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Guideline on the non-clinical requirements for radiopharmaceuticals

Draft

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This guideline replaces the non-clinical part of the Note for Guidance on Radiopharmaceuticals/ Eudralex 3AQ20a and 3Q21a. For quality aspects, 3AQ20a has been replaced by the 'Guideline on Radiopharmaceuticals' (EMEA/CHMP/QWP/306970/2007).

Comments should be provided using this template. The completed comments form should be sent to SWP-H@ema.europa.eu

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Executive summary

This guideline describes the non-clinical data that need to be submitted in relation to the non-radioactive part of radiopharmaceuticals, in the context of applications for marketing authorisations or clinical trials.

1. Introduction (background)

The need for a guidance paper focusing specifically on the non-clinical testing requirements for radiopharmaceuticals has emerged since currently there is no detailed guidance available. Therefore, in addition to the general non-clinical requirements described in e.g. ICH M3(R2), ICH S9 and ICH S6(R1), the principles for non-clinical data generation in support of the specific clinical uses of radiopharmaceuticals are laid down in this guideline.

2. Scope

This guideline covers radiodiagnostics as well as radiotherapeutics, and provides guidance for a targeted approach to assess pharmacology and safety of the non-radioactive part of a radiopharmaceutical. The principles explained in this document address the non-clinical evaluation as prerequisite for a clinical trial authorisation as well as for a marketing authorisation application. According to the categorisation of the "Guideline on radiopharmaceuticals" (EMEA/CHMP/QWP/306970/2007) "ready to use" radiopharmaceuticals will be covered. However, some of the principles outlined in this guideline might also apply to the non-radioactive component of so called “kits” and non-radioactive chemical precursors. The toxicity induced by the radiation of the radionuclide (which for radiotherapeutics is the wanted property) is not addressed in this guideline, since radiation induced clinical toxicity is covered by Directives of EURATOM (Directive 2013/59/Euratom).

3. General principles

Scientific innovation and the ability to generate highly-targeted ligands led to the development of many different types of radiopharmaceuticals which show a large variety of clinical uses. They may be used as radiodiagnostics for scintigraphy imaging, for measurement of biodistribution or as radiotherapeutics administered to humans only once or with a low frequency of repeated administrations at doses lacking a measureable pharmacological effect. One common feature is that many of these radiopharmaceuticals are prepared in small-scale quantities for the use in exploratory trials and will not undergo a full development programme aiming to marketing authorisation. However, like for other medicinal products, the same principles of safety evaluation should apply prior to the use of radiopharmaceuticals in humans in clinical trials as well as for marketing authorisation purposes. Therefore, a non-clinical risk assessment in line with the respective legislation is needed prior to the first in human (FIH) administration of a radiopharmaceutical and subsequent clinical development. The risk assessment will in general be covered in the non-clinical programme and will influence the risk mitigation plan included in the clinical study protocol.

In the case of radiopharmaceuticals it has to be considered that they represent a special class of pharmaceuticals due to their conjugated design and radiolabel. They are composed of a non-radioactive, “cold”, part with a radionuclide attached. The radionuclide may be linked to the non-radioactive ligand by a linker and/or chelators also called “carrier”. In the following, all possible forms of the non-radioactive moiety will be named “non-radioactive part” throughout the paper.

General guidance, especially for the timing and duration of nonclinical safety studies, can be received from ICH M3(R2) EMA/CPMP/ICH/286/1995. However, in many cases knowledge of the non-clinical characteristics and a clinical experience already exists for the non-radioactive part. In common with any other submission the presence of published or clinical data may obviate the need to conduct the complete non-clinical programme in line with ICH M3(R2). This would also contribute to a reduction of animal use in line with the principles of 3Rs. Factors that are important to consider are the level of evidence on the pharmacological properties and toxicological characteristics of the non-radioactive part, the anticipated mass dose of the radiopharmaceutical in the clinical trial or for marketing authorisation and the duration of treatment.

The need for physiological distribution studies for the sole purpose of ensuring quality of the investigational radiopharmaceutical should be avoided by any means. Instead, appropriate characterisation of the relevant product parameters is expected by state-of-the art methods.

4. Legal basis

This guideline has to be read in conjunction with:

- Directives of the European Atomic Energy Community (EURATOM) (Directive 2013/59/Euratom).
- Directive 2001/83/EC, as amended in particular Directive 2001/83/EC Art 10(4) and Part II of the Annex I of Directive 2001/83/EC, as amended.
- Directive 2010/63/EU on the protection of animals used for scientific purposes.
- Directive 2004/10/EC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.
- CHMP/SWP/28367/07 (July 2017): "Guideline on strategies to identify and mitigate risks for first in human and early clinical trials with investigational medicinal products".
- EMEA/CHMP/QWP/306970/2007:"Guideline on Radiopharmaceuticals".
- 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".
- ICH S7A (June 2001): “Note for guidance on safety pharmacology studies for human pharmaceuticals”.

5. "Targeted" non-clinical evaluation of radiopharmaceuticals

5.1. Basic considerations

Toxicity of radiopharmaceuticals may be driven by the non-radioactive as well as the radioactive components of the radiopharmaceutical. The radiation emitted by the radionuclide is a wanted property of radiotherapeutics. In the case of radiodiagnostics, however, radionuclides with much lower emission of radiation and with usually a very short physical half-life are used.

For characterisation of a new radiopharmaceutical, a biodistribution study in animals is usually conducted with the radiolabelled compound allowing to measure tissue distribution and elimination. In addition, calculation of dosimetry in order to predict the radioactive exposure in humans and to mitigate radiation induced toxicity, is performed. However, as mentioned in the scope, recommendations for the non-clinical development of the non-radioactive part are the focus of this guideline.

For different scenarios as outlined below, where evidence needs to be only partly generated, a targeted (in the sense of a reduced) non-clinical programme for the non-radioactive part of the radiopharmaceutical can be considered:

a) Radionuclide changed in a known radiopharmaceutical: only the radionuclide is changed and the non-radioactive part was already used in numerous clinical trials or even authorised with other radionuclides. In this case, evidence should be provided by the applicant on the availability and results of the non-clinical testing already performed for the non-radioactive unchanged part of the formerly used radiopharmaceutical(s). Reference in the dossier to previous applications with the investigational radiopharmaceutical may be possible in cases the applicant is the same or has obtained permission to use non-clinical data of other applications. The use of literature or other publicly available data is possible but should be of good scientific quality and justified by the applicant.

   In these cases a flexible, but targeted approach is required to identify possible remaining gaps in the safety information for the new investigational radiopharmaceutical especially with focus on pharmacology.

b) Radionuclide added to a known non-radioactive pharmaceutical: information is needed that the radiolabelling does not significantly alter the pharmacology of the whole molecule when the radionuclide is replacing an existing non-radioactive atom.

c) Minimal change of the non-radioactive part of a radiopharmaceutical: this could be a small change in the amino acid sequence of a peptide or another small change in the molecular structure of the non-radioactive part of a known radiopharmaceutical, intended for example to improve stability. For this new but structurally closely related entity, the applicant should bridge from existing non-clinical data of the known radiopharmaceutical and address possible changes in its pharmacology and safety in order to allow for a possible reduced non-clinical programme.

The microdose approach described in ICH M3(R2) is reflecting single as well as multiple administrations up to five including a wash out period and implies a reduced non-clinical testing in which safety assessment in a single (rodent) species can suffice.

Due to possible peculiarities as outlined above a reduced non-clinical testing could be anticipated for additional scenarios. For example at dosages outside microdose toxicities related to the non-radioactive part are usually still minor compared to radiation-induced toxicities of a radiotherapeutic in oncology treatment. The amount of non-clinical data needed for the non-radioactive part is therefore dependent on risk–benefit considerations and exposure levels to the non-radioactive part. Hence, also in these cases a study in one species could be considered to be sufficient.

The aspects outlined above give rise to specific considerations regarding the extent and type of the non-clinical data package to support clinical trial 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. In this regard, such a targeted non-clinical programme represents an opportunity for limiting animal testing in accordance with the 3Rs principles and is strongly encouraged.

However, the spectrum of possible combinations of molecules to construct a radiopharmaceutical in addition to the possible therapeutic targets of radiopharmaceuticals is very broad. Therefore, a flexible approach on a case by case basis might still be needed despite this guideline.

5.2. Non-clinical safety programme for a known or minimally changed non-radioactive part of a new radiopharmaceutical

In case no reference is possible to previous applications or other public data using the identical non-radioactive part of the investigational radiopharmaceutical, the reduced non-clinical programme outlined below for a known or minimally changed non-radioactive part should be considered.

5.2.1. Pharmacology

The appropriate characterisation of pharmacology of the non-radioactive part alone is also expected in the case where the non-radioactive part of an already known radiopharmaceutical is claimed to be minimally changed. Emphasis should be laid on in vitro target/ receptor profiling. The selectivity and specificity of the non-radioactive part as well as secondary pharmacodynamics, defined as effects on other than the desired therapeutic targets, should be critically evaluated and documented. Measureable pharmacodynamic effects are normally not expected to be seen from the non-radioactive part of most radiopharmaceuticals for diagnostic or therapeutic purposes. However, evidence for the absence of pharmacodynamic effects is expected, and should be supported by appropriate data.

If no data are provided, the applicant has to justify the absence of in vitro/in vivo pharmacology data even in the case of a minimal change to the molecule.

5.2.2. Pharmacokinetics

For such minimally changed radiopharmaceuticals information on in vivo stability should be available. In addition, the biodistribution study performed in healthy animals of a relevant species including dosimetry should be thoroughly evaluated to detect any change in biodistribution and target organs related to the non-radioactive part compared to the former, known molecule. For radiotherapeutics, the study may be performed in an animal model of disease, if appropriate, to support that the targeted area / organ will still be reached adequately.

5.2.3. Toxicology

Main focus should be laid on the evaluation of the target organs of biodistribution and possible persistence of the modified non-radioactive part possibly leading to so far unknown toxic effects even if the change is claimed to be minimal. A biodistribution study in one species with single application and integrated measurement of toxicity endpoints can be generally considered sufficient. If off target binding is likely to be minimal from the results of the dosimetry study, histopathological examination may be limited to target organs.

In the case of an exploratory trial with intended clinical dose of the radiopharmaceutical being a microdose according to approach 1 or approach 2 as outlined in ICH M3(R2) (see also 5.3) and if, in addition, the absence of pharmacological activity of the non-radioactive part could be demonstrated, such a biodistribution study could be waived.

5.3. Non-clinical safety programme of a new radiopharmaceutical using microdose

The majority of clinical trials performed with radiopharmaceuticals falls under the scope of exploratory trials. Therefore, the microdose approach as outlined in ICH M3(R2) can be applied. According to the definition given there, a microdose is a total dose ≤ 100 µg (no inter-dose interval limitations) and total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (approach 1), or a total cumulative dose ≤ 500 µg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted half-lives) and each dose ≤ 100 µg and each dose ≤ 1/100th of the NOAEL and ≤ 1/100th of the pharmacologically active dose (approach 2). Due to differences in molecular weights between biologicals and chemicals, and due to the fact that pharmacological and toxicological effects are usually driven by the molar amount and not by the mass, a maximum dose above 100 µg based on molar amount can be accepted for high molecular weight molecules taking into account the potency of the molecule (approach 1 for biologicals). Approach 2 may be less relevant for biologicals with a long elimination half-life.

Accordingly, the minimal requirements for the non-clinical development of a radiopharmaceutical carrying a new non-radioactive part using the microdose approach are outlined below. This non-clinical package is usually also considered sufficient for marketing authorisation applications using the same dosing regimen.

5.3.1. Recommendations for Radiodiagnostics

In most cases microdose approach 1 of ICH M3(R2) will be used for radiodiagnostics since no pharmacological effect is intended and only a very small mass dose is administered after single administration.

5.3.1.1. Pharmacology

Radiodiagnostics are not intended to exert pharmacological activity, but evidence for the absence of pharmacological activity of the non-radioactive part should be provided. In this context, in vitro target/ receptor profiling is usually sufficient.

5.3.1.2. Pharmacokinetics

A biodistribution study including dosimetry should be performed with a single dose of the radiodiagnostic. Information on in vivo stability, distribution and elimination should be available to allow estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for distribution and persistence of the radiodiagnostic. If relevant, information should be provided on absorption and biotransformation.

5.3.1.3. Toxicology

According to microdose approach 1 outlined in ICH M3(R2), the results of an extended single dose toxicity study using the intended route of administration (usually i.v. route for radiodiagnostics), with toxicokinetic data should be available for the non-radioactive part.

When using the microdose approach 2, a repeat dose study for at least 7 days would be expected. A study of shorter duration may be considered on a case by case basis.

For both approaches a study in one species, usually rodent, can be generally considered sufficient.

In the extended single dose, as well as in repeat dose studies, haematology, clinical chemistry, necropsy data and histopathology will be fully evaluated.

Investigation of local tolerance, where applicable, should be done as an integral part of the extended single dose study.

5.3.1.4. Genotoxicity

Genotoxicity studies are not recommended. However, if e.g. data on structure-activity relationship (SAR) assessment are available they should be submitted.

5.3.2. Recommendations for Radiotherapeutics

The same testing strategy as outlined above for radiodiagnostics will also apply for new radiotherapeutics when using the microdose approach. The only additional aspect to consider in these cases is that the dosimetry study might be performed in an animal model of disease, if appropriate, to support that the targeted area will be reached adequately.

5.4. Non-clinical safety programme of a new radiopharmaceutical using single sub-pharmacological or pharmacologically active doses

The minimal requirements for the non-clinical development of a radiopharmaceutical carrying a new non-radioactive part using single sub-pharmacological (but above microdose) or pharmacologically active doses are outlined below. This non-clinical package is usually also considered sufficient for marketing authorisation applications using the same dosing regimen.

5.4.1. Recommendations for Radiodiagnostics

5.4.1.1. Pharmacology

Radiodiagnostics may exert pharmacological activity at doses above a microdose. The pharmacological activity of the non-radioactive part or its absence has to be shown by the applicant. In this context, in vitro target/ receptor profiling is usually sufficient.

5.4.1.2. Pharmacokinetics

A biodistribution study including dosimetry should be performed with a single dose of the radiodiagnostic. Information on in vivo stability, distribution and elimination should be available to allow estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for distribution and persistence of the radiodiagnostic. If relevant, information should be provided on absorption and biotransformation.

5.4.1.3. Toxicology

Generally, extended single dose toxicity studies in both a rodent and non-rodent should be available using the intended clinical route of administration with toxicokinetics, haematology, clinical chemistry, necropsy data and histopathology as evaluated endpoints.

If the non-radioactive part of the radiopharmaceutical does not show pharmacological activity at the intended clinical dose only one relevant species, usually rodent, is sufficient.

Investigation of local tolerance, where applicable, should be done as integral part of the extended single dose study.

In addition, the standard core battery for safety pharmacology may be included as integral part of the extended single dose toxicity study.

5.4.1.4. Genotoxicity

For the genotoxicity testing of the non-radioactive part of the radiodiagnostic, if not a biotechnology derived product, e.g. an Ames test, would be expected.

5.4.2. Recommendations for Radiotherapeutics

The same testing strategy as outlined above for radiodiagnostics will apply for new radiotherapeutics in the case using single sub-pharmacological or pharmacologically active doses are used. The only additional aspect to consider in these cases is that the dosimetry study might be performed in an animal model of disease, if appropriate, to support that the targeted area will be reached adequately.

5.5. Non-clinical safety programme for radiopharmaceuticals using multiple dosing

In absence of complete clearance between administration of multiple doses in the therapeutic range standard ICH M3(R2) requirements should be followed for the non-radioactive part. There are no general differences in this respect between the expected non-clinical data package for radiodiagnostics and radiotherapeutics. In the case of a radiotherapeutic used in oncology, ICH S9 should be considered if applicable.

5.5.1. Pharmacology

Pharmacological activity of the non-radioactive part or its absence has to be shown by the applicant. In this context, in vitro target/ receptor profiling is usually sufficient.

5.5.2. Pharmacokinetics

A biodistribution study including dosimetry after administration of the whole radiodiagnostic should be performed. Information on in vivo stability, distribution and elimination should be available to allow estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for distribution and persistence of the radiodiagnostic.

5.5.3. Toxicology

In the case of complete washout between dosing an extended single dose toxicity study in both a rodent and non-rodent should be available using the intended clinical route of administration with toxicokinetics, haematology, clinical chemistry, necropsy data and histopathology as evaluated endpoints. If the non-radioactive part of the radiopharmaceutical does not show pharmacological activity at the intended clinical dose only one relevant species, usually rodent, is sufficient.

Investigation of local tolerance, where applicable, should be done as an integral part of the extended single dose study.

In addition, the standard core battery for safety pharmacology may be included as integral part of the extended single dose toxicity study.

5.5.4. Genotoxicity

For the genotoxicity testing of the non-radioactive part of the radiotherapeutic, if not a biotechnology derived product, e.g. an Ames test would be expected. In the case of a radiotherapeutic used in oncology, an Ames assay may not be required for advanced cancers where ICH S9 is applicable.

5.5.5. Reproductive toxicity and Carcinogenicity

For radiopharmaceuticals carrying a radionuclide with a high emission of radiation and a long half-life such as anticancer drugs, carcinogenicity and reproductive toxicity studies could be waived since the radiation emission of these medicinal products is causing well known DNA damage with consequences for carcinogenicity and reproductive toxicity. However, the respective risk should be outlined in the product labelling.

Reproductive toxicity and a carcinogenicity studies for the non-radioactive part alone are usually not required unless there is concern due to the duration of the treatment while the radiation emission of the attached radionuclide is low.

6. GLP

It is generally expected that non-clinical safety studies are carried out in conformity with the principles of GLP (Dir 2004/10/EC), but also principles of animal welfare should be applied. However, it is recognized that, due to the specific characteristics of radiopharmaceuticals, it might not be possible to conduct every study in conformity with GLP, in particular when the radiation emission is high. Frequently, such non-GLP results come from biodistribution and dosimetry studies. Therefore, in practice the relevant safety aspects are usually sufficiently addressed by conducting the non-clinical studies with the non-radioactive part of the radiopharmaceutical according to GLP.

If a pivotal non-clinical safety study has not been conducted in conformity with the GLP principles, a scientific justification should be submitted. This justification should also address the potential impact of the non-compliance on the reliability of the safety data. In any case the study should run according to the principles of GLP as close as possible. Detailed documentation of the study conduct, results and archiving of data should be ensured. In addition, the study should be performed in accordance with a prospectively designed study protocol.

7. Definitions

DNA - Deoxyribonucleic Acid

EURATOM - European atomic energy community

FIH – First in human

GLP – Good laboratory practice

NOAEL – No observed adverse effect level