



European Medicines Agency

London, 26 June 2008
Doc. Ref. EMEA/CHMP/SWP/302413/2008

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

CONCEPT PAPER ON SINGLE DOSE/ACUTE TOXICITY

AGREED BY SAFETY WORKING PARTY (SWP)	June 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 June 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2008

The proposed guideline will replace NfG on Single Dose Toxicity 3BS1a

Comments should be provided to monika.croton@emea.europa.eu
Fax +44 20 7418 8613

KEYWORDS	acute toxicity, single dose toxicity, timing on non-clinical studies
-----------------	--

1. INTRODUCTION

The non-clinical safety studies needed to support human clinical trials of a given scope and duration are reflected in the ICH M3 guideline (CPMP/ICH/286/95) (ref. 1). Currently, this guideline recommends that the single dose (acute) toxicity for a pharmaceutical should be evaluated in two mammalian species prior to the first human exposure but that a dose-escalation study is considered as an acceptable alternative to simple dose design. Directive 2003/63/EC (ref.2) states that the single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the EMEA. The currently available guidance addressing marketing authorisation states that single dose toxicity testing must be conducted on at least two mammalian species and that two routes of administration should be used (ref. 4).

2. PROBLEM STATEMENT

The usefulness of specific acute (single dose) toxicity studies for the conduct of clinical studies has been questioned. In a recently published survey (ref. 3), it has been shown that data from acute toxicity studies are not used to support the planning and conduct of early clinical studies. It was found that data from acute toxicity studies were never used to select doses for first time in human studies, nor to determine parameters to monitor or for identification of target organs of toxicity. Furthermore, no additional information was gained from acute toxicity testing in a second species or via a second administration route. Data from short term repeated dose toxicity studies, which should be undertaken to support clinical studies in humans (ref. 1), were more informative and fulfilled the purposes of providing data for an adequate risk assessment and mitigation for participants in clinical studies.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Based on the review presented above, as well as from experience in assessing data to support an approval of a marketing authorisation, the CHMP Safety Working Party (SWP) concludes that data from specific acute toxicity studies have very limited value for the safety assessment of a medicinal product. The SWP further finds that acute toxicity endpoints can generally be evaluated in a well conducted repeat dose toxicity study, which includes administration of maximally tolerated doses. Data from such studies together with data from safety pharmacology for example, are more useful than acute toxicity studies for adequate information on the mitigation of risk for participants in clinical studies as well as to support marketing approval.

There may be situations when data addressing the risk with overdose in human may be needed, e.g. to support an out-patient study in a patient population at high risk for overdosing. If adequate information cannot be gained from available data sources (e.g. repeat dose toxicity studies and safety pharmacology studies), specific acute toxicity testing may be necessary, in a single species and using one relevant route of administration.

Thus, taking all available information into account, the SWP proposes that the need for acute toxicity studies in support of the conduct of clinical studies of in the EU should be reconsidered

Situations when single dose toxicity studies alone are used to support single dose administration to human (e.g. microdose, ref. 5), are exempted from this recommendation.

Vaccines and advanced therapies are also exempted from this revision as specific guidance is available or under development for such products.

4. RECOMMENDATION

The CHMP Safety Working Party recommends revising the existing guideline on single dose toxicity, to reflect conclusions based on currently available data on the limited usefulness of acute toxicity studies for the safety assessment of medicinal products.

5. PROPOSED TIMETABLE

It is anticipated that a draft of the revised guideline may be available within 6 months after adoption of this concept paper. The final guideline is planned to be published in the 2nd semester 2009.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this revised guideline will involve the Safety Working Party and the Committee on Herbal Medicinal Products.

7. IMPACT ASSESSMENT (ANTICIPATED)

The number of animals used for toxicity testing will be reduced by omitting the requirement for specific acute toxicity studies to support the conduct of clinical studies and marketing approval.

8. INTERESTED PARTIES

The pharmaceutical industry, animal welfare organisations and national competent authorities involved in safety assessment of pharmaceuticals.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. ICH M3 - Non-clinical studies for conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)
2. Legislative basis Commission Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use; Annex 1, part 4.
3. Robinson, S. et al., A European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development, Regul. Toxicol. Pharmacol. (2008), 50 (3): 345-52
4. Eudralex vol3; 3BS1a Single Dose Toxicity
5. Position Paper on the non-clinical safety studies to support clinical trials with a single micro dose (CPMP/SWP/2599/02).