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Pharmacokinetics: Repeated Dose Tissue Distribution Studies

Step 5

NOTE FOR GUIDANCE ON PHARMACOKINETICS: REPEATED DOSE TISSUE DISTRIBUTION STUDIES
(CPMP/ICH/385/95)

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PHARMACOKINETICS:
REPEATED DOSE TISSUE DISTRIBUTION STUDIES

ICH Harmonised Tripartite Guideline

INTRODUCTION

A comprehensive knowledge of the absorption, distribution, metabolism and elimination of a compound is important for the interpretation of pharmacology and toxicology studies. Tissue distribution studies are essential in providing information on distribution and accumulation of the compound and/or metabolites, especially in relation to potential sites of action; this information may be useful for designing toxicology and pharmacology studies and for interpreting the results of these experiments.

In the EC, US and Japan, there has been a general agreement on the need to conduct single dose tissue distribution studies as part of the non-clinical programme. These studies often provide sufficient information about tissue distribution.

There has been no consistent requirement for repeated dose tissue distribution studies. However, there may be circumstances when assessments after repeated dosing may yield important information.

This paper provides guidance on circumstances when repeated dose tissue distribution studies should be considered and on the conduct of such studies.

CIRCUMSTANCES UNDER WHICH REPEATED DOSE TISSUE DISTRIBUTION STUDIES SHOULD BE CONSIDERED

1. When single dose tissue distribution studies suggest that the apparent half-life of the test compound (and/or metabolites) in organs or tissues significantly exceeds the apparent half life of the elimination phase in plasma and is also more than twice the dosing interval in the toxicity studies, repeated dose tissue distribution studies may be appropriate.

2. When steady-state levels of a compound/metabolite in the circulation, determined in repeated dose pharmacokinetic or toxicokinetic studies, are markedly higher than those predicted from single dose kinetic studies, then repeated dose tissue distribution studies should be considered.

3. When histopathological changes, critical for the safety evaluation of the test substances, are observed that would not be predicted from short term toxicity studies, single dose tissue distribution studies and pharmacological studies, repeated dose tissue distribution studies may aid in the interpretation of these findings. Those organs or tissues which were the site of the lesions should be the focus of such studies.

4. When the pharmaceutical is being developed for site-specific targeted delivery, repeated dose tissue distribution studies may be appropriate.

DESIGN AND CONDUCT OF REPEATED DOSE TISSUE DISTRIBUTION STUDIES

The objectives of these studies may be achieved using radiolabelled compounds or alternative methods of sufficient sensitivity and specificity.

Dose level(s) and species should be chosen to address the problem that led to the consideration of the repeated dose tissue distribution study.

Information from previous pharmacokinetic and toxicokinetic studies should be used in selecting the duration of dosing in repeated dose tissue distribution studies. One week of dosing is normally considered to be a minimum period. A longer duration should be selected when the blood/plasma concentration of the compound and/or its metabolites does not reach steady state. It is normally considered unnecessary to dose for longer than three weeks.

Consideration should be given to measuring unchanged compound and/or metabolites in organs and tissues in which extensive accumulation occurs or if it is believed that such data may clarify mechanisms of organ toxicity.

SUMMARY

Tissue distribution studies are an important component in the non-clinical kinetics programme. For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half life, incomplete elimination or unanticipated organ toxicity. The design and timing of repeated dose tissue distribution studies should be determined on a case-by-case basis.