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Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity'

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Background

The requirement for single dose studies in the Directive 2001/83/EC [9] is based essentially on the need to evaluate acute toxic reactions (see Question 1).

In June 2008, the CHMP issued a concept paper on single/acute toxicity [1], where it was recommended to revise the existing guideline on single dose toxicity [2].

Following additional discussions within the Safety Working Party of the CHMP (SWP), it has been agreed to remove the guideline on single dose toxicity [2]. The guideline ICH M3 [4] and the guideline on repeat dose toxicity [8] are the main regulatory and scientific basis for supporting this approach.

This decision is based mainly on the recognition that data obtained in traditional single dose toxicity studies are of limited value and on the fact that information on acute toxicity can be obtained in other types of toxicity studies.

In addition, removing the need for traditional single dose toxicity studies will reduce the number of animals used for testing and will contribute to animal welfare (3R's principles) [3].

The aim of this Q&A document is to provide clarification on the views of the SWP and on how to obtain information on acute toxicity from other sources.

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Questions and answers

Question 1. In available guidance and discussion papers, both single dose toxicity and acute toxicity are mentioned. Is there a difference?

Single dose toxicity relates to a study design aimed at obtaining acute toxic effects after administration of a single dose of a substance.

Acute toxicity generally refers to adverse effects observed after a short time following administration (within 24 hours) of a single or multiple doses of a substance.

Traditionally, acute toxicity information has been obtained from single dose toxicity studies, with the objective to determine the mode of death and a quantitative evaluation of the approximate lethal dose.

However, the current view is that adequate information on acute toxicity can be obtained from other sources than specific single dose toxicity studies (see below).

Question 2. What is the difference between a single dose toxicity study and an "extended" single dose toxicity study?

Single dose toxicity study is the term used for traditional study design. Clinical observations are recorded regularly for a period of observation of at least 14 days after a single administration of high doses of a substance (up to sub-lethal or lethal doses). An autopsy with macroscopic observation (and histological examination of relevant macroscopic findings) is performed on animals dying during the observation period and at the end of the study. Additional measurements such as laboratory testing (e.g. haematology, clinical chemistry), toxico-kinetics, histological examination are not routinely included in this design.

The "extended" single-dose toxicity study (term used in the guideline ICH M3 R2) should be designed to evaluate haematology, clinical chemistry, necropsy, and histopathology data after a single administration, with further evaluations conducted 2 weeks later to assess delayed toxicity and/or recovery. Compared with the single dose study described in the first paragraph, the toxicological information obtained from an extended single dose toxicity study, such as target organ toxicity, is more extensive and similar to data obtained from a repeat-dose study.

Question 3. What sources other than single dose toxicity studies can be used to obtain information on acute toxicity?

In most cases, acute toxicity can be assessed based on data from appropriately conducted dose-escalation studies or short-duration dose-ranging studies. It is therefore important to plan for collection of data on acute toxicity when designing dose-escalation or short-duration dose-ranging studies. Data from one species, and following use of one route of administration are considered sufficient. Data can be obtained from non-GLP studies. A valuable source of information for predicting potential short-term safety in humans is also provided by safety pharmacology studies conducted according to the guidelines ICH S7A and S7B [5,6].

Question 4. Are there certain situations when single dose toxicity studies can be useful?

There are some specific situations, where single dose toxicity studies are the only support for human safety assessment. Those include certain types of exploratory clinical trial options [4], or for development within certain therapeutic fields such as for oncology products [7].

Single dose toxicity studies for such purposes follow the design of an “extended” single dose toxicity studies as describe above (Question 2). They should be undertaken according to GLP, and the principles described in the guideline for repeat dose toxicity [8] adhered to.

Single dose toxicity studies may be also conducted to provide a mechanistic understanding of a particular toxicological endpoint. In these cases, the study design is usually tailor-made.

However, acute toxicity studies are considered to be of very limited value (if any) for predicting consequences of overdose in humans.

References

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7. ICH Topic S 9 Nonclinical evaluation for anticancer pharmaceuticals, CHMP/ICH/646107/08.
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9. Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use; Annex I (Part I, Module 4: Non-clinical reports).