

IMPURITIES IN NEW ACTIVE SUBSTANCES *)

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Additional Notes	This note for guidance concerns the application of Part 2, section C of the Annex to Directive 75/318/EEC as amended, with a view to the granting of a marketing authorisation for a new medicinal product. It replaces the section on impurities in the guideline entitled <i>Chemistry of Active Substances</i> in relation to new active substances.

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IMPURITIES IN NEW ACTIVE SUBSTANCES *)

1. PREAMBLE

This document is intended to provide guidance for applicants on the content and qualification of impurities in new active substances produced by chemical syntheses and not previously authorised in a Member State. It is not intended to apply to the regulation of new substances used during the clinical research stage of development. Biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin are not covered.

Impurities in new substances are addressed from two perspectives:

Chemistry Aspects includes classification and identification of impurities, report generation, setting specifications, and a brief discussion of analytical procedures; and,

Safety Aspects includes specific guidance for qualifying impurities which were not present in batches of new substance used in safety and clinical studies and/or impurity levels substantially higher than in those batches. Threshold limits are defined, below which, qualification is not needed.

2. CLASSIFICATION OF IMPURITIES

Impurities may be classified into the following categories:

- Organic Impurities (Process and Substance Related)
- Inorganic Impurities
- Residual Solvents

Organic impurities may arise during the manufacturing process and/or storage of the new substance. They may be identified or unidentified, volatile or non-volatile, and include:

- Starting Materials
- By-Products
- Intermediates
- Degradation Products
- Reagents, Ligands and Catalysts

Inorganic impurities may derive from the manufacturing process. They are normally known and identified and include:

- Reagents, Ligands and Catalysts
- Heavy Metals
- Inorganic Salts
- Other Materials (e.g., Filter Aids, Charcoal, etc.)

Solvents are organic or inorganic liquids used during the manufacturing process. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished.

Excluded from this document are: extraneous contaminants which should not occur in new substances and are more appropriately addressed as GMP issues; polymorphic forms, a solid state property of the new substance; and, enantiomeric impurities.

3. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

3.1 Organic Impurities

The applicant should summarise those actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials which could contribute to the impurity profile of the new substance, and possible degradation products. This discussion may include only those impurities that may reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarise the laboratory studies conducted to detect impurities in the new substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as results of intentional degradation studies used to identify potential impurities arising during storage. Assessment of the proposed commercial process may be deferred until the first batch is produced for marketing. The impurity profile of the active substance lots intended for marketing should be compared with those used in development and any differences discussed.

The studies conducted to characterise the structure of actual impurities present in the new substance at or above an apparent level of 0.1% (e.g., calculated using the response factor of the substance) should be described. Note that all recurring impurities at or above the 0.1% level in batches manufactured by the proposed commercial process should be identified. Degradation products observed in stability studies at recommended storage conditions should be similarly identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities below the 0.1% level, it is useful to also report the results of these studies

Identification of impurities below apparent levels of 0.1% is generally not considered necessary. However, identification should be attempted for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level lower than 0.1%. In all cases, impurities should be qualified as described later in this guide. Although it is common practice to round analytical results of between 0.05 and 0.09% to the nearest number (i.e., 0.1%), for the purpose of these guidelines, such values would not be rounded to 0.1% and these impurities would not require identification.

3.2 Inorganic Impurities

Inorganic impurities are normally detected and quantitated using pharmacopoeial or other appropriate procedures. Carry-over of catalysts to the new substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new substance specifications should be discussed. Limits should be based on pharmacopoeial standards or known safety data.

3.3 Solvents

The control of residues of the solvents used in the manufacturing process for the new substance should be discussed. Any solvents which may appear in the substance should be quantified using analytical procedures with an appropriate level of sensitivity.

Pharmacopoeial or other appropriate procedures should be utilised. Limits should be based on pharmacopoeial standards or known safety data taking into consideration dose, duration of treatment, and route of administration. Particular attention should be given to quantitation of toxic solvents used in the manufacturing process

4. ANALYTICAL PROCEDURES

The application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantitation of impurities. Differences in the analytical procedures used during development and proposed for the commercial product should be discussed in the marketing authorisation application.

Organic impurity levels can be measured by a variety of techniques, including those which compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterised according to their intended uses. It is considered acceptable to use the substance to estimate the levels of impurities. In cases where the response factors are not close, this practice may still be acceptable, provided a correction factor is applied or the impurities are, in fact, being overestimated. Specifications and analytical procedures used to estimate identified or unidentified impurities are often based on analytical assumptions (e.g., equivalent detector response, etc.). These assumptions should be discussed in the marketing authorisation application.

5. REPORTING IMPURITY CONTENT OF BATCHES

Analytical results should be provided for all batches of the new substance used for clinical, safety and stability testing, as well as for batches representative of the proposed commercial process. The content of individual identified and unidentified and total impurities, observed in these batches of the new substance, should be reported with the analytical procedures indicated. A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, e.g., retention time. Levels of impurities which are present but are below the validated limit of quantitation need not be reported. When analytical procedures change during development, reported results should be linked with the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of such representative

batches, from method validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The applicant should ensure that complete impurity profiles (i.e., chromatograms) of individual batches are available if requested.

A tabulation should be provided which links the specific new substance batch to each safety study and each clinical study in which it has been used.

For each batch of the new substance, the report should include:

- Batch Identity and Size
- Date of Manufacture
- Site of Manufacture
- Manufacturing Process
- Impurity Content, Individual and Total
- Use of Batches
- Reference to Analytical Procedure Used

6. SPECIFICATION LIMITS FOR IMPURITIES

The specifications for a new substance should include limits for impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. The selection of impurities to include in the new substance specifications should be based on the impurities found in batches manufactured by the proposed commercial process. Those impurities selected for inclusion in the specifications for the new substance are referred to as “specified impurities” in these guidelines. Specified impurities may be identified or unidentified and should be individually listed in the new substance specifications.

A rationale for the inclusion or exclusion of impurities in the specifications should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of material manufactured by the proposed commercial process. Specific identified impurities should be included along with recurring unidentified impurities estimated to be at or above 0.1%. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical methods should be commensurate with the level at which the impurities must be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Unidentified impurities included in the specifications should be referred to by some appropriate qualitative analytical descriptive label (e.g., “unidentified A” unidentified with relative retention of 0.9”, etc.). Finally, a general specification limit of not more than 0.1% for any unspecified impurity should be included.

Limits should be set no higher than the level which can be justified by safety data, and, unless safety data indicate otherwise, no lower than the level achievable by the manufacturing process and the analytical capability. In other words, where there is no safety concern, impurity specifications should be based on data generated on actual batches of the new substance allowing sufficient latitude to deal with normal manufacturing and analytical variation and, the stability characteristics of the new substance. Although

normal manufacturing variations are expected, significant variation in batch to batch impurity levels may indicate that the manufacturing process of the new substance is not adequately controlled and validated.

In summary, the new substance specifications should include, where applicable, limits for:

Organic Impurities

- Each Specified Identified Impurity
- Each Specified Unidentified Impurity at or above 0.1%
- Any Unspecified Impurity, with a limit of not more than 0.1%
- Total Impurities

Residual Solvents

Inorganic Impurities

A summation of assay value and impurity levels generally may be used to obtain mass balance for the test sample. The mass balance need not add to exactly 100% because of the analytical error associated with each analytical procedure. The summation of impurity levels plus the assay value may be misleading, e.g., when the assay procedure is non-specific (e.g., potentiometric titrimetry) and the impurity level is relatively high.

7. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data which establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for selecting impurity limits based on safety considerations. The level of any impurity present in a new substance which has been adequately tested in safety and/or clinical studies is considered qualified. Impurities which are also significant metabolites present in animal and/or human studies do not need further qualification. A level of a qualified impurity higher than that present in a new substance can also be justified based on an analysis of the actual amount of impurity administered in previous safety studies.

If data are not available to qualify the proposed specification level of an impurity, studies to obtain such data may be needed when the usual qualification threshold limits given below are exceeded:

Maximum Daily Dose	Qualification Threshold
≤ 2g/day	0.1% or 1 mg per day intake (whichever is lower)
> 2g/day	0.05%

Higher or lower threshold limits for qualification of impurities may be appropriate for some individual substances based on scientific rationale and level of concern, including product class effects and clinical experience. For example, qualification may be especially important when there is evidence that such impurities in certain substances or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold limit may be appropriate. Conversely, a higher qualification threshold limit may be appropriate for individual substances when the level of concern for safety is less than usual based on similar considerations (patient population, substance class effects, clinical considerations, etc.). Technical factors (manufacturing

capability and control methodology) may be considered as part of the justification for selection of alternative threshold limits. Proposals for alternative threshold limits are considered on a case by case basis.

The “Decision Tree for Safety Studies” (Attachment I) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity below the threshold may be simpler than providing safety data. Alternatively, adequate data may be available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered. The studies desired to qualify an impurity will depend on a number of factors, including the patient population, daily dose, route and duration of medicinal product administration. Such studies are normally conducted on the new substance containing the impurities to be controlled, although studies using isolated impurities are acceptable.

8. NEW IMPURITIES

During the course of a substance development program, the qualitative impurity profile of the new substance may change, or a new impurity may appear as a result of synthetic route changes, process optimisation, scale-up, etc. New impurities may be identified or unidentified. Such changes call for consideration of the need for qualification of the level of the impurity unless it is below the threshold values as noted above. When a new impurity exceeds the threshold, the “Decision Tree for Safety Studies” should be consulted. Safety studies should compare the new substance containing a representative level of the new impurity with previously qualified material, although studies using the isolated impurity are also acceptable (these studies may not always have clinical relevance).

9. GLOSSARY

Chemical Development Studies: Studies conducted to scale-up, optimise, and validate the manufacturing process for a new substance.

Enantiomers: Compounds with the same molecular formula as the substance, which differ in the spatial arrangement of atoms within the molecule and are non- superimposable mirror images.

Extraneous Substance: An impurity arising from any source extraneous to the manufacturing process.

Herbal Products: Medicinal products containing, exclusively, plant material and/or vegetable preparations as active substances. In some traditions, materials of inorganic or animal origin may also be present.

Identified Impurity: An impurity for which a structural characterisation has been achieved.

Impurity: Any component of the new substance which is not the chemical entity defined as the new substance.

Impurity Profile: A description of the identified and unidentified impurities present in a new substance.

Intermediate: A material produced during steps of the synthesis of a new substance which must undergo further molecular change before it becomes a new substance.

Ligand: An agent with a strong affinity to a metal ion.

New Substance: The designated therapeutic moiety which has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved substance.

Polymorphism: The occurrence of different crystalline forms of the same substance.

Potential Impurity: An impurity which, from theoretical considerations, may arise from or during manufacture. It may or may not actually appear in the new substance.

Qualification: The process of acquiring and evaluating data which establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Reagent: A substance, other than a starting material or solvent, which is used in the manufacture of a new substance.

Safety Information: The body of information that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new substance.

Specified Impurity: Identified or unidentified impurity that is selected for inclusion in the new substance specifications and is individually listed and limited in order to assure the safety and quality of the new substance.

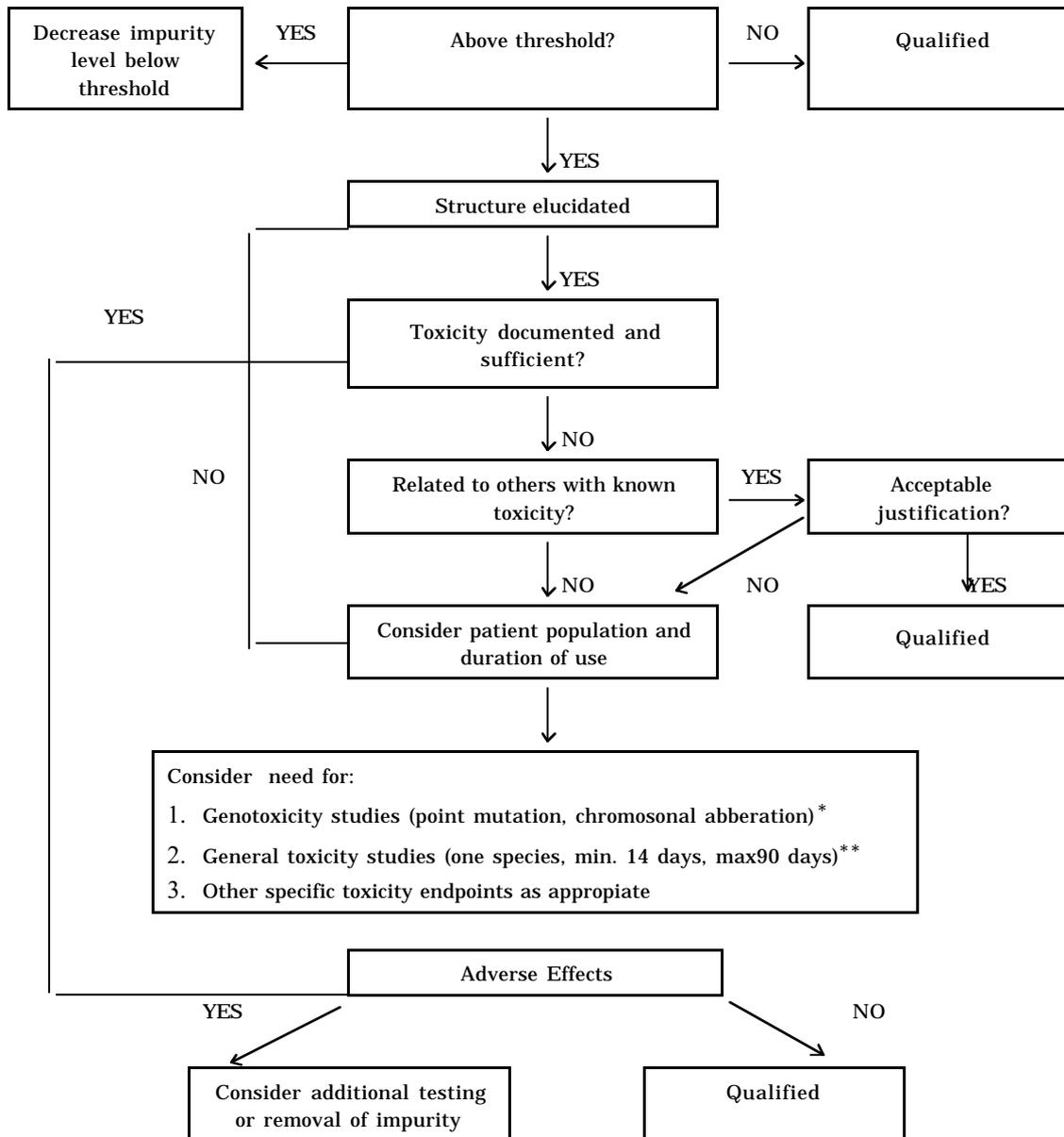
Starting Material: A material used in the synthesis of a new substance which is incorporated as an element into the structure of an intermediate and/or of the new substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Toxic Impurity: Impurities having significant undesirable biological activity.

Unidentified Impurity: An impurity which is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Validated Limit of Quantitation: For impurities at a level of 0.1%, the validated limit of quantitation should be less than or equal to 0.05%. Impurities limited at higher levels may have higher limits of quantitation.

Decision Tree for Safety Studies



* If considered desirable, a minimum screen for genotoxic potential should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are seen as an acceptable minimum screen.

** If general toxicity studies are desirable, study(ies) should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximise the potential to detect the toxicity of an impurity. In general, a minimum duration of 14 days and a maximum duration of 90 days will be acceptable.