The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

ICH Topic Q 3 B
Impurities in New Medicinal Products

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NOTE FOR GUIDANCE ON IMPURITIES IN NEW MEDICINAL PRODUCTS (CPMP/ICH/282/95)

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IMPURITIES IN NEW MEDICINAL PRODUCTS (CPMP/ICH/282/95)

[ICH Harmonised Tripartite Guideline]

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1. INTRODUCTION

1.1 Objective of the Guideline

This guideline provides guidance recommendations for applications for marketing authorisation on the content and qualification of impurities in new medicinal products produced from chemically synthesised new active substances not previously registered in a member state.

1.2 Background

This Guideline is an annex to the Impurities in New Active Substances Guideline which should be consulted for basic principles.

1.3 Scope of the Guideline

This Guideline addresses only those impurities in medicinal products classified as degradation products of the active substance or reaction products of the active substance with an excipient and/or immediate container/closure system (collectively referred to as "degradation products" in this Guideline). Impurities arising from excipients present in the product are not covered by this Guideline. This Guideline also does not address the regulation of products used during the clinical research stages of development. Biological/ biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin are not covered. Also excluded from this Guideline are: extraneous contaminants which should not occur in medicinal products and are more appropriately addressed as good manufacturing practice issues, polymorphic form, a solid state property of the new active substance, and enantiomeric impurities. Impurities present in the new active substance need not be monitored in medicinal products unless they are also degradation products.

2. GUIDELINES

2.1 Analytical Procedures

The application for a marketing authorisation should include documented evidence that the analytical procedures have been validated and suitable for the detection and quantitation of degradation products. Analytical methods should be validated to demonstrate that impurities unique to the new active substance do not interfere with or are separated from specified and unspecified degradation products in the product.

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

marketing authorisation. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed.

2.2 Rationale for the Reporting and Control of Impurities

The applicant should summarise those degradation products observed during stability studies of the medicinal product. This summary should be based on sound scientific appraisal of potential degradation pathways in the medicinal product and impurities arising from the interaction with excipients and/or the immediate container/closure system. In addition, the applicant should summarise any laboratory studies conducted to detect degradation products in the medicinal product. This summary should include test results of batches manufactured during the development process and batches representative of the proposed commercial process. A rationale should be provided for exclusion of those impurities which are not degradation products, e.g., process impurities from the active substance and excipients and their related impurities. The impurity profile of the batches representative of the proposed commercial process should be compared with the profiles of batches used in development and any differences discussed.

Degradation products observed in stability studies conducted at recommended storage conditions should be identified when the identification thresholds given in Attachment I are equaled or exceeded (although it is common practice to round analytical results of between 0.05 and 0.09 percent to the nearest number, i.e., 0.1 percent, for the purpose of these guidelines such values would not be rounded to 0.1 percent). When identification of a degradation product is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application for marketing authorisation.

Degradation products below the indicated levels generally would not need to be identified. However, identification should be attempted for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacologic effects at levels lower than indicated.

2.3 Reporting Impurity Content of Batches

Analytical results should be provided in tabular format for all relevant batches of new medicinal product used for clinical, safety and stability testing, as well as batches which are representative of the proposed commercial process. Because the degradation test procedure can be an important support tool for monitoring the manufacturing quality as well as for deciding the expiration dating period of the product, the reporting level should be set below the identification threshold. The recommended target value for the reporting threshold (expressed as a percentage of the active substance) is found in Attachment I. A higher reporting threshold should only be proposed, with justification, if the target reporting threshold cannot be achieved.

In addition, where an analytical method reveals the presence of impurities in addition to the degradation products (e.g., impurities arising from the synthesis of the active substance) the origin of these impurities should be discussed. Chromatograms, or equivalent data (if other methods are used), from representative batches including long-term and accelerated stability conditions should be provided. The procedure should be capable of quantifying at least at the reporting threshold and the chromatograms should show the location of the observed degradation products and impurities from the new active substance.

The following information should be provided:

- Batch identity, strength and size
- Date of manufacture
- Site of manufacture
- Manufacturing process, where applicable
- Immediate container/closure
- Degradation product content, individual and total
- Use of batch
- Reference to analytical procedure(s) used
- Batch number of the drug substance used in the drug product
- Storage conditions

2.4 Specification Limits for Impurities

The specifications for a new medicinal product should include limits for degradation products expected to occur under recommended storage conditions. Stability studies, knowledge of degradation pathways, product development studies and laboratory studies should be used to characterise the degradation profile. Specifications should be set taking into account the qualification of the degradation products, the stability data, the expected expiry period, and the recommended storage conditions for the product, allowing sufficient latitude to deal with normal manufacturing, analytical and stability profile variation. The specification for the product should include, where applicable, limits for:

- Each specified degradation product
- Any unspecified degradation product
- Total degradation products.

Although some variation is expected, significant variation in batch to batch degradation profiles may indicate that the manufacturing process of the new medicinal product is not adequately controlled and validated. 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 studies, together with a consideration of the impurity profile of the product manufactured by the proposed commercial process.

2.5 Qualification of Impurities

Qualification is the process of acquiring and evaluating data which establishes the biological safety of an individual degradation product or a given degradation profile at the level(s) specified. The applicant should provide a rationale for selecting degradation product limits based on safety considerations. The level of any degradation product present in a new medicinal product which has been adequately tested and found safe in safety and/or clinical studies is considered qualified. Therefore, it is useful to include any available information on the actual content of degradation products in the relevant batches at the time of use in safety and/or clinical studies. Degradation products which are also significant metabolites, present in animal and/or human studies, do not need further qualification. It may be possible to justify a higher level of a degradation product than the level administered in safety studies. The

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