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Overview of the Regulatory Framework for Radiopharmaceuticals

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Abstract

Radiopharmaceuticals are products that have the particularity of combining two very restrictive regulatory requirements depending on two different authorities: that of the drug in the pharmaceutical sense and that of a radioactive source linked to a specific authorization system.

Radiopharmaceuticals are a new reality in the pharmaceutical industry and are considered to be an indicator of modern medicine and the technological industry. The exponential increase in their use is attributed to their dual use as diagnostic and therapeutic agents. They represent a group of pharmaceutical preparations, which contain radionuclides with short half-lives and are mainly administered intravenously. Maximum care should be taken during their production, distribution, storage, and disposal because their radiant nature is a concern for both patients and medical staff. All stages of production must be done by the requirements of Good Manufacturing Practice. Therefore, radiopharmaceuticals must meet the requirements of the pharmaceutical regulator, the same as those of the nuclear regulator. The largest number of regulatory bodies in the world have different perspectives in terms of their production, distribution, transportation, storage, and disposal. However, in developed countries, the regulator of radiopharmaceuticals is in its infancy.

In this article, we will shed light on the various regulatory limitations imposed by these statutes, emphasizing that these regulations are therefore

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likely to evolve in the years to come and to demonstrate the importance of their development, proper use, and perspective.

Keywords: radiopharmaceuticals, FDA guidelines, EMA guidelines, regulatory framework

INTRODUCTION

Radiopharmaceuticals are a very special group of medicinal products. They contain a radionuclide that emits ionizing radiation that can be detected externally for diagnostic purposes or as a therapeutic tool for treating severe diseases.

Therefore, radiopharmaceuticals have the peculiarity of combining two very restrictive regulatory requirements depending on two different authorities (1):

- that of medicine in the pharmaceutical sense, governed by the medicine laws;
- a radioactive source associated with a specific licensing system regulated by radiation protection laws.

The great majority of radiopharmaceuticals are applied for diagnostic purposes using gamma cameras for conventional scintigraphy and tomographic imaging, called single photon emission computed tomography (SPECT). Recently, positron emission tomography (PET) has become increasingly important, providing improved sensitivity and resolution (2).

Among the several applications of radioisotopes, medical applications were considered to be of the highest priority. Radiopharmaceuticals must be used quickly while limiting the risk of radioactivity in the medium term. These are radionuclides whose activity decreases rapidly. The initial activity must therefore be significant.

The production of radionuclides is different. It occurs in two types of facilities: in a nuclear research reactor - bombarding atoms with neutrons - or in a cyclotron-type particle accelerator.

Most of the medium and high flux research reactors are now routinely used to produce radioisotopes for medical and industrial applications. The most commonly used reactor-produced isotopes in medical applications are Molybdenum-99 (for production of Technetium-99m), Iodine-131, Phosphorus-32, Chromium-51, Strontium-89, Samarium-153, Rhenium-186 and Lutetium-177 (3).

Some radiopharmaceutical preparations are obtained in hospitals, in radiopharmaceutical preparation laboratories, from generating systems by the natural decay of the source radionuclide. This is the case with technetium 99m - the radionuclide most commonly used in conventional nuclear medicine - derived from its "parent" radionuclide, molybdenum 99.

Aspects that need to be addressed in the production of radiopharmaceuticals include radioisotope management production, import, operation, and maintenance of processing facilities, current good manufacturing practice (cGMP) requirements, ensuring adequate provision of and quality assurance and quality control systems (QA & QC), registration of products with national/regional health responsibility and transportation of radioactive materials.

PET has molted light on this field, enabling invention in disquisition and its clinical value. The topmost work worth when radiopharmaceuticals are mentioned has been

done with (18F)-2-fluoro-2-deoxyglucose (FDG). Since the 1989 Directive, nothing has been done to clarify the situation of radiopharmaceuticals. Arguably, since also, the situation has worsened because pharmaceutical regulations have concentrated mainly on conventional medicinal products, and nonsupervisory bodies have been reticent to borrow specific regulations for specific situations, similar to the case of radiopharmaceuticals. European directives must be enforced by a member state.

The elaboration of regulations has introduced stricter rules; Recent directives have extended GMP to medical products R&D and non-profit and academic studies. Lately, AIPES has made a lobbying effort to draw the attention of regulatory bodies to simplifying the registration procedures of radiopharmaceuticals or, adopting a separate regulation which would be much better (4).

RADIOPHARMACEUTICALS AS MEDICINE IN THE PHARMACEUTICAL SENSE

Radiopharmaceuticals as a pharmaceutical product

Pharmaceuticals are medicinal products prepared in advance, presented in a unique package, and characterized by a particular name. All medicinal products must have marketing authorization before being placed on the market.

This evaluation is based on pharmaceutical quality, diagnostic efficacy, and safety criteria for using radiopharmaceuticals.

The main statutes of radiopharmaceuticals are as follows:

- *Pharmaceutical products* - any medicine prepared in advance, presented in special packaging, and characterized by a unique name. Need to obtain Marketing Authorization.
- *Temporary authorization* - does prevent the use, on an exceptional basis, of certain medicinal products intended to treat severe or rare diseases when there is no appropriate treatment.
- *Magistral preparation* - any medicinal product prepared according to a medical prescription intended for a specific patient, either extemporaneously in a pharmacy or under the conditions provided for in the regulation for magistral preparation
- *Hospital preparations* - Any medicine prepared according to the indications of the Pharmacopoeia and in compliance with the good practices mentioned due to the absence of a pharmaceutical product available or suitable in a pharmacy for internal use in a health establishment or by the pharmaceutical establishment of this licensed healthcare facility. Hospital preparations are dispensed on medical prescription to one or more patients by a pharmacy for the establishment's internal use (5).

Radiopharmaceuticals as a radioactive source

Radiopharmaceuticals contain a radioactive source and, also, are controlled as radioactive

sources with specific authorization by an independent body that ensures that croakers and apothecaries who use ionizing radiation misbehave with the principles of radiation protection. These principles cover all diagnostic or therapeutic applications related to the use of radiopharmaceuticals.

Although the nuclear physician who prescribes the radiopharmaceutical is completely responsible (as well as the procedure index) for the case's radiation protection, its practical implementation also depends on the resources made available by the head of the facility. The institution responsible for radiation protection is responsible for covering the radiation protection of the population in general and, particularly, of cases (6).

Regulatory authorities

The main role of the regulatory agencies consists in the protection and improvement of the public health. It is veritably necessary to have cooperation between the nonsupervisory authorities in order to ensure essential public conditions.

The sector with which public health is in endless cooperation is the marketable medicinal sector, the sector for the development of medicines and their quality assurance bodies, to grease the introduction of new pharmaceutical products to the market.

Radiopharmaceuticals are still a small, technical sector with most of the medical staff being not familiar with, and thus good communication is essential to ensure that the appropriate requirements are set for the approval process to proceed.

Non-commercial directors should be apprehensive of specialist knowledge when communicating with nonsupervisory agencies and take this into account in their approach, seeking expert advice or training individuals in their organizations specifically for this topic. It may be possible to use professional nonsupervisory bodies or other government agencies as intermediaries to facilitate good communication with regulators and to borrow applicable processes to apply the applicable regulation (7).

Marketing authorization

Applications for marketing authorization in respect of radiopharmaceuticals should be accompanied, as in the case of all medicinal products, by the particulars and documents referred to in Directives 65/65/EEC and 75/319/EEC, as amended and in the Annex of Directive 75/318/EEC as amended. The provisions of Directive 89/343/EEC also apply. The relevant provisions of the European Pharmacopoeia should always be observed. Other relevant CPMP guidelines must be considered.

The time limits for determining the pharmaceutical formulation, control tests, and marketing of these medicines are grounded based on the regulations/guidelines depending on the half-life of these medicines.

Radiopharmaceuticals have changing composition with time, associated with radioactive decay. The physical half-life of these radionuclides is in numerous cases so short that, in these cases, the final medication must be prepared incontinently before administration to the patient. For this reason, there is a need for the use of semi-finished products similar to radionuclide generators, precursors, and kits.

Assessing the safety and efficacy of radiopharmaceuticals is also concerned with the specifications of generators, kits, and other semi-manufactured products. Specifications may also bear special attention in cases where samples from the case are labeled with a radioactive substance before administration (precursor radiopharmaceuticals). When radiopharmaceuticals go directly from the generator to the case (e.g. ultra short-lived radioactive gases), the production process's thickness is pivotal (8).

Radiopharmaceuticals not included in Pharmacopoeia

It's frequently the case that numerous countries or certain geographical regions do not have their own approved pharmacopeia. Also, not all pharmacopeias have a radiopharmaceutical section. For this reason and under these circumstances, the requirements and concerns for the approval of a radiopharmaceutical will be ever greater.

Even in countries that have national pharmacopeias with general parts dedicated to radiopharmaceuticals, it is possible that radiopharmaceuticals approved for routine diagnostic purposes have not yet been included in the pharmacopeia.

For radiopharmaceuticals not yet included in the pharmacopeia, current recommendations can be applied. In these cases, responsibility for product specifications falls on the manufacturer (7).

CURRENT STATUS OF THE REGULATORY FRAMEWORK

In Europe, medicinal products are regulated in Directive 2001/83/EC (9,10). It defines a medicinal product as "*any substance or combination of substances presented for treating or preventing disease in human beings… and any substance or combination of substances which may be administered to human beings to make a medical diagnosis….*" Radiopharmaceuticals are covered by the directive, including diagnostic and therapeutic applications unless they are viewed as a sealed source, then the Medical Device regulation applies (11), such as in the case of SIR-Spheres (Y-90 resin microspheres, SIRTEX®) (12).

The rate of adoption of directives varies between countries, and each member state may introduce changes, provided each directive's general scope and limits are maintained. Specific articles have been placed concerning radiopharmaceuticals to receive marketing authorization or are prepared to start from licensed products (radionuclide Radiopharmaceuticals kits, and precursor radionuclides) (13).

Radiopharmaceuticals have been accepted for quite a long time, along with other exclusive products - such as allergens, vaccines, and blood-derived products- from adopted pharmaceutical regulations. Applicable rules were on radiation protection and compliance with Pharmacopoeia monographs. As of 1992, European Pharmacopoeia had more than 30 monographs covering the majority of routinely used radiopharmaceuticals. Directive 89/343/EC extended the existing rules of medicinal products to radiopharmaceuticals compounds used as diagnostic or therapeutic agents (radiometabolic therapy). In particular, this Directive mentioned cold kits used to prepare Tc-labelled radiopharmaceuticals and Mo-Tc generators. This Directive was due for preparation by EU Member States in two years. The immediate consequence was the need to file an enrollment of radiopharmaceutical products, about 50, that have been on the market for further than twenty years. This posed no minor problems: on one side, numerous diligence involved did not have the experience to manage the complete enrollment dossier, and on the other side, running all standard protocols, including preclinical and clinical trials, would bear years. Controllers also accepted an abridged procedure: a single file of pharmacological, toxicological, and clinical support using available data or published literature was judged as applicable (4).

In the United States, the regulation of radiopharmaceuticals is carried out by the Center for Drug Evaluation and Research (CDER), which is under the governance of the US Food and Drug Administration (FDA). Multiple analyzes and research in the field of radiopharmaceuticals have enabled the creation of a fairly important and powerful regulation.

Presently, radiopharmaceuticals are regulated in the US, from assay development, and half-life to ADR reporting.

The FDA Modernization Act (Public Law 105-115) of 1997 (14) was the major regulatory moment that gave special attention to PET medicinal products, which had previously been left out of some of the FDA's requirements. Section 121 of the Modernization Act required the FDA to establish Current Good Manufacturing Practices (CGMPs) and appropriate procedures necessary for the approval of PET medicinal products.

All procedures were completed and their implementation began on December 10, 2009, when the FDA finally published the regulation outlining the minimum cGMP standards that every PET medical product manufacturer must follow when manufacturing a PET medical product (21 CFR part 212) and the PET Medicinal Product – Current Good Manufacturing Practice (CGMP) guideline in 2009 (4, 12).

List of the latest guidelines of EMA and FDA

European Union - EMA

- Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals – September 2011 (15).

- Pediatric Radiopharmaceutical Administration: Harmonization of the 2007 EANM Pediatric dosage card (Pediatric.5.2008) and the 2010 North American Consensus Guidelines – February 2013 (16).
- Guideline on the Acceptability of Names for Human Medicinal Products Processed through the Centralized Procedure - May 2014 (17).
- EANM Guideline for the Preparation of an Investigational Medicinal Product Dossier (IMPD) - August 2014 (18).
- Concept Paper on the Development of Guidance on the Non-clinical Evaluation of Radiopharmaceuticals - July 2017 (19).
- Guideline on the Requirements for the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials - September 2017 (20).
- European Medicines Agency pre-authorisation Procedural Advice for users of the Centralized Procedure – December 2017 (21).
- Guideline on the non-clinical requirements for radiopharmaceuticals – November 2018 – Draft format¬ (22).

US – FDA

- PET Drugs - Current Good Manufacturing Practice (CGMP): Small Entity Compliance Guide - August 2011 (23).
- PET Drug Applications - Content and Format for NDAs and ANDAs – August 2011 (24).
- Non-clinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals - November 2011 (25).
- Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs - December 2012 (26).
- Clinical Trial Imaging Endpoint Process Standards Guidance for Industry - March 2015 (27).
- Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities - December 2016 (28).
- Compounding and Repackaging of Radiopharmaceuticals by State Licensed Nuclear Pharmacies and Federal Facilities - December 2016 (29).
- Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations - September 2017 (30).
- Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry (2018) (31).

CONCLUSION

Regulatory bodies in the US and Europe need a more detailed review of radiopharmaceuticals in the transition from preclinical development to clinical application. Some documents have been

published lately, but some are in the draft interpretation.

FDA guidelines do not define legally enforceable responsibilities. Still, these guidelines describe the Agency's current opinion on a particular topic and should only be seen as recommendations unless specific nonsupervisory conditions are demanded.

The guidelines in the United States are more industry-oriented, and vice versa. The EU Guideline is formulated in a way that will help the development of diagnostic and therapeutic radiopharmaceuticals for use in the pharmaceutical industry.

A thorough examination of the various regulatory bodies can aid in developing a harmonized guide allowing radiopharmaceuticals to trade across borders freely.

Therefore, regulations will likely need to evolve in the coming years, and this evolution, whether in the field of medicine or radiation protection, should, to be optimal, be established in collaboration with nuclear physicians and their learned society.

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