity profile by HPLC, and the water content, (by the Karl Fischer method). From the purity profile and the water content, the content of the impurity can then be calculated. As a rule it is also possible to obtain certificates with an extended analytical spectrum if the customer requires this additional information. ♦

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2. Impurities in New Drug Products, ICH Guideline Q3B (R2), found at <http://www.ich.org/LOB/media/MEDIA421.pdf>

3. Directive 2001/83/EU p311, L105, 6th November 2001, found at [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir\\_2001\\_83/dir\\_2001\\_83\\_en.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83/dir_2001_83_en.pdf)

4. LGC Promochem internal communication

5. *European Pharmacopoeia* 6.0, 5.10, p653

6. *European Pharmacopoeia* 6.0, General monograph (2034), p704

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10. LGC Standards internal communication