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GUIDELINE ON THE NON-CLINICAL DOCUMENTATION FOR MIXED MARKETING AUTHORISATION APPLICATIONS

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7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (+44-20) 74 18 84 00 Fax: (+44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

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1 INTRODUCTION

1.1 Objective of the guideline

This note for guidance is intended to give advice to applicants who plan to submit a Mixed Marketing Authorisation Application for medicinal products for human use, as defined in the Annex I Part II .7 of Directive 2001/83/EC, as amended and the legal basis is set out in Article 8(3) of the same Directive. The non-clinical dossier requirements are laid down in Part I, Module 4 of the Annex I.

A number of medicinal products already in use in humans for a long time contain active substance(s) for which there is limited or no non-clinical information. In order to obtain a better understanding of the inherent risks of such products and to avoid blind repetition of animal experiments, the minimum requirements for non-clinical studies are described in this guideline. A combination of limited non-clinical and/or clinical studies and of literature references from published pharmaco-toxicological information including scientifically accepted monographs and clinical trials, as well as results of post-marketing experience gained by widespread clinical use in man constitute the body of knowledge for such products.

1.2 Scope of the guideline

The guideline applies to conventional chemical active substances of defined structure. Biologicals, biotechnology and herbal products are excluded.

2 2 NON-CLINICAL DOCUMENTATION

2.1 General Considerations

Non-clinical investigations are normally not required when there is sufficient well-documented clinical experience to establish all aspects of clinical efficacy and safety.

Non-clinical investigations may be needed if a safety concern is recognised or suspected based on the pharmacological class or the clinical experience with the product.

The lack of some specific non-clinical studies particularly reproductive toxicity, genotoxicity or carcinogenicity may also pose a safety concern. Therefore, non-clinical investigations may be necessary to study such effects that are difficult or even impossible to detect clinically.

2.2 Individual Study Types

2.2.1 Single and Repeat-dose Toxicity

Single dose and repeated dose toxicity, as well as local tolerance investigations are normally not necessary. Likewise pharmacological investigations including safety pharmacology and pharmacokinetics are normally not necessary.

2.2.2 Reproductive and Developmental Toxicity

Investigations regarding fertility and general reproductive performance are generally not necessary unless there is cause for concern.

The reproductive toxicological potential with regard to embryo-foetal and peri-post-natal development should be assessed. Although such data are available for many active substance(s), their quality is often insufficient for an adequate safety assessment.

Investigations of embryo-fetal toxicity and peri/post-natal development are not necessary if sufficient data from exposures in pregnant women and neonates are available or if the medicinal product is not intended for use in women of child-bearing potential or during pregnancy and lactation.

2.2.3 Genotoxicity

The genotoxic potential of the active substance(s) should be assessed.

Genotoxicity data are available for many active substance(s), however, their quality is often inadequate for safety assessment. When an adequate assessment of mutagenicity and/or chromosomal damage cannot be made, further genotoxicity testing is required.

Occasionally, genotoxic properties of active substance(s) in a particular pharmacological class (e.g. cytostatic agents) can be extrapolated from other substances in the same class. In these cases no genotoxicity studies are required.

2.2.4 Carcinogenicity

Carcinogenicity investigations are not needed in cases where there is no suspicion of a carcinogenic potential.

Carcinogenicity investigations do not necessarily have to be performed even if there is a suspicion of a carcinogenic effect. Some points which should be considered in deciding the need for carcinogenicity studies are:

- Does a positive result alter the benefit-risk assessment?
- Is tumour induction predictable from previous testing of substances with similar molecular structure and/or mode of action?
- Is the suspicion based on positive results of genotoxicity studies and can it be clarified in further genotoxicity studies, mainly *in vivo*?
- Is the suspicion based on epidemiologically proven positive findings in humans (e.g. oestrogen-induced mammary tumours)?
- Is the weight of scientific evidence sufficient to refute the suspicion (of a carcinogenic effect)?

Toxicokinetic data are only required in connection with new tests in animals.

3 NON-CLINICAL OVERVIEW

The expert should discuss the collective information available on which to base an acceptable level of safety for the active substance. For active substances that appear to have a gap in toxicological data, the expert should discuss the results of relevant pharmacological and toxicological tests by detailed references to published scientific literature and/or provide a scientific justification to demonstrate an acceptable level of safety for the active substance, taking also available information from wide-spread clinical use into account. The importance of deviations from currently accepted quality standards (e.g. GLP compliance) for the interpretation of study results should also be addressed.

In addition, proposals for the wording of the SPC, sections 4.6 (Pregnancy and Lactation) and 5.3 (Pre-clinical data), should be included.