DECISION

No. 4/29.02.2008

on approval of the Guideline on pharmacokinetics: tissue distribution studies after repeated doses

The Scientific Council of the National Medicines Agency, set up based on Minister of Public Health Order No. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 29.02.2008, in accord with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

DECISION

Single article. – The Guideline on pharmacokinetics: tissue distribution studies after repeated doses is approved, according to the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE

on pharmacokinetics: tissue distribution studies after repeated doses

CHAPTER I
Introduction

Art. 1. - (1) A comprehensive knowledge of the absorption, distribution, metabolism and elimination of a compound is important for the interpretation of pharmacology and toxicology studies.

(2) 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.

Art. 2. - (1) 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.

(2) These studies often provide sufficient information about tissue distribution.

Art. 3. - (1) However, there has been no consistent requirement for repeated dose tissue distribution studies.

(2) However, there may be circumstances when assessments after repeated dosing may yield important information.

Art. 4. - (1) This paper provides guidance on circumstances when repeated dose tissue distribution studies should be considered and on the conduct of such studies.

(2) This document is a translation and an adaptation into Romanian of the EC Guideline CPMP/ICH/385/95.

CHAPTER II
Circumstances under which repeated dose tissue distribution studies should be considered

Art. 5. - The circumstances under which repeated dose tissue distribution studies should be considered are as follows:

a) 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.

b) 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.

c) 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.

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

CHAPTER III
Design and conduct of repeated dose tissue distribution studies

Art. 6. - The objectives of these studies may be achieved using radio labelled compounds or alternative methods of sufficient sensitivity and specificity.

Art. 7. - Dose level(s) and species should be chosen to address the problem that led to the consideration of the repeated dose tissue distribution study.

Art. 8. - (1) Information from previous pharmacokinetic and toxicokinetic studies should be used in selecting the duration of dosing in repeated dose tissue distribution studies.

(2) One week of dosing is normally considered to be a minimum period.

(3) A longer duration should be selected when the blood/plasma concentration of the compound and/or its metabolites does not reach steady state.

(4) It is normally considered unnecessary to dose for longer than three weeks.

Art. 9. – 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.

CHAPTER IV
Conclusions

Art. 10. - (1) Tissue distribution studies are an important component in the non-clinical kinetics programme.

(2) 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.

(3) 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.

(4) Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies.

(5) The repeated dose studies may be most appropriate for compounds which have an apparently long half life, incomplete elimination or unanticipated organ toxicity.

(6) The design and timing of repeated dose tissue distribution studies should be determined on a case-by-case basis.