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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Advanced Accelerator Applications USA, Inc. (ADACAP), a Novartis Company, submits this citizen petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law. ADACAP holds the new drug application (NDA) for Lutathera® (lutetium Lu 177 dotatate). Lutathera is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. As described herein, we respectfully request that the Commissioner of Food and Drugs take the actions described below with respect to any abbreviated new drug application (ANDA) under section 505(j) of the Food, Drug and Cosmetic Act (FDCA), and any new drug application (NDA) under section 505(b)(2) of the FDCA, that references and relies on Lutathera for approval.

ADACAP is a pioneer in the development of radioligand therapeutics. Radioligand therapeutics are an emerging class of complex drugs. Unlike most other drug products, they are not static or fixed. They are dynamic systems involving several interacting components that change from manufacture to administration. These systems must maximize radiation to the target while ensuring that the radioactivity remains localized to avoid adverse off-target radiotoxicity.

A radioligand therapeutic typically consists of a ligand and a radionuclide. The ligand is designed to bind to specific receptors on the surface of tumor cells and deliver cytotoxic levels of radiation selectively to tumor sites. The ligand itself can be a complex entity composed of multiple functional subcomponents, typically including: (i) a targeting moiety, (ii) a radionuclide chelator moiety, and (iii) a linker joining the chelator moiety with the targeting moiety.

The FDCA and its implementing regulations require a generic product to have, *inter alia*, the same strength as the listed product; typically meaning that the generic drug product contains the same amount

of the same drug substance as the reference listed drug.[1] Similarly, a 505(b)(2) applicant that relies in part on pharmaceutical equivalence to bridge to the listed drug, must demonstrate that it includes identical amounts of the identical active ingredient.[2] The statute requires FDA to refrain from approving an ANDA or a 505(b)(2) NDA if the methods and controls used for manufacture of the drug are inadequate to assure its identity, strength, quality, and purity.[3]

The Food and Drug Administration's (FDA's) official list, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), and the approved labeling for Lutathera, show the strength of Lutathera solely in terms of Volumetric Activity, *i.e.*, the total amount of radioactivity per unit volume. Specifically, the drug product strength, listed in terms of Volumetric Activity, is 10 mCi/mL (370 MBq/mL). The recommended dosage, described in the labeling in terms of Total Activity, is 7.4 GBq (200 mCi) at the time of injection. These metrics quantitate the radioactivity of the drug product, but fail to specifically measure or quantitate the total mass and concentration of the ligand (known as dotatate or $DOTA^0$-Tyr^3-Octreotate), which includes the ligand labeled with the radionuclide lutetium 177 (Lu-177), as well as unlabeled ligand. Both of these entities (labeled and unlabeled) compete for binding to the same cell surface receptors. The former, the labeled ligand, constitutes the active ingredient, lutetium Lu 177 dotatate (^{177}Lu-$DOTA^0$-Tyr^3-Octreotate).

The total mass and concentration of the ligand is most efficiently expressed by the Specific Activity of the product, defined as the amount of radioactivity per mole of the ligand. A proposed lutetium Lu 177 dotatate product defined only as having a nominal strength of 10 mCi/mL may not necessarily have the same Specific Activity as Lutathera. It may have a different total mass of ligand, along with different ratios of ligand labeled with Lu-177 versus unlabeled ligand. Such differences may impact the biodistribution of the product, *i.e.*, the amount of labeled ligand which binds to non-tumorous tissue (off-target) and to the tumor to deliver radiation. Accordingly, such a proposed lutetium Lu 177 dotatate product may not have the same clinical profile as Lutathera.

We therefore request that any proposed generic product submitted under section 505(j) of the FDCA, or proposed product submitted under section 505(b)(2) of the FDCA that relies on Lutathera, must demonstrate that it contains the same amount of the same active ingredient as Lutathera, and that the active ingredient has the same strength and potency as Lutathera based on criteria that are appropriate and necessary for radioligand therapeutics, including the Specific Activity and total mass of ligand, in addition to Volumetric Activity and Total Activity, to show that a proposed product is pharmaceutically equivalent

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[1] 21 USC 355(j)(2)(A)(iii); 21 CFR 314.92(a)(1), 314.127(a)(4)(i).

[2] 21 USC 505(b)(2); *see also* 21 CFR 314.54 (defining procedures and requirements for submission of a 505(b)(2) application).

[3] 21 USC 355(d), (j)(4)(A).

and can be expected to have the same clinical effect and safety profile as Lutathera when administered to patients under the conditions specified in the labeling.

ACTIONS REQUESTED

ADACAP respectfully requests the Commissioner to ensure that applications submitted under 505(j) and 505(b)(2) that rely on Lutathera include data necessary to show that a proposed product is pharmaceutically equivalent, bioequivalent, and can be expected to have the same clinical effect and safety profile as Lutathera when administered to patients under the conditions specified in the labeling, including Total Activity at time of injection, Specific Activity at time of calibration, and individual patient doses filled in the range 20.5-25.0 mL to ensure Total Activity of 7.4 GBq at time of injection.

STATEMENT OF GROUNDS

I. BACKGROUND

A. Lutathera® (lutetium Lu 177 dotatate)

Lutathera is the first in an emerging class of target specific radioligand therapeutics. The active ingredient is a radiolabeled somatostatin analog designed to target somatostatin receptors expressed in high concentrations on the surface of GEP-NET cells.[4]

Lutetium Lu 177 dotatate includes the somatostatin analog, Tyr^3-Octreotate, which functions as a targeting moiety. The targeting moiety is linked covalently to a chelator, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), to form the ligand, $DOTA^0$-Tyr^3-Octreotate (also known as dotatate). The ligand is then complexed with the 177 isotope of the heavy-metal lutetium, in the form of $^{177}Lu^{3+}$, to form the final drug substance.[5] The active ingredient is therefore a complex comprising $^{177}Lu^{3+}$ chelated to the DOTA moiety of $DOTA^0$-Tyr^3-Octreotate, to form ^{177}Lu-$DOTA^0$-Tyr^3-Octreotate.

Lutathera is manufactured with an excess of $DOTA^0$-Tyr^3-Octreotate ligand relative to $^{177}Lu^{3+}$ such that the drug product comprises both ^{177}Lu-$DOTA^0$-Tyr^3-Octreotate ("labeled $DOTA^0$-Tyr^3-Octreotate" or "labeled ligand") and $DOTA^0$-Tyr^3-Octreotate not complexed to $^{177}Lu^{3+}$ ("unlabeled $DOTA^0$-Tyr^3-Octreotate" or "unlabeled ligand") in defined proportions. Unlabeled ligand includes ligand complexed to metal ions other than $^{177}Lu^{3+}$, including the decay product of ^{177}Lu and other isotopes of

[4] *See* Lutathera Prescribing Information (Lutathera PI), Section 12.1; Merola E, Grana CM. Peptide Receptor Radionuclide Therapy (PRRT): Innovations and Improvements. *Cancers (Basel)*. 2023 May 30;15(11):2975 (Tab A).

[5] *See* Lutathera PI, Section 11.

lutetium that may be present.

Lutathera is available in one nominal strength, expressed in terms of Volumetric Activity (*i.e.*, radioactivity per unit volume) as 370 MBq/mL (10 mCi/mL) at time of calibration (Tc). The finished drug product is presented in a clear, colorless 30 mL single-dose vial containing a Total Activity of 7.4 GBq (200 mCi) ± 10% at the time of injection.[6] The entire contents of the vial are administered to deliver the recommended dosage of 7.4 GBq (200 mCi) of radioactivity. Each single-dose vial also contains acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), sodium hydroxide (0.64 mg/mL), ascorbic acid (2.8 mg/mL), diethylene triamine pentaacetic acid (DTPA) (0.05 mg/mL), sodium chloride (6.85 mg/mL), and Water for Injection. The recommended dosage regimen is 7.4 GBq every 8 weeks (±1 week) for a total of 4 doses.[7]

The drug substance and final drug product are dynamic systems. Lu-177 decays to stable hafnium-177 with a half-life of 6.647 days, by emitting beta-minus radiation with a maximum energy of 0.498 MeV (79%), and photonic radiation of 0.208 MeV (11%) and 0.113 MeV (6.2%).[8] Due to the decay of Lu-177, the relative proportions of labeled ligand and unlabeled ligand in the drug product change over time.

Once administered, the ligand binds to somatostatin receptors on the surface of the tumor cells, and then enters the cell via endocytosis. The beta-minus emission from Lu-177 induces formation of free radicals and DNA single-strand breaks, causing targeted cellular damage.[9] The constant radioactive decay means that Lutathera must be manufactured as an individual patient dose unit, and administered to that patient at a predetermined and fixed time in order to deliver the intended therapeutic dosage of the active ingredient.

B. Legal and Regulatory Background

Section 505(j) of the FDCA establishes an abbreviated approval pathway for a generic drug product that is "the same as" a drug product previously approved under section 505(b) (known as the reference listed drug, or RLD).[10] An applicant seeking to market a generic version of the RLD submits

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[6] *Id.* at Section 16.

[7] *Id.* at Section 11.

[8] *Id.*

[9] *See id.* at Section 12; Merola at 2.

[10] 21 USC 355(j).

an ANDA.[11] The ANDA approval process allows a generic applicant to rely entirely on FDA's previous finding of safety and effectiveness for the RLD rather than to independently demonstrate the safety and effectiveness of the proposed drug.[12] A generic applicant must demonstrate that the proposed generic drug product is "the same as" the RLD in all relevant respects—including active ingredient, dosage form, strength, route of administration, and (with narrowly permitted exceptions) labeling—and that it is bioequivalent to the RLD.[13]

One benefit of approval under an ANDA is to receive an A-rating as therapeutically equivalent to the RLD in the Orange Book. Therapeutic equivalence entails a finding of pharmaceutical equivalence (same active ingredient, dosage form, route of administration, and strength) and bioequivalence.[14] With an A-rating in the Orange Book, the generic drug product would be eligible in most states to be automatically substituted for the approved reference product at the pharmacy level. The underlying premise is that drug products sharing the characteristics that must be demonstrated for ANDA approval are necessarily pharmaceutically equivalent and bioequivalent, and therefore therapeutically equivalent to each other and to the RLD, meaning one can be substituted for the other "with the full expectation that the substituted product can be expected to have the same clinical effect and safety profile as the prescribed product."[15]

In contrast, Section 505(b)(2) of the FDCA establishes a pathway for NDAs that contain full reports of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference for those studies.[16] A 505(b)(2) applicant may rely on FDA's finding of safety and/or effectiveness for a listed drug only to the extent that the proposed product shares characteristics (*e.g.*, active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug.[17] A 505(b)(2) applicant is expected to establish a scientific bridge between the proposed product and the listed drug in order to demonstrate that reliance on the listed drug is scientifically

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[11] *Id.*

[12] *Id*.

[13] 21 USC 355(j)(2)(A)(ii)-(v).

[14] Orange Book, 2024, Preface 1.2.

[15] *Id*.

[16] 21 USC 505(b)(2); *see also* 21 CFR 314.54 (defining procedures and requirements for submission of a 505(b)(2) application).

[17] *See* 21 CFR 314.54(a)(1)(iii). As a technical matter, the FDA-approved product relied upon by a 505(b)(2) application is referred to as a "listed drug" in FDA's regulations rather than "reference listed drug" used for ANDAs. *Compare* 21 CFR 314.54 (referencing "listed drugs" for 505(b)(2) applications) *with* 21 CFR 314.3 (defining "reference listed drug" as the product relied upon by an ANDA). For ease of drafting, RLD and "listed drug" are treated as synonyms in this petition.

justified.[18] A 505(b)(2) NDA must also include original data to address any differences between the listed drug or drugs upon which it relies.[19]

C. Product-Specific Bioequivalence Guidance

FDA published a draft product-specific guidance (PSG) on bioequivalence requirements for proposed generic versions of lutetium Lu 177 dotatate in November 2019.[20] The PSG recommended that sponsors seek a waiver of bioequivalence based on regulatory provisions that instruct FDA to waive *in vivo* bioequivalence studies for products that are parenteral solutions for injection and that include the same composition of ingredients. Specifically, the PSG states as follows:

> To qualify for a waiver from submitting an in vivo bioequivalence (BE) study on the basis that BE is self-evident under 21 CFR 320.22(b), a generic Lutetium dotatate Lu-177 10 mCi/mL product must be qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD).
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> An applicant may seek approval of a drug product intended for parenteral use that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Under the regulations, an ANDA for a parenteral solution must include information to show that the proposed product is Q1 and Q2 the same as the RLD.[21] According to FDA's draft PSG for Lutathera, Q1 (qualitative sameness) means that the test product uses the same inactive ingredients as the RLD product, and Q2 (quantitative sameness) means that the concentrations of the inactive ingredients in the proposed generic product are within ±5% of the RLD. Certain additional departures in Q1/Q2 sameness with respect to preservatives, buffers, or antioxidants can be permitted. These so called "exception excipients" do not need to be the same as the RLD provided the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The PSG included no recommendations regarding demonstrating the strength of the proposed

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[18] Guidance for Industry, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019) at 4.

[19] *Id.*

[20] The PSG refers to "lutetium dotatate Lu-177" which is synonymous with "lutetium Lu 177 dotatate."

[21] 21 CFR 314.94(a)(9)(iii).

product relative to the listed drug, or other instructions to ensure pharmaceutical equivalence. ADACAP submitted comments proposing a number of changes to the draft version of the PSG in March 2021. To date, FDA has not responded to these comments or made any revisions to the PSG.

II. ARGUMENT

Radioligand therapeutics are an emerging class of complex drugs. Unlike most other drug products which are static and fixed, radiotherapeutics are dynamic systems involving several interacting and changing components. The safety and effectiveness of the system relies on delivery of cytotoxic levels of radiation directly to tumor sites. The drug product includes both the labeled ligand, *i.e.*, the active ingredient, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, and unlabeled ligand in defined quantities. Both of these components compete for binding sites on the surface of GEP-NET cells.

The key properties in ensuring that each dose of Lutathera contains and delivers the same amount of the same active ingredient to each patient, with the same activity at the site of drug action, include the following:

Activity Measurement	**Definition**
Volumetric Activity	Radioactivity per unit volume at time of calibration (Tc)
Total Activity	Total radioactivity per vial at time of injection
Specific Activity	Amount of radioactivity per mole of the ligand, DOTA^{0}-Tyr^{3}-Octreotate, at time of calibration (Tc)

Because labeled and unlabeled ligand compete for binding to the same cell surface receptors, the ratio of labeled ligand to unlabeled ligand, as well as total amount of ligand have an effect on target engagement by the labeled ligand. Therefore, the Specific Activity, Total Activity, and the Volumetric Activity, as defined, of the final drug product, must be specified and controlled within the ranges shown to be safe and effective in the clinical investigations.

A 505(j) generic version of Lutathera must demonstrate pharmaceutical equivalence, including an evaluation of product strength based on analytical considerations that are tailored to radioligand therapeutics, and necessary to assure product sameness. Such an evaluation should accurately measure not only the amount of active ingredient in the dosage unit in terms of Volumetric Activity, but also the Specific Activity and total mass of ligand (both labeled and unlabeled), and Total Activity at the time of injection. Similarly, any 505(b)(2) NDA seeking to rely on Lutathera, must bridge to the listed drug, including an evaluation of Specific Activity, Total Activity, and the Volumetric Activity relative to the listed drug. If data are not included or do not show sameness with respect to these measurements,

additional studies must be required to demonstrate the safety and effectiveness of the proposed product.

A. FDA Must Refrain from Approving an ANDA or 505(b)(2) NDA Unless Data Show that the Proposed Product has the Same Total Activity and Specific Activity as Lutathera

1. Determining the Strength and Pharmaceutical Equivalence of Lutetium Lu 177 Dotatate Products Requires an Assessment of the Total Activity at Time of Injection, Total Mass of Ligand, and Specific Activity at Time of Calibration

To rely on FDA's finding of safety and effectiveness for a previously approved drug product, the sponsor of a generic drug product submitted under an ANDA must be pharmaceutically equivalent to the RLD. Among other things, the proposed product must be the same as the listed drug with respect to its active ingredient, route of administration, dosage form, and the strength. Similarly, a 505(b)(2) NDA that seeks to rely on a listed drug must bridge to the drug, which may include, among other things, information and data showing that that it includes the same active ingredient or active moiety, has the same strength, and/or is bioequivalent to the listed drug.

FDA defines the term "strength" as follows:

> *Strength* is the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes:
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> (1)(i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable.
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> (ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume); or
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> (2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in paragraph (i) of this definition do not apply (e.g., certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).[22]

The weights and measures used to determine the "strength" of a drug product may differ based on the type of drug product or dosage form. For liquid parenteral drug products in an injection dosage form,

[22] 21 CFR 314.3(b); Orange Book, 2024, Preface 1.2.

FDA has a longstanding history of considering a difference in either the total quantity of drug substance, or the concentration, to be a difference in the "strength" of the product.[23] The agency has explained that differences in either the concentration or the total drug content of a parenteral drug product can introduce risks for medication errors and incorrect dosing of patients. Defining strength to include both concentration and total drug content mitigates these risks. [24] Accordingly, the agency routinely lists the strength of a parenteral drug product in the Orange Book in terms that reflect both the total quantity of drug substance in the drug product container, and the concentration of the active ingredient in the drug product in units of activity or mass, over a denominator in units of volume or mass.

In addition, FDA defines pharmaceutical equivalence as follows:

> *Pharmaceutical equivalents* are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.[25]

Pharmaceutical equivalence captures the concept of "sameness" of strength by requiring that drug products "contain identical amounts of the identical active ingredient" or "deliver identical amounts of the active drug ingredient over the identical dosing period."[26] The regulatory definition of strength and the related concept of pharmaceutical equivalence center on the total amount or concentration of the drug substance present in a drug product, or alternatively, on the amount of drug substance delivered or deliverable from the dosage form. Strength is therefore a quantitative measurement of the active ingredient contained in the dosage form, or delivered or deliverable from the dosage form. As illustrated by FDA's concerns for parenteral products, the criteria used for evaluating strength are designed to allow administration of the correct dosage and reduce the risk of medication error. Pharmaceutical equivalent drug products must also "meet the identical compendial or other applicable standard of identity, strength,

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[23] *See* 80 FR 6802, 6816 (Feb. 6, 2015).

[24] *See id.*

[25] 21 CFR 314.3(b); Orange Book, 2024, Preface 1.2.

[26] *See id*.

quality, and purity, including potency."[27] Under the statute, FDA should refrain from approving an ANDA or a 505(b)(2) NDA if the methods and controls used for manufacture of the drug are inadequate to assure its identity, strength, quality, and purity.[28]

For a radioligand therapeutic, strength, potency, and pharmaceutical equivalence are complicated by the impact of the mass dose of the ligand. The total mass of the ligand includes labeled ligand (*i.e.*, the active ingredient lutetium Lu 177 dotatate) and unlabeled ligand, both of which compete for binding to the same cell surface receptors. This is further complicated by the dynamism of the system. The amount of the active ingredient per unit of volume or mass, changes over time. The drug product is manufactured with a defined Volumetric Activity and Specific Activity at Tc to provide a Total Activity of 7.4 GBq (200 mCi) ±10% at the time of injection. Since Lutetium-177 decays to stable hafnium-177 with a half-life of 6.647 days, the active ingredient (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, *i.e.*, the labeled ligand) is therefore in a constant state of change to the unlabeled ligand, ^{177}Hf-DOTA^{0}-Tyr^{3}-Octreotate. Thus, between Tc and time of injection the amount of labeled ligand decreases, the amount of unlabeled ligand (including ^{177}Hf-DOTA^{0}-Tyr^{3}-Octreotate) increases, the Total Activity decreases, the Specific Activity decreases, and the Volumetric Activity decreases. To compensate for these changes, and to deliver the recommended dosage having a Total Activity of 7.4 GBq (200 mCi) at the planned time of injection, the volume of drug product dispensed into the vial during manufacture is adjusted within defined ranges (20.5 mL to 25.0 mL) (see Section II.B, *infra*).

In summary, determining the strength and potency of the product for comparative purposes is challenged both by the changing radioactivity over time, the specific radioactivity associated with the active ingredient, and the other complex and dynamic variables of the product.

FDA has not issued any comprehensive guidance on the issue of pharmaceutical equivalence for radiopharmaceuticals generally, or radioligand therapeutics specifically.[29] In the regulations governing good manufacturing practices for positron emission tomography (PET) drugs (which are imaging agents rather than therapeutic agents), the strength of the product is defined to mean "the concentration of the active pharmaceutical ingredient (radioactivity amount per volume or weight at time of calibration)."[30]

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[27] *See id*.

[28] 21 USC 355(j)(4)(A), (d).

[29] FDA has issued a number of important guidances relating to nonclinical and quality considerations for radiopharmaceuticals. *See, e.g.*, Guidance for Industry, *Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations* (Aug. 2019); Guidance for Industry, *Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations* (Aug. 2018); Guidance for Industry, *Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals* (Nov. 2011). None of these documents directly address the issue of assessing the strength of a radiopharmaceutical.

[30] 21 CFR 212.1.

Similarly, in a 2012 guidance on PET drugs, the agency stated "[f]or PET drugs, the radioactive concentration (*e.g.*, mCi/mL) at the calibration time is generally considered to be the strength."[31] However, many PET drugs and other approved radiopharmaceuticals, including products that may be shipped cold to be completed on site, are listed in the Orange Book without a specific strength.

Lutathera's strength is listed in the Orange Book in terms of Volumetric Activity as 10 mCi/mL (which is 370 MBq/mL) at Tc. For all the reasons described above, this static volumetric measurement is not on its own an adequate measure of Lutathera's strength. It does not provide any information about the total mass of the ligand present (both labeled and unlabeled ligand), nor does it fully express the dynamic nature of the activity of the product. In addition to Volumetric Activity, two further attributes of strength must be assessed to show pharmaceutical equivalence to Lutathera.

First, as for most parenteral drug products, the strength should also reflect the total quantity of the active ingredient within the dosage container, in relevant units of mass or activity. As the agency has explained, it has a longstanding policy of considering either a difference in concentration or in the total quantity of drug substance to be a difference in the "strength" of the product.[32] Defining strength to include both concentration and total drug content mitigates the risk of medication error.[33] Lutathera is supplied in a single-dose, ready-to-use vial, containing the full dosage expressed as a Total Activity of 7.4 GBq (200 mCi) ±10% at the time of injection. A proposed lutetium Lu 177 dotatate product relying on Lutathera should include the same amount of drug substance in the container closure expressed in terms of Total Activity at time of injection.

Second, an accurate evaluation of the strength and pharmaceutical equivalence of a proposed product must include the Specific Activity of the active ingredient at Tc. Volumetric Activity and Total Activity do not specifically measure or quantitate the total mass and concentration of the ligand $DOTA^0$-Tyr^3-Octreotate, which includes labeled ligand (*i.e.*, ^{177}Lu-$DOTA^0$-Tyr^3-Octreotate) and unlabeled ligand. As discussed above, labeled ligand and unlabeled ligand compete for binding to the same cell surface receptors, and their relative proportions in the drug product must fall in a specific range between Tc and time of injection. Specific Activity measures radioactivity per mole of the ligand $DOTA^0$-Tyr^3-Octreotate and is widely considered one of the most important parameters in radiopharmaceutical development.[34] A

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[31] Guidance for Industry, *FDA Oversight of PET Drug Products – Questions and Answers* (Dec. 2012).

[32] *See* 80 FR at 6816.

[33] *See id.*

[34] Welch, M. J., *et al.* A historical perspective on the specific activity of radiopharmaceuticals: What have we learned in the 35 years of the ISRC? *Nuclear Medicine and Biology*, 40(3), 314–320 (2013) (Tab B). The European Medicines Agency scientific guideline on radiopharmaceuticals provides that specifications for radiopharmaceutical drug products "should also include radiochemical identity and purity, chemical purity and, where relevant specific radioactivity, radionuclidic identity

proposed lutetium Lu 177 dotatate product having the same Volumetric Activity at Tc, and Total Activity at time of injection does not necessarily have the same Specific Activity as Lutathera. It may have a different total mass of ligand and/or different relative amounts of labeled ligand versus unlabeled ligand. A product that does not match the Specific Activity of Lutathera may therefore result in different levels of engagement between the active ingredient and the target cell surface receptors. Unless the proposed product demonstrates sameness with respect to Specific Activity, it cannot be presumed that it will result in the same biodistribution as Lutathera and hence the same clinical profile. Even if the proposed product matches Lutathera in terms of Volumetric Activity at Tc and Total Activity at time of injection it still cannot be presumed to deliver the same amount of radiation to the target tissue unless it also has the same Specific Activity as Lutathera.

FDA must refrain from approving an ANDA or a 505(b)(2) NDA if the methods and controls used for manufacture of the proposed drug product do not assure its identity, strength, quality, and purity.[35] Accordingly, in order for a proposed product to be considered the same strength as Lutathera, and to allow a finding of pharmaceutical equivalence, including equivalent potency, the applicant must include information on Specific Activity at Tc, in addition to Volumetric Activity at Tc, and Total Activity at time of injection.

2. Evaluation of Specific Activity is Also Required for Formulation Sameness (Q1/Q2) and Bioequivalence

Under the regulations, an ANDA for a parenteral solution must demonstrate Q1/Q2 sameness with regard to its composition of inactive ingredients (except for narrowly permitted difference in preservatives, buffers, or antioxidants).[36] Similarly, for certain drug products, FDA regulations permit a biowaiver; for example, if the drug product "[i]s a parenteral solution intended solely for administration by injection . . . and [c]ontains the same active and inactive ingredients in the same concentration" as the listed drug, FDA may waive the usual requirement for *in vivo* bioequivalence.[37]

A finding that a proposed lutetium Lu 177 dotatate product and Lutathera are Q1/Q2 the same requires quantitation of the total mass of ligand, as well as the relative proportions of labeled ligand and

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and purity." EMEA/CHMP/QWP/306970/2007 – Guideline on radiopharmaceuticals (Tab C). Similarly, the national regulatory authority for drugs and medical products in Switzerland, Swissmedic, notes that "attributes to be specifically verified for radiopharmaceutical medicinal products also include. . . . specific activity." Swissmedic Guidance document – Authorization radiopharmaceutical (Tab D).

[35] 21 USC 355(j)(4)(A), (d).

[36] 21 CFR 314.94(a)(9)(iii).

[37] *Id.*

unlabeled ligand. The total mass of ligand, along with the relative proportions of labeled ligand and unlabeled ligand, are controlled components.[38] By definition, an inactive ingredient is any component other than the active ingredient. Unlabeled ligand is therefore a controlled component that must be evaluated as part of the overall determination of Q1/Q2 sameness.

Furthermore, the inferences that permit FDA to waive bioequivalence studies for certain drug products, do not apply to lutetium Lu 177 dotatate unless total mass of ligand and ratio of unlabeled ligand to labeled ligand are shown to match the listed drug. A finding of bioequivalence requires FDA to determine that there is no significant difference in the rate and extent to which the active ingredient reaches the proximate site of molecular action of the drug.[39] FDA's rationale for bioequivalence waivers is scientifically reasonable only when formulation-dependent variables that could affect bioavailability at the site of drug action have been eliminated. In this case, differences in quantities of unlabeled ligand, labeled ligand, and total ligand mass delivered to patients may result in clinically meaningful differences at the site of drug action by the active ingredient because labeled ligand and unlabeled ligand compete for binding to the same cell surface receptors.

In sum, in order to be approved under an ANDA an applicant must demonstrate Q1/Q2 sameness. Similarly, to qualify for a biowaiver under the regulations, an ANDA or 505(b)(2) NDA must show that the proposed product is Q1/Q2 the same as the listed drug it relies on. In this case, Q1/Q2 sameness requires quantitation of the total mass of ligand, as well as the relative proportions of labeled ligand and unlabeled ligand.

B. Filling to an Individualized Patient Dose is an Integral Aspect of Pharmaceutical Equivalence and Therapeutic Equivalence for Lutetium Lu 177 Dotatate Products

An integral aspect of Lutathera is the necessity for individualized patient doses. The finished drug product is a sterile ready-to-use solution for infusion containing a suitable volume of solution to deliver the recommended dose of 7.4 GBq (200 mCi) of radioactivity *at time of injection*. Certificates of release report the Total Activity at both Tc and the time of injection. Considering the variable injection time and constant decay of the radionuclide, the filling volume needed for an activity of 7.4 GBq (200 mCi) at the time of injection is calculated and can range from 20.5 mL to 25.0 mL. The longer the time between Tc and the time of injection, the greater the fill size to take into account the half-life of Lu-177.

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[38] 21 CFR 314.3(b). A component is "any ingredient intended for use in the manufacture of a drug product . . . ." *Id.*

[39] "Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available *at the site of drug action* when administered at the same molar dose under similar conditions in an appropriately designed study." 21 CFR 314.3(b) (emphasis added).

To guarantee that a proposed drug product delivers the same amount of the active ingredient at the time of injection, applicants must address the logistical challenge of filling the vial to an individually timed dose. In the case of Lutathera, the total radioactivity and total quantity of the active ingredient contained in the vial at the time of calibration will necessarily be higher than the quantities that are contained in the dosage form and available to the patient at the time of injection. FDA must require applicants to provide for patient-specific volumetric fill, calibrated based on the specific time of injection and Tc. As described above (Section II.A.1, *supra*) this range of filling to an individually-timed dose is another aspect of the product's strength—to obtain a ready-to-use vial containing 7.4 GBq at time of injection.

In addition, generic 505(j) ANDA products, with limited exceptions, must have the same labeling as the RLD—and to be considered therapeutically equivalent two products must be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Lutathera's labeling provides three alternate methods of administration: (1) by gravity method, (2) by infusion (peristaltic) pump, or (3) by syringe pump. The recommended dosage of 7.4 GBq (200 mCi) is administered using any of these three methods. In all cases, to administer the recommended dosage of 7.4 GBq (200 mCi) no less than the total content of the vial (ranging from 20.5 mL to 25.0mL depending on the intended time of injection) must be infused.

A generic 505(j) ANDA version of Lutathera must include the same labeling. In order to do so, and to facilitate administration in accordance with the approved labeling, it must be supplied in the same fill size range of 20.5 mL to 25.0 mL, and no less than the total contents of the vial must be infused to deliver the 7.4 GBq (200 mCi) recommended dosage. A proposed generic cannot, for example, be labeled with instructions to administer only a portion of the vial to administer the recommended 7.4 GBq dose because it would require substantial labeling changes. Such omissions and/or supplanting the labeling with new Preparation and Administration information would fail to comply with FDA's labeling regulations for generic drugs. [40]

In sum, in order for a proposed generic lutetium Lu 177 dotatate product to be labeled the same strength as Lutathera, to be approved as pharmaceutically equivalent, and include the same labeling—to avoid medication error, and to facilitate administration in accordance with the labeling—an equivalently calibrated, variable fill, conforming to the listed drug, must be required. A proposed generic lutetium Lu

[40] Under the statute, generics must have the same labeling as the RLD except for differences due to the drugs being produced or distributed by different manufacture. 21 USC 355(j)(2)(A)(v). Under the regulations, allowable differences may include the "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity" so long as "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 CFR 314.94(a)(8)(iv); 21 CFR 314.127(a)(7). Addition of language other than minor attendant changes so that the labeling reads correctly is generally not permitted. FDA Petition Response, Docket No. FDA-2010-P-0087 (Aug. 3, 2010).

177 dotatate product that does not conform to these conditions must be submitted under section 505(b) of the FDCA, with clinical data showing safety and effectiveness.

III. CONCLUSION

Successful treatment with Lutathera relies on the delivery of the complex moiety, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, to the GEP-NET cell. An assessment of the strength and pharmaceutical equivalence for a proposed drug product that references Lutathera requires an accounting of the dynamism of the product. For the reasons discussed above, FDA must ensure that generic and 505(b)(2) versions of Lutathera can demonstrate pharmaceutical equivalence, including an evaluation of product strength based on analytical considerations that are tailored to radioligand therapeutics. Most critically, Specific Activity and total mass of ligand are necessary for determining the strength of lutetium Lu 177 dotatate products. If data are not included or do not show sameness of strength with respect to these measurements, additional clinical studies would be required to demonstrate the safety and effectiveness of the proposed product.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: November 13, 2023. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None, other than my compensation as an employee of Novartis Pharmaceuticals Corporation. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Kang Barinder

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