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Committee for Human Medicinal Products (CHMP)

## Questions and answers on the withdrawal of the 'Guideline on pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (3BS11A)'

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| Adoption by CHMP                     | 25 April 2014 |

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| Keywords | Pharmacokinetics, toxicokinetics |
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<sup>1</sup> Link to withdrawn "Guideline on pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (3BS11A)" was replaced by the guideline itself in annex for information.



## Background

The current guideline on pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (3BS11A) [1] contains concise statements on the type of animal pharmacokinetic data that are needed for the safety evaluation. This is a Commission guideline which was issued in October 1983.

Following discussions within the Safety Working Party of the CHMP (SWP), the CHMP agreed to remove the guideline 3BS11A. This decision is based mainly on the recognition that other EU guidelines issued since the release of this guideline cover the same requirements.

The aim of this Q&A document is to provide clarification on the views of the CHMP on how to obtain information on pharmacokinetics from other sources.

## Questions and answers

**Question 1. Is there still a need for non-clinical pharmacokinetic studies after the withdrawal of the guideline on pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (3BS11A)?**

Yes, such studies will still be needed for pharmacokinetic characterization of the medicinal product in animals used in pharmacological and toxicological studies as required in the Annex I, Part I, module 4 of Directive 2001/83/EC [2].

**Question 2. Where can scientific guidance on pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals be found after the withdrawal of guideline 3BS11A?**

General guidance on pharmacokinetic and toxicokinetic studies is provided in ICH guideline M3 (R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995) [3]. These requirements concern the need to characterise exposure to parent and metabolites in animals as compared to humans to assess the suitability of the animal species for safety testing and to assess the need for specific non-clinical evaluation of human metabolites. Information on pharmacokinetics after repeated administration is often obtained from repeated dose toxicology studies. The evaluation of toxicokinetics in these studies is addressed in ICH Topic S3A: the assessment of systemic exposure in toxicity studies (CPMP/ICH/384/95) [4].

The need for repeated dose tissue distribution studies is discussed in ICH Topic S3B: Pharmacokinetics: Guidance for repeated dose tissue distribution studies (CPMP/ICH/385/95) [5]. This guideline provides guidance on circumstances when repeated dose tissue distribution studies should be considered and on the conduct of such studies.

## References

1. Pharmacokinetics and Metabolic Studies in the Safety Evaluation of New Medicinal Products in Animals (3BS11a, 1983). See Annex .
2. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. L 159/70 EN Official Journal of the European Union 27.6.2003  
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:159:0046:0094:en:PDF>

3. ICH guideline M3 (R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995)  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC50002720.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002720.pdf)
4. Toxicokinetics: the assessment of systemic exposure in toxicity studies (ICH S3A)  
[http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500002770](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500002770).
5. Pharmacokinetics: Guidance for repeated dose tissue distribution studies (ICH S3B)  
[http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500002771](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500002771).

# PHARMACOKINETICS AND METABOLIC STUDIES IN THE SAFETY EVALUATION OF NEW MEDICINAL PRODUCTS IN ANIMALS

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| Guideline Title          | Pharmacokinetics and Metabolic Studies in the Safety Evaluation of New Medicinal Products in Animals                                                                                                                                                                                                                                                                                                                                                                                      |
| Legislative basis        | Directive 75/318/EEC as amended                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Date of first adoption   | October 1983                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Date of entry into force | April 1994                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Status Last revised      | 1983                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Previous titles/other    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| References               | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Additional Notes         | This note for guidance concerns the application of Part 3, section II. G of the Annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a medicinal product. Sections of this text have been revised as part of the ICH process. The relevant parts of this guideline may be replaced by the notes for guidance on <i>The Assessment of Systemic Exposure in Toxicity Studies</i> and on <i>Repeated Dose Tissue Distribution Studies</i> . |

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# PHARMACOKINETICS AND METABOLIC STUDIES IN THE SAFETY EVALUATION OF NEW MEDICINAL PRODUCTS IN ANIMALS

## 1. INTRODUCTION

These notes are concerned with the time course of the absorption, distribution and excretion of new medicinal products and with their metabolism in relation to their safety. For many steps in the evaluation of a medicinal product such data are essential, for example:

- a) to assess the levels of the substance and of its metabolites and their kinetics in blood, body fluids and organs;
- b) to obtain information on the relationship between target organ toxicity and the blood, body fluids and organ concentrations of the substance;
- c) to assess the possibility of enzyme induction and of cumulation of the substance with repeated administration;
- d) to choose where possible the animal species to be used in toxicological studies on the basis of their similarity to man in handling the medicinal product, and to determine the relevance of these toxicity studies to man.

## 2. SUBSTANCE SPECIFICATION

Specification of the physical and chemical properties of the substance must be given and the stability of the preparation should be provided.

When a labelled substance is used the position of the label in the molecule and the specific activity of the material must be stated. Consideration should be given when selecting the position of the label to its likely metabolic fate.

## 3. METHODS

Data on the levels of substance and metabolites in blood, body fluids, organs and in the excreta can be obtained by physical, chemical or biological methods. The investigator should justify the details of the methods used, their validity and reproducibility, including the specificity, precision and accuracy. (The study of the time course of its pharmacodynamic effects may provide useful additional information).

When using labelled substances attention must be given to the fact that the measured label in body fluids may not correspond to that of the unmodified substance, but may include labelled metabolites and conjugates. Attention should be given to the possibility of isotope exchange with endogenous compounds.

## 4. SPECIES

The animal species in these studies usually should be those normally used in the laboratory for pharmacological and toxicological investigations. The reasons for selection of any other species should be given.

A preliminary study of kinetics and metabolism of the medicinal product in a few human subjects could provide useful information in choosing the animal species to be used in repeated dose toxicity studies.

## 5. DRUG ADMINISTRATION

Doses and routes of drug administration should be related, when possible, to the proposed clinical use of the substance. One of the routes selected should ensure the absorption of the substance if this is relevant to human usage.

## 6. PRESENTATION OF RESULTS

Information should be presented on the following items:

- i) absorption (fractional absorption, kinetics);
- ii) distribution in the principal organs and tissues and the time course in body fluids;
- iii) blood, plasma or serum half-life;
- iv) plasma protein binding;
- v) characterisation of the pattern of metabolites in excreta, and where practicable, identification of major metabolites;
- vi) route and time course of excretion of substance and metabolites;
- vii) if biliary excretion is a major route of elimination, then the possibility of enterohepatic recycling should be investigated;
- viii) a quantitative account of the fate of the administered dose should be attempted;
- ix) possibilities of enzyme induction should be investigated. If enzyme induction is found its relevance in the context of the proposed use of the medicinal product should be examined.

## 7. CONCLUSIONS

Appropriate conclusions should be drawn from these studies in the context of the objectives indicated in paragraph 1.