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Committee for Medicinal Products for Human Use (CHMP)

# Concept paper on the development of guidance on the non-clinical evaluation of radiopharmaceuticals

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# 1. Introduction

The development and marketing authorisation of radiopharmaceuticals are regulated by the Directive 2001/83/EC for medicinal products for human use. Radiopharmaceuticals include radiodiagnostic as well as radiotherapeutic agents. Currently, there is no detailed guidance available specifically addressing non-clinical testing of radiopharmaceuticals other than the regulation of dosimetry (Directive 96/29/Euratom and 97/43/Euratom). Therefore, in addition to the general non-clinical requirements described in ICH M3(R2), ICH S9 and ICH S6(R1), the need for guidance expanding on the principles for non-clinical data generation in support of the specific clinical uses of radiopharmaceuticals was deemed appropriate.

# 2. Problem statement

ICH M3(R2) provides general guidance on the nonclinical safety studies recommended to support human clinical trials. However, since the replacement of "Note for Guidance on Radiopharmaceuticals" (3AQ20a) with the "Guideline on Radiopharmaceuticals" (EMEA/CHMP/QWP/306970/2007), no guidance is available to specifically support non-clinical development of this type of medicinal products. Radiation is an inherent – and intended - property of this class of compounds and, from this perspective, safety is considered to be appropriately addressed by dosimetry. Therefore, it is not anticipated to discuss the non-clinical safety assessment of the radionuclide in detail in the new guidance. However, due to the conjugated design of radiopharmaceuticals (i.e. radionuclide linked to a cold ligand, possibly with a linker in between them and/or chelators) the safety of each individual “cold” part needs to be evaluated. The cold moiety may be an already known/ characterised part of the construct or a new chemical or biological requiring a complete characterisation. In addition, radiopharmaceuticals developed in recent years show a large variety of clinical uses ranging from single to multiple administrations.

The aspects outlined above give rise to specific considerations regarding the extent and type of the non-clinical data package to support clinical use and marketing authorisation of radiopharmaceuticals. Specific approaches will avoid the unnecessary use of animals, allowing an optimal use of resources and, ultimately, facilitate the progression of these medicinal products into clinical use.

# 3. Discussion (on the problem statement)

Scientific innovation and the ability to generate highly-targeted ligands has led to the development of many new different types of radiopharmaceuticals. These radiopharmaceuticals are often prepared in small-scale preparations and at non-industrial sites without the intention to receive a marketing authorisation (e.g. PET tracers). In addition, mainly for radiodiagnostics, single application as well as very short clinical trial duration can be anticipated. Like for other medicinal products, the same principles of safety evaluation should apply prior their use in humans.

However, in cases of well-known molecular structures and/or microdoses with negligible pharmacological activity in humans, a reduced non-clinical development might be justified even for marketing authorisation applications.

In the framework of currently available guidelines (such as ICH M3(R2), ICH S6(R1), ICH S9 and the EMA Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products) the new guidance document will provide basic considerations for a non-clinical data package taking into account the specific features of radiopharmaceuticals.

Namely, the following aspects of the radiopharmaceutical with regard to the non-clinical evaluation will be addressed:

- Extent of pharmacological activity of the cold part (in vitro and in vivo); whether the cold part of the radiopharmaceutical is a known substance or not
- Outcome of biodistribution/ADME studies for the cold part(s) of the radiopharmaceutical including extent of off-target binding where appropriate
- Types of clinical settings for the radiopharmaceutical such as:
    - First-in-human clinical trial
    - Dosing frequency, microdose use (in the case of radiodiagnostics)
- Marketing authorisation intended
- GLP requirements

Given the wide variety of product types and clinical contexts of use in the field of radiopharmaceuticals, generally-applicable development principles will be outlined taking into account the above mentioned aspects.

## 4. Recommendation

The Safety Working Party (SWP) of the CHMP recommends the issuing of guidance on guiding principles for the non-clinical development of radiopharmaceuticals. The paper will be based on current guidelines and the scientific review of the different intended uses of radiopharmaceuticals including radiodiagnostics as well as radiotherapeutics. Focus will be on opportunities to targeted non-clinical programs according to specific development settings and product types.

## 5. Proposed timetable

It is anticipated that draft guidance will be available 6 month after the end of the public consultation phase of this concept paper.

## 6. Resource requirements for preparation

The preparation of this guidance document will be led by the Safety Working Party of the CHMP.

## 7. Impact assessment (anticipated)

The new guidance is anticipated to provide an updated view on the non-clinical evaluation of radiopharmaceuticals complementing currently available guidelines.

## 8. Interested parties

Pharmaceutical industry developing radiopharmaceuticals (radiotherapeutics as well as radiodiagnostics), consultants, EU national competent authorities and other regulatory agencies. Research Organisations and Societies being involved in the development and use of radiopharmaceuticals.

# 9. References to literature, guidelines, etc.

CHMP/SWP/28367/07:"Guideline on strategies to identify and mitigate risks for first in human clinical trials with investigational medicinal products". (currently under revision)

EMEA/CHMP/QWP/306970/2007:"Guideline on Radiopharmaceuticals"

Eudralex 3AQ20a:"Note for guidance on radiopharmaceuticals" (in force until 2009)

ICH S6(R1) (December 2011):"Preclinical safety evaluation of biotechnology–derived pharmaceuticals".

ICH S9 (Oct 29, 2009):"Nonclinical evaluation for anticancer pharmaceuticals".

ICH M3(R2) (Dec. 2009):"Non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals".