COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

DRAFT

NOTE FOR GUIDANCE ON THE NON-CLINICAL DOCUMENTATION OF MEDICINAL PRODUCTS WITH WELL ESTABLISHED USE

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Note:
Comments should be sent to the EMEA, SWP Secretariat (fax no +44 20 74 18 86 13), before the end of May 2003.
NOTE FOR GUIDANCE ON THE NON-CLINICAL DOCUMENTATION FOR MEDICINAL PRODUCTS WITH WELL ESTABLISHED USE

1 INTRODUCTION

1.1 Objective of the guideline

This note for guidance should be read in light of the general requirements set out in Directive 2001/83/EC, Art 10 (1)(a)(ii) and its Annex I Part 3/4.

A number of medicinal products marketed in the EU 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 with such products and to facilitate a continuous safety assessment, it is necessary to state the minimum requirements for non-clinical testing. Results of clinical trials as well as post-marketing experience gained by widespread clinical use in man contribute to the body of knowledge. A blind repetition of animal experiments should be avoided.

Non-clinical investigations may be needed if a safety concern is recognised or suspected. The lack of some specific non-clinical studies may also pose a safety concern.

The use of inter-company data sharing arrangements on essentially similar active ingredients is encouraged.

1.2 Scope of the guideline

The guideline applies to medicinal products with well-established use, specifically to conventional organic active substances of defined structure. Different considerations may apply to other types of actives substances such as herbals.

2 NON-CLINICAL DOCUMENTATION

2.1 General Considerations

Non-clinical investigations are normally not required when there is sufficient clinical experience to establish clinical efficacy and safety as outlined in Annex I Part 3/4 to Directive 2001/83/EC.

However, non-clinical investigations may be necessary to study effects that are difficult to detect clinically.
2.2 Individual Study Types

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. Non-clinical investigations may be necessary to study effects that are difficult or even impossible to detect clinically. These effects could include reproduction toxicity, genotoxicity and carcinogenicity.

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.

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.

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 pharmacological properties?
- 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.

2.3 Impurities

Data on the impurity profile of the currently marketed old active substance and on that of the test material used in toxicity studies should be reviewed in light of ICH and CPMP requirements on impurities, degradation products and residual solvents.

4 NON-CLINICAL OVERVIEW

The expert should discuss whether it is possible to replace the results of pharmacological and toxicological tests by detailed references to published scientific literature and, in so doing, to demonstrate that the active substance(s) have a well established use and an acceptable level of safety. Particular attention should be paid to any missing information and justification should be given why demonstration of an acceptable level of safety can be supported although some studies are of insufficient quality or lacking. The importance of deviations from the current state-of-the-art (e.g. GLP compliance) for the interpretation of study results should also be discussed.

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