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GUIDELINES

Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU

Alfons Verbruggen · Heinz H. Coenen · Jean-Robert Deverre · Denis Guilloteau · Bengt Langstrom · Piero A. Salvadori · Christer Halldin

Abstract The purpose of this guideline is to help investigators by giving an overview of relevant current EU requirements concerning the quality of starting materials and final drug products (the radiopharmaceuticals), the non-clinical safety studies and dosimetry considerations whilst designing a human clinical trial which includes the use of radiopharmaceutical compounds.

Keywords Radiopharmaceuticals · Early phase · Clinical trials · Regulations · Quality requirements · Toxicology · Dosimetry

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A. Verbruggen (✉)
Laboratory of Radiopharmacy,
Onderwijs en Navorsing 2, Box 821, Herestraat 49,
3000 Leuven, Belgium
e-mail: Alfons.Verbruggen@pharm.kuleuven.be

H. H. Coenen
Institut für Neurowissenschaften und Biophysik
INB-4 (Nuklearchemie) Forschungszentrum Jülich,
52425 Jülich, Germany

J.-R. Deverre
CEA Service Hospitalier Frédéric Joliot,
Orsay, France

D. Guilloteau
INSERM Unité 619 CHRU de Tours,
Université François-Rabelais de Tours,
Tours, France

B. Langstrom
Radiopharmaceutisk organisk kemi, UPPSALA UNIVERSITET,
Institutionen för biokemi och organisk kemi,
Uppsala, Sweden

P. A. Salvadori
Radiopharmaceutical Chemistry Department,
CNR Institute of Clinical Physiology,
Pisa, Italy

C. Halldin
Karolinska Institutet, Department of Clinical Neuroscience,
Stockholm, Sweden

Introduction

In Europe, radiopharmaceutical compounds are considered a special group of medicines. Therefore, their preparation and use are regulated by a number of EU directives, regulations and rules that have been adopted by member states. The rate of adoption of directives varies between countries and each member state may introduce changes, provided the general scope and limits of each directive are maintained. Specific articles have been set concerning radiopharmaceuticals that are to receive marketing authorisation (MA) or are prepared starting from licensed products (radionuclide generators, labelling kits and precursor radionuclides).

However, radiopharmaceuticals may also be prepared outside the MA track or used outside the indications they have been registered for. Small-scale preparations in both industrial sites (GMP licensed facilities) and non-industrial sites (hospital pharmacies, nuclear medicine departments, PET centres) indeed represent an important segment of application. Although at this moment still non-binding documents, the 'Guidelines on Good Radiopharmacy Practice (GRPP)' issued by the Radiopharmacy Committee of EANM [1] and the 'PIC/S guide to good practices for preparation of medicinal products in healthcare establishments' edited by the Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Co-operation Scheme [2] may be useful references for quality assurance into the small-scale

preparation of radioactive pharmaceuticals and their non-radioactive precursors.

Different situations may be faced with respect to the nature and intended application of radiopharmaceuticals within a clinical trial or depending on the fact whether the relevant product is or is not described in a monograph of a pharmacopoeia or approved following a MA. From a practical point of view the following situations might occur:

- Licensed radiopharmaceutical products used within their authorised indications,
- Licensed radiopharmaceutical products used outside their authorised indications,
- Radiopharmaceuticals having established clinical use that are prepared in accordance with approved regulations and meet approved quality requirements (e.g. as described in a monograph of a pharmacopoeia),
- New radiopharmaceuticals or tracer agents outside the previous categories.

Users must comply with different requirements as a function of such a distinction and the application of good clinical and/or pharmaceutical practice (GCP and GPP) standards, which may have been implemented at different levels in some European countries.

Product quality and safety during clinical trials are a crucial part of GCP. In the case of radioactive medicines, radiation burden (dosimetry) also deserves a careful analysis before any experimental trial is performed.

In the EU, a clinical trial application (CTA) needs to be submitted to the responsible national authority and the ethical committee involved before any research in humans may be started. Such an application must include information on any anticipated safety risk, based on results of pharmacologic and toxicological data collected during studies of the drug in animals and genotoxicity tests [3]. Quality assurance during the manufacturing of the medicine should be maintained throughout the production phase and non-clinical safety studies should be adequate at any stage to characterise potential adverse effects under the condition of the trial. For details on the information to be provided in a CTA, see the Eudralex documents 'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities' [4] and 'Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials'[5].

The present guideline provides investigators with an overview of EU requirements concerning quality of starting materials and finished drug products, non-clinical safety studies and dosimetry considerations whilst designing a human clinical trial which includes the use of radiopharmaceutical compounds. Where cited in this document, the EU regulations are written in italics. Most of the existing rules are, however, intended for medicinal products in general and not specific for radiolabelled compounds. Moreover, some of the current regulations even do not take into account the special characteristics of radiopharmaceutical compounds, such as the short physical half-life of the radionuclide. However, it is not the goal of the present guideline to propose at this stage more adapted rules which could facilitate early phase clinical studies with radiopharmaceuticals, but to guide the reader through the extensive existing legislation. Proposals for more appropriate regulations will be the subject of a follow-up paper from the Drug Development Committee of the European Association of Nuclear Medicine.

In addition, it should be noted that this guideline has no binding value and must be considered as reference only. Investigators must consult their competent authority to verify specific national requirements and regulations.

Finally, this guideline does refer only to radiopharmaceuticals used in clinical trials for diagnostic procedures. On the other hand, most of the regulations discussed are valid also for tracer agents without marketing authorisation used by a physician, not in the framework of a clinical trial, but for a diagnosis in a patient (e.g. ^{18}F-fluoromethylcholine) on his own responsibility, e.g. in the form of a magistral preparation.

Purpose

This guideline thus aims to provide useful legal information for the conduct of early phase clinical trials with radiopharmaceuticals by summarising and explaining regulations regarding:

- quality requirements for starting materials of radiolabelled drug substances (radiolabelled active ingredients), e.g. the starting material tetraacetyl mannose triflate as a precursor of the drug substance ^{18}F-fluorodeoxyglucose,
- quality requirements for active ingredients of radiopharmaceuticals, e.g. medronic acid as an active ingredient of ^{99m}Tc-MDP injection,
- quality requirements for radiopharmaceuticals, e.g. ^{18}F-fluorodeoxyglucose injection as the finished drug product,
- minimal range of toxicological data,
- dosimetry data.

Definitions as described in Eudralex documents [6] and in the European Pharmacopoeia [7]

Directives are rules addressed by the EU commission to the Member States to be translated into the respective national

legislation and effectively implemented. Directives are mandatory.

Guidelines are not mandatory but recommendations for the effective implementation of Directives by the Member States.

European *regulations* are mandatory in all countries, being directly applied without translation into the national legislation.

Radiopharmaceutical means any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

Finished product means a medicinal product which has undergone all stages of production, including packaging in its final container.

Manufacture means all operations of purchase of materials and products, production, quality control, release, storage, distribution of medicinal products and the related controls.

Starting material means any substance used in the production of a medicinal product, but excluding packaging materials.

A *radionuclide precursor* is any radionuclide produced for the radiolabelling of another substance prior to administration.

A *chemical precursor* can be an 'active pharmaceutical ingredient' or an 'API starting material'.

An *active pharmaceutical ingredient* (API; synonyms: *active ingredient*, *drug substance*, *medicinal substance*) is any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

With respect to radiopharmaceutical preparations, a recent Guideline on Radiopharmaceuticals states that *the daughter radionuclide of a radionuclide generator is to be considered as active pharmaceutical ingredient* [8]. As a logical consequence, every radionuclide used in the manufacture of a radiopharmaceutical without a purification of the final preparation before administration must be considered an API. The same guideline states that *for radiopharmaceutical kits, the active ingredient is considered to be that part of the formulation that is intended to carry or bind the radionuclide or to permit its binding. Radioactive drug substances are as a rule not isolated* [8].

An *API starting material* (or *active substance starting material*) is a raw or intermediate material that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be a material purchased on the market from one or more suppliers or produced by a manufacturer under a contract or a commercial agreement or produced in-house.

Excipients are the constituents of a pharmaceutical form apart from the active substance. Excipients include, e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances, etc., and the constituents of the outer covering of the medicinal products, e.g. gelatine capsules [9].

The term *investigational radiopharmaceutical* for early phase clinical trials refers to a radioactive pharmaceutical form of a substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Non-investigational medicinal products (NIMPs) are products which are not the object of investigation (i.e. other than the tested product, placebo or active comparator) but which may be supplied to subjects participating in a trial and used in accordance with the protocol. For instance, some clinical trial protocols require the use of medicinal products such as support or rescue/escape medication for preventive, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response.

Substances for pharmaceutical use are any organic or inorganic substances that are used as active substances or excipients for the production of medicinal products for human or veterinary use. They may be used as such or as starting materials for subsequent formulation to prepare medicinal products.

A *qualified person* (QP) shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study or a course recognised as equivalent by the Member State concerned, extending over a period of at least 4 years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology. The qualified person shall have acquired practical experience over at least 2 years in one or more undertakings which are authorised to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products. The duration of practical experience may be reduced by 1 year where a university course lasts for at least 5 years and by a year and a half where the course lasts for at least 6 years [10]. The requirement for responsibility by a QP has been extended to material for use in clinical trials

since the introduction of EU Directive 2001/20/EC. In countries that are part of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), the same role may be termed responsible person (RP) or authorised person (AP).

The term *microdose* refers to the mass amount of the test substance and is defined as less than 1/100 of the amount calculated to yield a pharmacological effect based on primary pharmacodynamic data obtained in vitro and in vivo (typically doses in or below the low microgram range) and at a maximum dose of 100 μg [11].

The term *toxicological data* represents information obtained from non-clinical safety studies required before an investigational radiopharmaceutical may be injected in humans.

The term *dosimetry data* represents information on the radiation exposure due to administration of an investigational radiopharmaceutical. Exposure is expressed as effective dose.

Risks associated with medical and biomedical research can originate from radiation and other unfavourable effects as well, such as pharmacological action of drugs or complications associated with the research protocol. The term "risk", used in this guideline when dealing with dosimetry issues, refers to the possibility of occurrence of stochastic effects due to the exposure to ionising radiation and includes the total detriment from such an exposure.

Requirements for starting materials of radiopharmaceuticals in early phase clinical trials

General

As stated above, some precursors of radiopharmaceuticals are to be considered as active pharmaceutical ingredients, e.g. the radionuclides for radiolabelling when the final preparation is released for use without further purification and also the compounds in a radiopharmaceutical kit intended to carry or bind the radionuclide (e.g. medronic acid) or to permit its binding (e.g. stannous chloride). More generally, all starting materials used during radiolabelling for the manufacture of a radiopharmaceutical that is not purified after the radiolabelling reaction must comply with the requirements for API's as described further in this text and in reference [6]. The same holds true for a radioactive drug substance containing a radionuclide with a sufficiently long half-life to allow a thorough analysis of the radioactive API.

Starting materials used in the radiolabelling reaction for manufacture of radiopharmaceuticals that are purified after the radiolabelling, such as most preparations radiolabelled with a short-lived positron emitting radionuclide (e.g. carbon-11, fluorine-18 or gallium-68), are, according to the Eudralex definitions (see above), NOT active pharmaceutical ingredients but are API starting materials. Also, the FDA document 'Current Good Manufacturing Practice for Positron Emission Tomography Drugs' considers them as components that yield the radioactive drug substance but not as part of the API [12]. As a consequence, they do NOT have to comply with all requirements set for active pharmaceutical ingredients and, more particularly, the requirement for manufacturing in accordance with Good Manufacturing Practice for starting materials [6].

However, as stated above, the radioactive drug substance (=active pharmaceutical ingredient) in these preparations is as a rule not isolated, which means that the API cannot be fully analysed and characterised before incorporation in the final radiopharmaceutical preparation. Moreover, the European Pharmacopoeia (Ph. Eur.) [7] also allows that some radiopharmaceuticals (=finished drug products), containing radionuclides with a relatively short half-life (up to about 6 h), are released for medical use before completion of some tests, such as determination of sterility, bacterial endotoxins and radionuclidic purity. It is, therefore, logical that, in this case, sufficient care must be devoted to an appropriate analysis of both the starting materials and the final radiopharmaceutical preparation, using validated methods.

For the same reason, the Committee for Human Medicinal Products (CHMP) of the EMEA states in its recently published draft 'Guideline on radiopharmaceuticals' [8] that *for radiopharmaceuticals containing radionuclides of short physical half-life (e.g. PET radiopharmaceuticals), that can be released for use before all results on finished product testing are available, special attention should be devoted to the purity and control methods for all starting materials, reactants, chemicals, reagents and solvents used in synthesis and purification*.

As a consequence, following general rules can be defined:

a. all starting materials used in radiolabelling reactions for the preparation of radioactive pharmaceutical ingredients (APIs) that are not isolated and/or fully analysed before incorporation in the final radiopharmaceutical preparation have to be analysed according to a monograph of a pharmacopoeia and must comply with the requirements of the pharmacopoeia. In case the substance is not described in a pharmacopoeia, it must be analysed using validated methods. All analyses have to be performed in accordance with national regulations.
b. all starting materials that are to be considered as active pharmaceutical ingredients (see above) must comply with the requirements described below (b.1 to b.3):

    b.1. API starting material produced by a GMP-certified pharmaceutical company

This is the preferred situation. In this case, the (radio) pharmacist or qualified person must:

- perform at least one test to verify the identity of each batch of material
- check the certificate of analysis including:
  - Identification
  - Chemical purity
  - Stability data
  - Storage conditions
  - Expiry or re-qualification date
  - Batch identity
  - Impurity profile

b.2. API starting material produced by a company certified for GMP production of the starting material in some countries but not the country of the user

In this case, a copy of the certificate of GMP production must be submitted to the competent authority of the country of the user for mutual recognition. After recognition, the same conditions apply as under b.1.

b.3. API starting material that has not been manufactured in accordance with Good Manufacturing Practice or new API starting material

The (radio)pharmacist or qualified person must:

(a) audit the manufacturing laboratory to verify that the API starting material has been manufactured in accordance with GMP for starting materials [6]. The audit report of another person may be used.

(b) have the substance analysed according to a monograph of the European Pharmacopoeia or, if such monograph does not exist, that of another pharmacopoeia, or if no pharmacopoeial monograph exists, using validated methods and in accordance with national regulations.

Moreover, the European Pharmacopoeia [7], in its general chapter on radiopharmaceutical preparations states that *for all starting material for radiopharmaceuticals, it is recommended testing the substance in production runs before its use for the manufacture of radiopharmaceutical preparations. This ensures that under specified production conditions, the substance yields the radiopharmaceutical preparation in the desired quantity and quality specified*.

c. starting materials present in a radiopharmaceutical preparation as excipients (solvents, buffers, stabilisers, additives, antimicrobial agents, …) must be of pharmacopoeial quality (as indicated on the label), or be accompanied by a certificate of analysis, or be analysed using validated methods and in accordance with national regulations.

Requirements for radiopharmaceuticals in early phase clinical trials

Radiopharmaceuticals can be used for different purposes in early phase clinical trials. They may be used as specific in vivo surrogate markers of a clinical end-point to monitor a candidate drug interaction with its target and pharmacodynamic properties (e.g. [^{18}F]-2-fluoro-2-deoxyglucose, FDG, as probe of response to chemotherapeutic drug treatment). They may also be used to demonstrate the relation between plasma drug concentration and target activation (e.g. receptor occupancy) and study the biodistribution and pharmacokinetics of the radiolabelled drug candidate itself.

To these purposes, the radiopharmaceutical to be used may be a licensed tracer agent (e.g. FDG) used within or outside the indication of its marketing authorisation, a well-established tracer described in a pharmacopoeia monograph but without MA (e.g. [^{11}C]methionine), or a newly developed tracer agent. As a result, different requirements may apply to the radiopharmaceutical in early phase clinical trials:

- Use of a licensed radiopharmaceutical within its MA within licensed indications represents a simple situation and nothing has to be performed but local quality assurance standards (Good Radiopharmacy Practice) have to be adhered to.
- Use of a licensed radiopharmaceutical outside its MA indications requires a CTA to be filed. The radiopharmaceutical may be considered a non-investigational medicinal product (NIMP) and submission/approval of an investigational medicinal product dossier (IMPD) may not be necessary. A simplified IMPD (=summary of product characteristics) may be sufficient in this case. However, a number of European countries (e.g. Germany, Ireland, Italy, Spain, Sweden, the Netherlands, UK) still consider such a radiopharmaceutical as an IMP and submission and approval of an IMPD may be required.
- The use of a radiopharmaceutical having no MA but that has been authorised by a competent authority for one or more other clinical trials may be granted on the basis of a simplified IMPD.
- First-time-into-man (FTIM) application of a new radiopharmaceutical, either when representing the target of the research or used to assess a candidate drug, requires the classification of such a radiopharmaceutical as an investigational medicinal product (IMP). Approval has to be obtained after submission of a full investigational medicinal product dossier to the national competent authorities. In the UK, however, when used as a biomarker, radiopharmaceuticals are not the subject of the clinical trial and, therefore, not

subject to the CTA-derived regulations. This is true whether the radiopharmaceutical is licensed, unlicensed or even first-time-into-man. Other regulations (e.g. ethics) may apply in these circumstances but not the obligation of a CTA dossier, so no IMPD for the radiopharmaceutical is required.

The requirements for an IMPD dossier are described in detail [13] and official forms and format may be obtained through the national authority. IMPD contents have to describe chemical pharmaceutical data such as:

- Drug substance: structure, general properties, procedure of manufacture, characterisation and quality control, container, stability, …
- Finished drug product (i.e. the radiopharmaceutical): pharmaceutical development, manufacturing process, process validation, control of excipients, control of medicinal product, validation of analytical procedures, reference materials, stability, container, labelling.

Licensed radiopharmaceuticals are to be used following the instructions and recommendations of the manufacturer. All other radiopharmaceuticals have to be analysed before use according to a monograph of the European Pharmacopoeia or another pharmacopoeia. If the radiopharmaceutical is not described in a pharmacopoeia, methods of analysis have to be developed and validated and should comprise for injectable preparations: appearance of solution, identity of radionuclide and of radiolabelled compound, radiochemical purity, level of chemical impurities, residual solvents, specific activity, pH, bacterial endotoxins, sterility, radionuclidic purity. Tests on bacterial endotoxins, sterility and radionuclidic purity may be performed after product utilisation for tracer agents labelled with a short-lived radionuclide provided the process has been duly validated. Reference to a general monograph on radiopharmaceutical preparations published by an official pharmacopoeia may represent a useful guidance [7].

Toxicological information with respect to radiopharmaceuticals used in early phase clinical trials

Radiopharmaceuticals to be administered in mass amounts exceeding the limits of a microdose [11] or intended for multiple administrations have to fulfil requirements concerning non-clinical safety studies as for any active substance before it is used in the conduct of human clinical trials [13].

When prepared at sufficiently high specific activity, radiopharmaceuticals may meet the limit dictated by microdose-based clinical trials. Under these circumstances, the preclinical information required to support the conduct of clinical studies is simplified. The recommendations as described in the EMEA Final Position Paper on non-clinical safety studies to support clinical trials with a single microdose [11] which relate to radiopharmaceuticals may be summarised as follows:

a) If in vitro data on metabolism and comparative data on primary pharmacodynamics and biological activity are available, the toxicity study can be limited to:
   - an extended single-dose toxicity study in only one (appropriate) mammalian species including a control group and both genders of animals. The number of animals must be sufficient to ensure reliable interpretation of the study results. 'Appropriate mammalian species' is specified as 'if the choice of species could be justified based on comparative in vitro metabolism data and by comparative data on in vitro primary pharmacodynamics/biological activity'.
   - the study period is 14 days with interim killing of a number of animals at day 2 (day of dosing=day 1);
   - allometric scaling from animal species to man with a safety factor of 1,000 with non-radioactive analogue (but possibly solubility problems for lipophilic tracers);
   - information to be collected on haematology and clinical chemistry (day 2+day 14) and on histopathology after killing the animal. Information must also be collected on any organs where the test substance localises and organ systems intended to be visualised by the test compound;
   - gross necroscopy should be performed on all animals.
b) Genotoxicity studies

In vitro genotoxicity studies should be performed as recommended in the relevant ICH guidance. However, if the test substance belongs to a well-known chemical class for which genotoxicity data are available on other class representatives, performance of reduced versions of mutation test in bacteria (Ames test) and chromosome aberration, mouse lymphoma or in vitro micronucleus tests may be sufficient.

On the other hand, the EMEA "Guideline on the limits of genotoxic impurities" [14] does not require genotoxicity testing in case the amount of test substance to be administered does not exceed 1.5 μg for a single administration or 1.5 μg/day for multiple administrations.

Dosimetry information with respect to radiopharmaceuticals used in early phase clinical trials

Exposure of patients and healthy volunteers to ionising radiation must comply with the Helsinki declaration and the

guidelines of its application prepared by the Council for International Organisation of Medical Sciences [15]. An Ethical Committee (EC) must examine and approve any early phase clinical trial that envisages exposure of a patient or volunteer to ionising radiation. Such an EC has to be set up in accordance with national procedures and/or by the competent authority. In most countries, the radiation protection authorities also need to approve the clinical trial.

Proposals of clinical trials involving a radiopharmaceutical sent for approval to an EC usually require clear indication of the three following basic principles of radiological protection:

- Justification of activities that could cause or affect radiation exposures,
- Optimisation of protection to keep doses as low as reasonably achievable,
- Use of dose limits (dose constraints).

Justification of activities that could cause or affect radiation exposures

All individual medical exposures must be justified in advance, taking into account the specific objectives of the exposure and the characteristics of the individual involved.

In general, exposure that cannot be justified should be prohibited. Medical exposure must show a sufficient net benefit compared with the individual detriment that the exposure might cause, taking into account the benefits and risks of available alternative techniques.

Optimisation of protection to keep doses as low as reasonably achievable

When a research project is of direct benefit to the individual patient, the ethical problems involved tend to be simpler. However, when a project is intended to extend medical and scientific knowledge without specific benefit to the individual concerned, the scientific and societal benefit should be made evident.

The method of radiation-absorbed dose calculation may be based on procedures suggested by the Medical Internal Radiation Dose Committee (MIRD) of the Society of Nuclear Medicine and the International Commission on Radiological Protection (ICRP). However, in some instances, it may be more appropriate to estimate the dose to a single organ, if irradiation is largely limited to that organ.

ICRP *Publication 62* [16] and *Publication 103* [17] have addressed ethical and procedural aspects also for the use of volunteers in biomedical research. Protection of subjects is based on the use of (a) reference anatomical and physiological models of the human being, (b) studies at the molecular and cellular level, (c) experimental animal studies and (d) epidemiological studies. ICRP risk estimates are 'nominal' because they relate to the exposure of a nominal population of females and males with a typical age distribution and are computed averaging over age groups and both genders. The estimates of fatality and detriment coefficients reported by ICRP are then adequate both for planning purposes and for general prediction of the consequences of exposures of a nominal population.

The ICRP has summarised a grid of evaluation to aid in the assessment of biomedical research projects (Table 1) and that is based on risk categories. In the ICRP scheme, the lowest risk is of the order of one in a million and is in the region where usually risk is considered trivial. ICRP concludes that "the level of benefit needed as the basis for approval of investigations with risks or doses in category I will be minor and would include those investigations expected only to increase knowledge".

The highest risk category (category III) refers to a greater than 1 in 1,000 probability to have direct consequences, such as cancer, from the exposure to 10 mSv or more (greater than the current annual dose limit for unclassified radiation workers) and can be justified if the expected benefit is substantial and usually related to the saving of life or the prevention or mitigation of serious disease.

Justification for intermediate categories can be based on the ability to produce advances in knowledge leading to health benefit (IIa, i.e. exposure level similar to that received by members of the public from controlled sources) or (IIb, i.e. exposure level similar to that received by special category of workers) benefits directly aimed at the cure or prevention of disease.

Table 1 ICRP categories of risk and corresponding societal benefit (from ICRP 62)

Level of risk	Risk category[a]	Corresponding effective dose range (adults; mSv)	Level of expected societal benefit
Trivial	Category I ($\sim 10^{-6}$ or less)	<0.1	Minor
Minor to intermediate	Category IIa ($\sim 10^{-5}$)	0.1–1	Intermediate to moderate
	Category IIb ($\sim 10^{-4}$)	1–10	
Moderate	Category III ($\sim 10^{-3}$ or more)	>10[b]	Substantial

[a] Expressed as absolute risk probability (number of events/population).
[b] To be kept below deterministic thresholds except for therapeutic experiments.

Pregnant women should not be involved in early phase clinical trials involving irradiation of the fetus unless the pregnancy itself is central to the research and only if any alternative technique, involving less risk, cannot be used. It is usually prudent to consider the possibility that a woman may be pregnant but not know it. The protocol involved in the investigation should recognise this possibility. Research on breast-feeding women should also be avoided.

The use of dose limits (=dose constraints)

From the legislation point of view, the 97/43/EURATOM Directive represents the reference to clinical research using ionising radiation; additional information, including reference to Table 1, may be found in "Radiation Protection 99" issued by the European Commission [18]. Within the European Community, dose constraints must be set for volunteers exposed to ionising radiation during clinical trials from where they are not receiving a direct medical benefit.

All doses due to medical exposure must be kept as low as reasonably achievable and consistent with obtaining the required final information.

When applicable, proponents must ensure that dose constraints are established for exposure of individuals in contact with exposed patients/subjects. Comportment instructions must be given to the patient (possibly to relatives and accompanying persons) before he/she leaves the medical institution.

Special care must be ensured that all reasonable steps are taken to reduce the probability and magnitude of accidental or unintended doses to subjects and patients.

Remark

This guideline summarises the views of the Drug Development Committee of the EANM and reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken into the context of good practice of nuclear medicine and radiopharmacy and do not substitute for national and international legal or regulatory provisions.

The guidelines were submitted for advice to the National Societies of Nuclear Medicine.

References

1. EANM Radiopharmacy Committee (2007) guidelines on current good radiopharmacy practice (CGRPP) in the preparation of radiopharmaceuticals. http://www.eanm.org/scientific_info/guidelines/gl_radioph_cgrpp.pdf.
2. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Cooperation Scheme: PIC/S guide to good practices for preparation of medicinal products in healthcare establishments—PE 010-1 (19 November 2007; into force on April 1 2008). http://www.picscheme.org/index.php?p=guides.
3. Maintenance of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals M3(R1). http://www.ich.org/cache/compo/502-272-1.html#M3.
4. Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities. ENTR/F2/BL D(2003). http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/11_ca_14-2005.pdf.
5. Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. CHMP/QWP/185401/2004 final. http://www.emea.europa.eu/pdfs/human/qwp/18540104en.pdf.
6. EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4: EU Guidelines to Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use. Part II: Basic Requirements for Active Substances used as Starting Materials. October 2005. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm.
7. European Pharmacopoeia. 6th ed. Strasbourg: European Directorate for the Quality of Medicines (EDQM); 2008.
8. Guideline on Radiopharmaceuticals, CHMP, EMEA/CHMP/QWP/306970/2007 (draft released for consultation). http://www.emea.europa.eu/pdfs/human/qwp/30697007en.pdf.
9. Guideline on excipients in the dossier for application for marketing authorization of a medicinal product. EMEA/CHMP/QWP/396951/2006. http://www.emea.europa.eu/pdfs/human/qwp/39695106en.pdf.
10. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. http://www.emea.europa.eu/pdfs/human/pmf/2001-83-EC.pdf.
11. Final Position Paper on non-clinical safety studies to support clinical trials with a single microdose (EMEA/CPMP/SWP/2599/02/Rev1). http://www.emea.europa.eu/pdfs/human/swp/259902en.pdf.
12. Current Good Manufacturing Practice for Positron Emission Tomography Drugs, Food and Drug Administration, Docket No. 2004N-0439. http://www.fda.gov/OHRMS/DOCKETS/98fr/cd0279.pdf.
13. Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals needed to support human clinical trials of a given scope and duration. EMEA/CPMP/ICH/286/95). http://www.emea.europa.eu/pdfs/human/ich/028695en.pdf.
14. EMEA committee for medicinal products for human use. Guideline on the limits of genotoxic impurities. EMEA/CHMP/QWP/251344/2006. http://www.emea.europa.eu/pdfs/human/swp/519902en.pdf.
15. Council for International Organizations of Medical Sciences (CIOMS)World Health Organization (WHO). International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS; 2002.
16. International Commission on Radiological Protection. ICRP publication 62: radiological protection in biomedical research, annals of the ICRP, vol 22/3. Oxford, UK: Pergamon; 1993.
17. International Commission on Radiological Protection. ICRP publication 103: Recommendations of the ICRP, annals of the ICRP, vol 37/2–3. Amsterdam: Elsevier; 2007.
18. Radiation Protection 99: Guidance on Medical Exposures in Medical and Biomedical Research, Directorate General Environment, Nuclear Safety and Civil Protection; 1998.