25 The Regulatory Review of Radiotherapeutics: United States of America

Serge K. Lyashchenko

25.1 The Fundamentals

In the United States, all radiopharmaceuticals—including therapeutic radiopharmaceuticals—are classified as medicines. Therefore, their clinical development, production, and clinical use are regulated by the United States Food and Drug Administration (FDA) in the same manner as traditional non-radioactive pharmaceuticals. The FDA is responsible for the oversight of all activities related to the use of radiopharmaceuticals in humans. Generally speaking, this oversight is accomplished in three ways: (i) regulations and guidance that specify requirements for the use of radiopharmaceuticals (e.g., conducting clinical trials, manufacturing), (ii) periodic surveillance audits to ensure compliance with the aforementioned rules, and (iii) the regulatory review and approval of new radiopharmaceuticals.

S. K. Lyashchenko (✉)
Department of Radiology, Memorial Sloan Kettering Cancer Center, New York CityNY, USA
e-mail: lyashchs@mskcc.org

25.2 The Details

25.2.1 The FDA Framework for Therapeutic Radiopharmaceuticals

Therapeutic radiopharmaceuticals hold a unique position within the world of radiopharmaceuticals. Radiotherapeutics share many characteristics with their diagnostic counterparts, including their emission of radioactivity, administration in sub-pharmacologic mass doses, relatively short shelf-lives, and small batch sizes in which quality control samples are homogeneous with entire batches. In the case of diagnostic radiopharmaceuticals, these traits spurred the creation of a special set of regulations. Yet therapeutic radiopharmaceuticals are currently subject to the same regulations as traditional, non-radioactive drugs. The principal reason for this choice is the potential toxicity of radiotherapeutics. Indeed, while the mechanisms of traditional therapeutics and radiotherapeutics are dramatically different (i.e., biochemical action vs. ionizing radiation), the overall safety and efficacy profiles of therapeutic radiopharmaceuticals are much more closely aligned with those of non-radioactive pharmaceuticals than those of diagnostic radiopharmaceuticals. Yet while the rationale for this regulatory framework is clear, the intrinsic differences between drugs that emit ionizing radiation and non-radioactive drugs—as well as the

L. Bodei et al. (eds.), *Radiopharmaceutical Therapy*, https://doi.org/10.1007/978-3-031-39005-0_25

advent of new classes of radiotherapeutics (i.e., α-emitters)—have necessitated a certain amount of regulatory flexibility.

In the United States, this regulatory flexibility is achieved via a combination of federal regulations, FDA-issued guidance documents, and the FDA's direct communication pathways. Because the terms "FDA regulations" and "FDA guidance" are often erroneously used interchangeably, an explanation of these terms is warranted. "Regulations" are laws that contain binding requirements related to the use of pharmaceuticals in humans. In practice, because passing laws is resource intensive and time consuming, regulations typically contain broad requirements that can be applied to all pharmaceuticals, for example, basic rules for the manufacture of medicines. "Guidance," on the other hand, describes the compilation of FDA-issued documents that contain the Administration's "recommendations" on a specific area. These recommendations are much more detailed than regulations yet are likewise designed to be as general as possible. In addition, while the word "recommendations" suggests that they need not be followed, most entities that are subject to FDA guidance recommendations voluntarily choose to do so.

While the use of therapeutic radiopharmaceuticals in humans is governed by the same regulations as non-radioactive drugs, the unique characteristics of the former have required the implementation of non-traditional processes and the generation of radiotherapeutic-specific FDA guidance documents. One extant example is *Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labelling Recommendations: Guidance for Industry*. This guidance document provides several recommendations specifically related to the clinical translation of therapeutic radiopharmaceuticals, including considerations with respect to the preclinical evaluation of radiotoxicity [1]. Other aspects of the use of therapeutic radiopharmaceuticals are currently covered by additional FDA-issued guidance documents that may also cover diagnostic radiopharmaceuticals and non-radioactive drugs. Finally, it is important to note that FDA guidance—unlike regulations—is not fixed. Therefore, as field of radiopharmaceutical therapy evolves, existing FDA guidance documents may be updated, or new ones may be issued.

25.2.2 The Role of the US Pharmacopeia

In the context of the manufacturing and handling of radiotherapeutics, the FDA may at times rely on published standards from other entities—most notably the US Pharmacopeia (USP)—as well as its own regulations and guidance documents. The USP is responsible for compiling and managing a collection of standards documents, also referred to as "chapters" that can be used by manufacturers of radiopharmaceuticals to demonstrate compliance with established standards. These compendial "chapters" usually contain descriptions of well-established processes and practices related to the production and handling of radiopharmaceuticals. For example, USP <825> *Radiopharmaceuticals-Preparation, Compounding, Dispensing, and Repackaging* sets standards relevant to the dispensing and compounding of radiopharmaceuticals, including radiotherapeutics [2].

It is important to recognize that the USP is not a governmental agency responsible for enforcing standards. Rather, it is a non-profit agency that documents and manages standard protocols that have been generated by expert groups or by the manufacturer of a specific drug. The underlying principle of the USP is that once a process or standard has been included in the USP, it is considered to be "compendial" or "validated." This system offers several benefits to both the regulatory agencies and the manufacturers of radiotherapeutics. Since the methodologies or standards described in the USP are considered to be valid, regulators often rely on USP standards in lieu of generating yet another guidance document. In addition, once a manufacturer has demonstrated that a process is USP-compliant, regulators have a complete understanding of the process being used. This approach saves

regulators effort and resources and ensures that particular aspects of manufacturing are standardized across the industry (at least as much as possible). In turn, manufacturers benefit from relying on the USP because once their manufacturing processes comply with a "compendial method," no additional effort is needed to demonstrate its suitability.

Significant differences exist between the degrees to which American and European manufacturers may rely on pharmacopeia documents for the production of unapproved radiotherapeutics for clinical use. In the EU, a specific non-approved drug monograph may be generated for the EU Pharmacopeia by a group of experts with relatively limited validation data. In this case, the chapter normally contains information on controls that, in the experts' opinion, should be applied during the production and quality control testing of the radiotherapeutic in question. Once published, these chapters allow manufacturers to produce radiopharmaceuticals that have not received regulatory approval on a limited basis for non-investigational treatments in patients under the auspices of nuclear medicine practice. This is often referred to as "in-house production" or "magistral compounding."

In the United States, on the other hand, radiopharmaceuticals cannot be used in patients unless they have been FDA-approved for a specific indication or investigational agents employed under the auspices of an FDA-acknowledged Investigational New Drug (IND) application. This policy eliminates the possibility of "magistral compounding" and means that there is no practical need to create USP monographs for investigational agents. Instead, drug monographs included in the USP are almost exclusively created by the manufacturer of FDA-approved drugs. Once a drug monograph is included in the USP, generic manufacturers of said drug are obliged to follow the published standards. The manufacturing controls for investigational radiopharmaceuticals are normally described in the "Chemistry, Manufacturing, and Controls" (CMC) section of IND applications, allowing the manufacturers of these investigational agents greater flexibility.

25.2.3 Special Considerations in the United States

Two aspects of the regulation of radiopharmaceuticals that are somewhat unique in the United States and that are absolutely essential for efficient regulation are: (1) the operation of a single regulatory agency (i.e., the FDA), and (2) the existence of well-established two-way communication channels between the regulators and those being regulated.

Regulation by a single agency offers several advantages. First, it ensures that the feedback provided by the regulator is both consistent and well informed. Secondly, it allows for the clear delegation of responsibilities within the regulatory agency. Practically, this means that those seeking regulatory advice are able to obtain information from the relevant division of the FDA quickly and easily.

Efficient communication with trained regulators who focus specifically on radiopharmaceuticals is another key factor that facilitates the development and human use of radiotherapeutics in the United States. The division of the FDA that is responsible for the regulation of radiopharmaceuticals is composed of radiochemists, radiopharmacists, medical physicists, and physicians that have a sound fundamental understanding of radiopharmaceuticals and their development. This expertise accelerates the creation of consensus between parties. In addition, the pathways of communication are well established, and initiating communication is easy. Depending on the matter at hand, communication may be written, verbal, in-person, or any combination thereof [3]. In order to ensure an appropriate response, the inquirer should include background on the problem at hand, the proposed solution alongside supportive reasoning, and a specific query as to the regulator's agreement (or lack thereof) with the proposed solution. In general, those developing radiopharmaceuticals are encouraged to contact regulators with questions prior to initiating their work in order to avoid situations in which the completed work does not satisfy regulatory requirements.

Depending on the urgency of the matter and the method of communication, response times vary from several hours to up to 90 days.

25.2.4 The Regulatory Approval Process

In a regulatory sense, radiotherapeutics can be divided into two broad categories: (1) investigational agents used in clinical trials and (2) drugs that have been approved by the FDA for routine clinical use for a specific indication. With respect to both, the FDA's remit is ensuring that the benefits of the therapeutic radiopharmaceutical outweigh its risks. Hence, investigators and clinicians must submit regulatory applications for drugs in each category so the FDA can determine whether all of the requirements for the use of the drug in humans have been met.

For investigational radiopharmaceuticals, this application is called an Investigational New Drug (IND) application. The IND application for therapeutic radiopharmaceuticals normally has several components: (i) information from preclinical non-human studies to provide a preliminary estimate of the drug's expected safety and efficacy, (ii) dosimetry and radiotoxicity estimates, (iii) a description of how the agent will be produced and tested, and (iv) a description of how the radiopharmaceutical will be evaluated in the clinic. Once the IND application is submitted, the FDA review period lasts 30 days. If no deficiencies are found, the FDA acknowledges the IND and allows the investigators to initiate their clinical trial. If deficiencies are found, however, the FDA will advise the applicants on how to remediate these problems.

Once clinical trials have demonstrated that a radiotherapeutic is a safe and effective treatment for a particular indication, another regulatory application—this one called a "New Drug Application" (NDA)—must be filed to receive approval for the use of the drug as part of standard clinical care as well as for its marketing. An NDA normally summarizes safety, efficacy, and pharmacokinetics data collected during clinical trials as well as additional data covering the production and quality control of the agent itself. Once the FDA grants an NDA approval for a particular drug, clinicians gain more flexibility with respect to how it is used in patients. For example, clinicians may decide to use the drug for "off-label" use beyond its approved indication if they believe their patients will benefit. Along these lines, clinician investigators may conduct a clinical trial of an FDA-approved drug for a different, non-approved indication. In these scenarios, an IND application may be required even though the drug is already FDA-approved. The need to submit an IND in a given situation may be clarified via communication with the FDA.

In general, the regulators in the United States do not allow clinicians to use drugs that have not been approved by the FDA for standard clinical care. As mentioned above, "magistral compounding" is not permitted in the United States. However, there is nonetheless a regulatory mechanism that allows clinicians to treat their patients using investigational (i.e., non-FDA approved) agents under extenuating circumstances. This mechanism—referred to as "expanded access" by regulators but "compassionate use" or "preapproval use" elsewhere—allows clinicians to petition regulators to use investigational agents for the treatment of patients with life-threatening conditions that have no approved therapeutic alternatives [4]. In practice, this approach is typically employed in the context of a single patient with a life-threatening disease who has run out of treatment options. However, it has also been applied to facilitate the treatment of groups of patients with a therapeutic that has already been found to be effective but has not yet received official regulatory approval.

This approach is particularly relevant to therapeutic radiopharmaceuticals because the majority of radiotherapeutics currently used in humans in the United States are investigational and employed in end-stage cancer patients. In this patient population, it is quite common to need emergency treatments for those who have run out of approved treatment options. Unlike magistral compounding, however, expanded access involves a significant degree of regulatory oversight. Since the radiopharmaceuticals used under

the "expanded access" mechanism are still investigational, the requestor must still have an FDA-acknowledged IND in place. Prior to granting approval for "expanded access" requests, regulators must determine that the potential benefits of using an investigational agent in a given patient or group of patients outweigh the risks *and* that granting access will not negatively impact the radiopharmaceutical's eventual case for NDA approval. The timing for granting approvals may vary from several hours to up to 30 days, depending on the urgency of the matter.

25.3 Conclusion

In summary, the last few years have played witness to a dramatic increase in the clinical study and use of therapeutic radiopharmaceuticals. Given the unique characteristics of these drugs, regulators and physicians must work together to ensure that the landscape governing the use of radiotherapeutics in the clinic allows patients adequate access to these valuable medicines while maintaining the appropriate degree of safety.

25.4 The Bottom Line

- Radiotherapeutics possess unique properties that influence the regulatory requirements that are applied to them.
- In the United States, the use of therapeutic radiopharmaceuticals in humans is governed by federal regulations. The US FDA is the government agency responsible for enforcing those regulations.
- The US Pharmacopeia (USP) is a non-governmental agency that issues compendial standards related to the manufacturing of FDA-approved radiopharmaceuticals. At times, the FDA may rely on USP standards in lieu of generating its own requirements.
- Maintaining well-established communication pathways with the FDA is essential for the efficient development of radiopharmaceuticals.
- It is absolutely paramount for regulators to consider possible impacts on the access of patients to radiotherapeutics when implementing new regulatory requirements.

References

1. United States Food and Drug Administration. Oncology therapeutic radiopharmaceuticals: nonclinical studies and labeling recommendations guidance to industry; 2019.
2. United States Pharmacopeia. USP <825>radiopharmaceuticals – preparation, compounding, dispensing, and repackaging; 2020.
3. United States Food and Drug Administration. Formal meetings between the FDA and sponsors or applicants of PDUFA products draft guidance to industry; 2017.
4. United States Food and Drug Administration. Expanded access to investigational drugs for treatment use – questions and answers. guidance for industry; 2017.