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BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
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CITIZEN PETITION

Hyman, Phelps & McNamara, P.C. submits this Citizen Petition pursuant to the Food and Drug Administration's ("FDA") regulations set forth at 21 C.F.R. § 10.30 and the Federal Food, Drug, and Cosmetic Act ("FDC Act").[1] For the reasons discussed herein, we respectfully request that the U.S. Food and Drug Administration refuse to approve any New Drug Application ("NDA"), including any 505(b)(2) NDA, seeking approval of Technetium-99m ("Tc-99m") produced in conventional generators (single-column chromatographic utilizing aluminum oxide ("alumina") column based separation systems) by way of neutron capture technology. As explained below, due to the limitations of conventional generators in producing safe and effective Tc-99m through neutron capture—including risks of breakthrough contamination and the potential for marketplace confusion that could result in medication errors—the benefits of such a Tc-99m product cannot outweigh the risks. Given the eradication of these safety concerns by newer technologies, approving such a drug product would needlessly expose patients to safety risks without enhancing efficacy. Consequently, FDA should refuse to approve a Tc-99m product produced through neutron capture in a conventional generator under section 505(d) of the FDC Act.

[1] To the best of our knowledge, no Abbreviated New Drug Applications or New Drug Applications filed under section 505(b)(2) of the FDC Act with a User Fee Goal Date within 150 days are pending. Consequently, this Petition is not filed under section 505(q) of the FDC Act.

I. ACTIONS REQUESTED

We respectfully request that FDA refuse to approve any NDA seeking approval of a conventional Tc-99m generator or Tc-99m product that relies on neutron capture technology given the advances in Tc-99m production that renders such an approach obsolete.

II. STATEMENT OF GROUNDS

A. Factual Background

Tc-99m is a radioactive isotope used in millions of medical diagnostic procedures each year. Easily detectable by gamma rays with photon energy, Tc-99m has a short half-life of approximately 6 hours, which helps keep patient total radiation exposure low. However, due to this short half-life, Tc-99m cannot be stockpiled and must be continuously produced and delivered to medical imaging centers. As a result, sponsors develop Tc-99m generators and "cold kits" for distribution to medical facilities that are used to produce Tc-99m on-site. The generators produce the parent isotope of Tc-99m, Molybdenum-99 ("Mo-99"), which is a radionuclide with a longer half-life of 2.75 days that ultimately decays into Tc-99m.

Tc-99m generators extract the metastable Tc-99m isotope from a decaying sample of Mo-99 relying on one of two primary procedures: fission of uranium-235 ("U-235") —either low enriched or high enriched uranium—and neutron capture of molybdenum-98 ("Mo-98"). Those relying on fission operate by irradiating U-235 with neutrons in research reactors. The irradiation causes the U-235 to absorb thermal neutrons and then fission, which produces multiple products, including Mo-99. Mo-99 is then recovered in liquid form, which is used to prepare Mo-99/Tc-99m generators that are shipped to nuclear pharmacies, hospitals, and clinics. In that generator, the Mo-99 decay to Tc-99m, which is periodically extracted via a physiologically acceptable solvent over the course of 1-2 weeks for use in Tc-99m-based imaging procedures for medical diagnostic use. U-235 Fission has emerged as the primary manufacturing method for producing Mo-99 and, by extension, Tc-99m. *See* National Academy of Sciences ("NAS"), Molybdenum-99 for Medical Imaging, 29 (2016) ("Uranium fission is considered to the 'gold standard' process for producing Mo-99 . . . ."). For that reason, most of the Tc-99m generators currently marketed in the U.S. use fission technology.

An alternative Tc-99m extraction process starts with procured (natural molybdenum or enriched) Mo-98, which is bombarded by neutrons. *Id*. The Mo-98 captures a neutron (i.e., "neutron capture") and is transmuted to Mo-99 while releasing

gamma emissions. Similar to fission Tc-99m, the resulting Mo-99 is dissolved and the ensuing solution used to prepare Mo-99/Tc-99m generators that are shipped to nuclear pharmacies and/or medical imaging centers. U.S. Dept. of Energy, Production of Molybdenum-99 Using Neutron Capture Methods (Jan. 2011). Again, in the generator, the Mo-99 decays into Tc-99m. Neutron capture is a less efficient process for producing Mo-99 than fission and has a lower specificity activity, requiring many more total molecules of molybdenum to produce equivalent mCi levels of daughter Tc-99m in comparison to U-235 fission Mo-99. NAS, Molybdenum-99 for Medical Imaging § 2.3.1 (2016).

"Conventional" Tc-99m generators separate Mo-99 from other by-products using alumina column separation systems designed for high specific activity Mo-99. These columns have the diameter of a large pencil and contain approximately 2 grams or less of alumina. The process, called elution, uses a saline solution to wash the daughter Tc-99m from the column. That Tc-99m may be administered to patients directly or mixed with a cold reagent kit to produce a variety of Tc-99m-labeled radiopharmaceutical imaging agents. Generator users are required to test each elution for Mo-99 breakthrough. 10 C.F.R. § 35.204(2)(b).

Typically, Mo-99 produced by neutron capture cannot be used in conventional Tc-99m generators designed for the production of fission Mo-99 generators because of the significantly lower specific activity of Mo-99 produced by neutron capture methods. NAS, Molybdenum-99 for Medical Imaging § 2.3.1 (2016). For that reason, most Tc-99m currently is produced by nuclear fission, but neutron capture (or irradiation) was the primary method of production in the 1960s and 1970s. These generators, however, required large columns packed with large quantities of alumina, as well as a large volume of saline because this process was so inefficient and the Mo-99 produced had a low specific activity. NDA 202158, Cross-Discipline Team Leader Review, at 2 (Oct. 11, 2013).[2] That large saline volume resulted in low Tc-99m concentration, which is suboptimal for imaging purposes. Because of these limitations, the market shifted to nuclear fission technology, relying on enriched uranium U-235 fission. *Id.*

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[2] "Low specific activity 99Mo, as used in the early technetium generators, required large columns, packed with large quantities of alumina (aluminum oxide). As a result, the generators were large and unwieldy for use in nuclear pharmacies. Moreover, with the large columns, the 99mTcO4 - (formed from nuclear decay of adsorbed 99MoO42-) had to move with saline elution through a large volume of alumina to the column exit. That resulted in 99mTcO4 - in a relatively large saline volume, leading to a low 99mTcO4 - concentration." NDA 202158, Cross-Discipline Team Leader Review, at 2 (Oct. 11, 2013).

Due to shortages of uranium, as well as potential for uranium diversion, the nuclear medicine industry—at government urging—has been exploring alternative methods for producing Tc-99m.[3] *Id.* As a result, interest in the reintroduction of neutron capture technology has surged. *See id.*

In 2018, FDA approved a new generator using neutron capture technology: the RadioGenix System. NDA 202158, Approval Letter (Feb. 8, 2018). Importantly, the RadioGenix System uses a novel automated multi-column generator that serves as an alternative to conventional generators manufactured with fission Mo-99 with small size alumina columns (i.e., 2 gram of alumina or less in pencil size columns) or as an alternative to the impractical and inefficient neutron irradiation process (which, given this limitation, is not currently used). NDA 202158, Risk Assessment, at 5 (Oct. 11, 2013). In addition to an alumina column, the RadioGenix System utilizes a novel primary separation column that extracts Tc-99m from Mo-99 using Aqueous Biphasic Extraction Chromatography (ABEC). This biphasic extraction technology allows the generator to effectively and efficiently use low specific activity Mo-99 to produce Tc-99m in relatively high concentrations. RadioGenix also utilizes a secondary alumina column to prevent Mo-99 breakthrough.

B. Legal Background

Under the FDC Act, FDA must approve a drug before it may be sold lawfully or distributed in interstate commerce. *See* 21 U.S.C. § 355(a). Sponsors seeking to market new drugs submit a New Drug Application ("NDA"), which must include studies demonstrating that the proposed product is safe and effective for its intended use. 21 U.S.C. § 355(b). NDAs that include "full reports of investigations" of safety and effectiveness are filed as "standalone NDAs" under section 505(b)(1) of the FDC Act while those that rely on studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference" must be submitted under section 505(b)(2). In practice, a 505(b)(2) NDA allows sponsors to receive FDA approval based on studies that are not developed by the applicant; such studies may have been submitted previously to FDA by another 505(b) applicant or published in literature. FDA, Guidance for Industry: Applications Covered by Section 505(b)(2), at 1 (Draft, Oct. 1999). If a new drug cannot be approved as a 505(b)(2) NDA, a sponsor must conduct clinical and non-clinical studies to demonstrate that the proposed drug is safe and effective for its intended use. *Id.*

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[3] "But, in recent years, there have been recurrent shortages of fission 99Mo, caused by aging nuclear reactors and the consequent shutdowns to make repairs to comply with safety regulations." *Id.*

Whether a 505(b)(1) or 505(b)(2) NDA is submitted, FDA may not approve the application if the investigations required are inadequate to support a finding of safety or provide evidence that the proposed drug is safe. 21 U.S.C. § 355(d)(1), (d)(2), (d)(4); 21 C.F.R. § 314.125(b)(1), (b)(2), (b)(4). In addition to adequate testing for safety and effectiveness, the NDA must also include data to demonstrate that the methods used in the manufacture or processing of the proposed drug product are adequate to preserve its identity, strength, quality, and purity. 21 U.S.C. § 355(d)(3). FDA may also refuse to an approve an NDA if "upon the basis of any other information before him with respect to such drug," there is "insufficient information to determine whether such drug is safe for use . . . ." *Id.* at (d)(4). FDA must apply "a structured risk-benefit assessment framework" to the new drug approval process "to facilitate the balanced consideration of benefits and risks . . . ." *Id.* at (d). These statutory factors are further codified in Agency implementing regulations set forth in 21 C.F.R. § 314.125.

Nor may FDA approve an NDA submitted under Section 505(b) where "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d)(5); 21 C.F.R. § 314.125(b)(5). "Substantial evidence" is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. § 355(d). Typically, substantial evidence requires two adequate and well-controlled trials.

Radioactive pharmaceuticals are subject to the same regulatory approval process as traditional pharmaceuticals and therefore sponsors must demonstrate the safety and efficacy of their proposed product. FDA, Guidance for Industry: Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments, at 1 (June 2004). But, because FDA has determined that special considerations apply to radioactive pharmaceuticals, the Agency adopted specific regulations governing approval of such products. Under this regulatory framework, both the radionuclide (the Tc-99m end product) ***and*** the radionuclide generator used to prepare the substance are considered the drug product. *See* 21 C.F.R. § 310.3(n). Therefore, FDA is required to review both the Tc-99m and its generator for safety and efficacy. *See* 21 C.F.R. Part 315. Effectively, however, FDA looks to the resulting drug ***substance*** to evaluate safety, using radiation dose, pharmacology and toxicology, adverse reaction profile, and clinical experience as

metrics. 21 C.F.R. § 315.5. For efficacy, FDA reviews data supporting the proposed diagnostic claims. 21 C.F.R. § 315.6. Overall, FDA examines the proposed use, the pharmacological and toxicological activity, and the estimated absorbed radiation dose of the radiopharmaceutical. 21 C.F.R. § 315.3. The amount of data required depends on the "available information regarding the safety of the diagnostic radiopharmaceutical" based on "safety risk." 21 C.F.R. § 315.6(c)(2). The generator itself is reviewed as a drug, with particular emphasis on Chemistry, Manufacturing, and Controls, and CDER typically requests consultation with the Center for Devices and Radiological Health to evaluate the device function. Tc-99m reagent kits are reviewed as drugs—separately from the generator—and must be compatible with all commercially available generators unless otherwise limited in labeling.

In practice, many Tc-99m kits and generators are approved through the 505(b)(2) pathway. Because Tc-99m has been FDA-approved since the 1970s, recently-approved Tc-99m NDAs have relied on safety and efficacy data submitted in already-approved NDAs without the need for additional clinical or preclinical data. *See e.g.,* Summary Review for Regulatory Action, NDA 202158, at 2 (Nov. 1, 2013) ("This NDA submission contains no new clinical or preclinical data and none are needed because the final drug product (NaO4 99Tc injection) for this NDA is the same product prepared with the two technetium generators marketed in the US."). In such circumstances, the sponsor must show only that Tc-99m end-product meets the purity and quality specifications set forth in the applicable United States Pharmacopeia ("USP") monograph. *Id.* USP has adopted different compendial standards for fission-derived and neutron capture-derived Tc-99m. Specifically, USP specifies a general limit of 0.5 µCi of gamma emitting impurities per mCi of Tc-99m for neutron derived Tc-99m, but has more restrictive and specific limits for fission derived Tc-99m: I-131-0.05µCi/mCi; Ru-103-0.05µCi/mCi; Sr-89-0.0006 µCi/mCi, Sr-90-0.00006 µCi/mCi, and other beta/gamma-0.1 µCi/mCi, alpha-0.000001 µCi/mCi. USP Pharmacopeia, National Formulary 38, Monograph, Sodium Pertechnetate Tc-99m Injection (May 2018 - present). Thus, the USP specifications for fission-derived and capture-derived Tc-99m differ.

C. FDA Should Refuse to Approve Any Tc-99m Produced Through Neutron Capture in Conventional Generators Because the Risks Outweigh the Benefits.

For the last 50 years, most production of Tc-99m has relied on nuclear fission using highly enriched uranium ("HEU"); however, due to widespread concerns of diversion, the federal government has incentivized the development of Tc-99m generators that do not rely on HEU. American Medical Isotopes Production Act, Pub. L. 112-239 (2012); National Nuclear Security Administration, NNSA's Molybdenum-99

Program: Establishing a Reliable Domestic Supply of Mo-99 Produced Without Highly Enriched Uranium (last visited Sept. 14, 2022), https://www.energy.gov/nnsa/nnsa-s-molybdenum-99-program-establishing-reliable-domestic-supply-mo-99-produced-without. To this end, the nuclear medicine industry is changing: Lantheus Medical Imaging and Curium Pharma, for example, have developed Tc-99m generators that use Low Enriched Uranium ("LEU") while North Star Medical Radioisotopes, LLC has developed a multi-column generator for neutron capture. *See e.g.,* Lantheus, Lantheus Medical Imaging Introduces Low-Enriched Uranium (LEU) TechneLite® Generator (Jan. 9, 2013); Curium, Curium Is the First North American Manufacturer Offering Exclusively 100% LEU Generators (Jan. 16, 2018); NDA 202158 (2018). This focus on developing new Tc-99m technology has led to new players in the industry announcing plans to recycle neutron capture technology to "drop in" to existing conventional generators. *See e.g.* BWXT Technologies Inc., BWXT Successfully Demonstrates Labeling of Cold Kits with its Mo-99 / Tc-99m Technology (last visited Sept. 14, 2022), https://www.bwxt.com/news/2020/02/25/BWXT-Successfully-Demonstrates-Labeling-of-Cold-Kits-with-its-Mo-99--Tc-99m-Technology. The potential resurgence of this previously obsolete nuclear capture technology raises serious safety and efficacy concerns.

1. Concerns with Tc-99m Product

Neutron capture conventional generators became obsolete for a reason: The risks associated with the safety, efficacy, and efficiency of their Tc-99m production greatly outweighed the benefits. And the same concerns that ultimately resulted in market withdrawal of conventional Tc-99m generators using neutron capture still exist today.

Safety—particularly with respect to radiopharmaceuticals—is paramount, and Tc-99m produced through neutron capture in conventional generators, manufactured with comparatively small pencil-sized columns containing approximately two grams or less of alumina, is significantly less safe than that produced using the high specific activity Mo-99 that is routinely achieved by U-235 fission. This is because significant Mo-99 breakthough is associated with the use of low-specific activity neutron Mo-99 to manufacture generators using conventional small size alumina columns. Breakthrough Mo-99—along with the potential for further isotopic contamination—is by far the most significant concern with Tc-99m production. Shameem Hasan & Mark Prelas, Molybdenum-99 production pathways and the sorbents for 99Mo/99mTc generator systems using (n, γ) 99Mo: a review, 2 SN Appl. Sci. 1782, at § 4.2 (Oct. 2020) ("Hasan and Prelas"). The amount of Mo-99 remaining in eluted Tc-99m is directly associated with increased radiation doses while simultaneously decreasing the efficacy of the Tc-99m. It therefore is important that the amount of Mo-99 eluted with the Tc-99m is as

small as possible so that patients are not exposed to radiation dose without benefit. NAS, 2016 Report, at 44. Thus, "[f]rom the stand point of patient radiation safety, the amount of [Mo-99] in the elution should be as low as possible because the presence of [Mo-99] in the elution may interfere with labeling process and lead to clumping of red blood cells and possible microemboli." Hasan and Prelas at § 4.2.

Unless a generator is specifically designed to address breakthrough concerns arising from neutron capture—which a conventional generator (with less than two gram alumina) is not—the risk of breakthrough is much more significant than with the fission process. The Mo-99 "produced by the neutron capture method is not 'carrier free'" and it therefore has a significantly lower specific activity than fission Mo-99; Isotope enrichment of natural Molybdenum can be used to artificially increase the abundance of Mo-98 fourfold, but the Mo-99 produced by neutron capture still contains an abundance of unreacted Mo-98, which is chemically identical to Mo-99. *Id.* at § 2.12. As neutron Mo-99 generators are eluted, trace amounts of the unreacted Mo-98 are released, *id.*—in addition to the Mo-99 breakthrough that occurs in all Tc-99m production, NAS, Medical Isotope Production without Highly Enriched Uranium, Appendix D, at 186 n.5 (2009). And, because "[t]he amount of breakthrough is roughly proportional to the amount of molybdenum present, both radioactive Mo-99 and nonradioactive Mo-98," neutron capture introduces additional risks of Mo-99 breakthrough. *Id.* Indeed, Mo-99 breakthrough frequency was the dominant safety factor in the demise of neutron capture Mo-99 generators.[4] While neutron-capture generators had difficulty meeting the original NRC specification limit for Mo-99 breakthrough—1 μCi Mo-99/mCi of Tc-99m with a total injected dose of 5 μCi Mo-99, 10 C.F.R. § 35.14(b)(4)(iii) (1986)—U-235 fission Mo-99 generators met, and continue to routinely meet, the current and more stringent Mo-99 breakthrough specification limit of 0.15 μCi Mo-99/mCi of Tc-99m, *see* 10 C.F.R. § 35.204(a)(1).

In addition to Mo-99 breakthrough, neutron capture is also associated with risk of half-life impurities, including radionuclidic, radiochemical, and biological impurities. Hasan and Prelas, at § 4.2. Such impurities, like beta decay for example, can cause unnecessary radiation doses to patients. IAEA, Product Issues with Eluted 99mTc ("IAEA Report") (last visited Sept. 14, 2022), https://humanhealth.iaea.org/HHW/Radiopharmacy/VirRad/Eluting_the_Generator/Generator_Module/Elution_of_the_99Mo99mTc_generator/Product_issues_with_eluted_99m

[4] The U.S. Nuclear Regulatory Commission reported several incidents where patients were injected with higher than permissible quantities of Mo-99 due to failure to check the Tc-99m for Mo-99 breakthrough in 1984. *See* Information Notice No. 84-85: Molybdenum Breakthrough from Technetium 99-m Generators (Nov. 30, 1984).

Tc/index.html. Yet, standards for neutron capture Tc-99m contain no specific limits for beta-emitting or alpha-emitting impurities. Conversely, specific limits do apply to Tc-99m from fission Mo-99 generators, ensuring that fission-produced Tc-99m is free from these impurities. Regardless of its source, if Tc-99m with any of these impurities is integrated into a Tc-99m cold kit, the formulation may be sensitive to the impurities in the product may not radio label adequately to provide the same level of diagnostic efficacy as with currently approved products. NAS 2016, at 44. Thus, fission-derived Mo-99, demonstrably free from such impurities, poses less risk to patients using such cold kits.

Further, because Mo-99 derived from Mo-98 usually depends on purchased Mo-98, there are higher risks of contaminant than Mo-99 produced from uranium. Indeed, even the highest-purity Mo-98 contains contaminants, and while facilities may purify that Mo-98 further, those contaminants may still permeate the resulting Mo-99. This is because natural molybdenum—as opposed to uranium-fission based molybdenum—contains residual impurities that become activated and are therefore present in the processed Mo-99. *See* U.S. Dep't of Energy, Production of Molybdenum-99 using Neutron Capture Methods, 4.2, at 22 (Jan. 2011). Contaminants vary from batch to batch and vendor to vendor, making it difficult to control when relying on procured Mo-98. *Id.* With limited analytical methods for trace analysis, it is not clear that the new isotopes or chemical elements that arise from the neutron capture activity—typically trace metals—can be detected by existing methods.

Efficacy with respect to the Tc-99m eluted from neutron capture using conventional less than 2 gram alumina generator columns is another concern. Mo-99 breakthrough can have disastrous effects on efficacy, as it can interfere with radiopharmaceutical production and reduce image quality. NAS 2016 Report, at 44. Generally, Mo-99 produced from neutron capture in conventional generators has a substantially lower specific activity than fission-derived Tc-99m. With such low specific activity, approximately 3 to 4 orders of magnitude more molecules of Mo-99 would need to be present on a neutron generator column than for fission to achieve comparable activity. And, as generators age, elution yield may degrade over time. As a result, the radioactivity of the eluates decrease, which has a direct effect on the quality of the Tc-99m produced. Eventually, the total product activity that can be recovered in an elution and the specific concentration (activity per unit volume) will reach a value that is too low to produce Tc-99m with the requisite radioactivity. IAEA Report. As radioactive value decreases, even more molecules are needed to achieve the requisite activity, which, in turn, implicates additional Mo-99 breakthrough. The only way to address these Tc-99 product quality concerns is to use a larger generator with larger columns: In other words, these concerns cannot be addressed in currently designed conventional generators.

2. Concerns with Tc-99m Generators

Neutron capture production of safe and effective Tc-99m inherently requires a new generator. FDA has explained that neutron capture in a conventional generator "is not practical, as it would require a large chromatography column and large elution volumes; in addition, all of the current 99mTc kits would need to be reformulated." NDA 202158, Deferral of Risk Evaluation and Mitigation Strategies Review, at 1 (Sept. 26, 2013). Research from the National Academy of Sciences ("NAS") supports this assessment; as noted in a 2009 study on the elimination of HEU in medical isotope production facilities, the low specific activity of Mo-99 produced by neutron capture has "practical implications." NAS, Medical Isotope Production without Highly Enriched Uranium, at 186 (2009). To effectively use neutron capture to produce Tc-99m, NAS determined that Tc-99m generators "would have to be redesigned" to include a larger column, "which would increase the size of the generator and weight of its shield." *Id.* Further, "a larger volume of liquid would be necessary to elute Tc-99m from the column, which may necessitate reformulation of several of the current Tc-99m kits." *Id.* Simply, NAS and FDA have raised questions about whether a conventional generator ***can*** even produce quality Tc-99m through neutron capture.

Without a new generator, a sponsor would need to develop new column technology far superior to existing alumina (or the hypothesized but not yet adopted gel-based) columns currently used in conventional generators. As FDA has noted, "the separation column is the 'guts' of the generator, because if it does not live up to its fundamental function, it does not matter what the remaining processes are in operating the generator." NDA 202158, Cross-Discipline, at 8 (2013). Again, the consequences of a faulty generator include both breakthrough and low concentration of the desired radionuclide product, affecting both safety and quality. *Id.* Alternatively, a sponsor could develop a significantly more efficient absorbent to effectively produce Tc-99m through neutron capture. *See* Hasan and Prelas, at § 4.2. But with such new technologies, the risk of contamination with other impurities must be considered. Traditional USP testing may not identify such impurities, and efficacy effects may not be realized until patients actually use the Tc-99m produced through such methods. Importantly, that technology may also come with increased risk to the operator. Consequently, FDA must not only assess the risks of the Tc-99m produced by the generator, but the risks of the of the generator itself. Such risks may not be fully assessed by reliance on the safety and effectiveness of currently approved Tc-99m products.

Though neutron capture technology undoubtedly has progressed since the 1970s—as clearly demonstrated by FDA's approval of North Star's RadioGenix System—the

success of such technology arises from the development of an alternative separation technology. FDA explained in its initial review of RadioGenix System (which ultimately resulted in a Complete Response) that it is only the automated multi-column Tc-99m manufacturing system that has enabled the safe and effective use of neutron capture technology. NDA 202158, Deferral of Risk Evaluation and Mitigation Strategies Review, at 1 (Sept. 26, 2013). Yet, despite the fact that FDA considered the RadioGenix System an "important advance to the public health," significant concerns arose with the new technology. *See* NDA 202158, Summary Review (Nov. 1, 2013). In addition to the concerns about product quality and microbiology, FDA raised questions about the risks involved in new technology, particularly when juxtaposed to the older, less complicated generator. *Id.* FDA explained that the new generator "is complex and involves many more steps for the user compared with production of 99mTc using conventional generators." NDA 202158, Risk Assessment, at 5 (2013). Thus, because the "RadioGenix is a more complex system that provides the same product . . . but requires more attention of the user than in the conventional version," NDA 202518, Cross-Discipline Review, at 10, FDA required human factors studies, training programs, and significant labeling revisions to evaluate such concerns. With a third technology option, these complexity and confusion concerns are even more tangible.

The risks of confusion arising from a new generator using neutron capture methods are compounded when neutron capture can also be performed in a conventional generator. Not only will technicians need to be cognizant of using the correct generator, a third option will also require technicians to distinguish between two technologies for use in the ***same*** generator. This is particularly a concern because discussions have centered around a mechanism to "drop in" neutron capture technology to a conventional generator, suggesting that an operator could use either neutron capture or uranium fission in the same generator. Inevitably, operator confusion is not only possible but probable. Indeed, even with only one neutron capture Tc-99m generator on the market, FDA raised safety risks arising from the likelihood of practitioner confusion; the introduction of yet another neutron capture Tc-99m generator—this time that uses a conventional generator—will result in even ***more*** market confusion

In the past, FDA has considered this type of confusion—predominantly occurring when a new formulation replaces an old formulation—a significant safety issue because the risks outweigh the benefits. For example, FDA determined that the original, non-abuse deterrent formulation of oxycodone was withdrawn for safety reasons when it approved a reformulated abuse-deterrent version in 2013. There, FDA concluded that, as a result of the introduction of the abuse-deterrent version, "the benefits of original Oxycontin no longer outweigh its risks." 78 Fed. Reg. 23,273, 23,275 (Apr. 18, 2013). Similarly, FDA initially approved a formulation of Protonix I.V. despite its risks due to

an unmet need, but when the product was reformulated, the existence of the reformulated product negated the original product's benefits so that they no longer outweighed its risks. FDA Response to Citizen Petitions (Docket Nos. FDA-2005-P-0082, FDA-2014-P-0142) (Nov. 28, 2016). *Id.* at 8. Thus, where there is a likelihood of confusion between two similar products, FDA has permitted marketing only of the safer version.

The same analysis should apply here. Proposed reintroduction of outdated Tc-99m production technology is analogous to the proposed reintroduction of old versions of reformulated products. As FDA's safety determinations explain, these older technologies have all been replaced by newer, safer, and more efficient technology. Reintroducing that older technology will serve only to reintroduce the safety and efficacy concerns that made it obsolete in the first place, as well as introduce marketplace confusion, while the benefits of the old technology can easily be obtained by safer, already-approved alternatives.

3. Benefit and Risk Profile

While the safety risks arising from neutron capture Tc-99m generators may have been tolerable in the 1970s when no other options existed, other options abound now. LEU fission-based Tc-99m generators are available, addressing Congressional concerns about HEU, as is a safe and effective multi-column neutron capture generator. These technologies address the "habitual shortage crises . . . with the production of fission [Mo-99] (aging nuclear fission reactors)," as well as "the mandate that HEU be replaced with LEU." NDA 202158, Cross-Discipline Team Leader Review (Oct. 11, 2013). Indeed, the fact that Congress had mandated "a shift in the manufacture of [Mo-99] from [HEU to LEU]" and that "the development of new production methods for [Mo-99] that are non-fission and also non-reactor based is a highly desirable public health objective" were integral aspects of the risk-benefit analysis for the RadioGenix System. NDA 202158, Summary Review (Nov. 1, 2013). But now, with the successful transition to LEU fission and the approval of the RadioGenix System, the benefit associated with neutron capture production using a conventional generator has decreased. As such, the risk profile involved in its market reentry outweighs the benefits.

Because Tc-99m produced through neutron capture in a conventional generator greatly increases risk to patients without any significant benefit over existing technology, FDA should refuse to approve such a product under section 505(d) of the FDC Act. FDA must refuse to approve a drug where testing is insufficient to demonstrate that a drug is safe for use under the conditions set forth in the proposed labeling. 21 U.S.C. § 355(d)(1), (2). FDA must also refuse to approve a drug where the production process is insufficient to ensure and maintain the identity, strength, quality, and purity. 21 U.S.C.

§ 355(d)(3). To make such approval determinations, the FDC Act requires FDA to apply a risk-benefit analysis to new drug approvals. 21 U.S.C. §355(d). Here, historic experience demonstrates that Tc-99m production using neutron capture in a conventional generator designed for high specific activity fission Mo-99 cannot produce safe and effective Tc-99m. The risks of breakthrough and contamination arising from the conventional process of neutron capture, as explained, precludes a finding that the Tc-99m produced is safe or effective. *See* 21 U.S.C. § 355(d)(1), (2), (4). Further, if neutron capture production in a conventional generator results in breakthrough and impurities, the production method for any Tc-99m derived from such a process is ineffective to maintain the identity, quality, and purity of the product. *See* 21 U.S.C. § 355(d)(3). Such problems are further exacerbated by the potential for marketplace confusion. With these risks, and the fact that market alternatives provide the same—if not more—benefit, refusal to approve a conventional Tc-99m generator that operates through neutron capture is consistent with FDA's statutory responsibilities. Thus, FDA should refuse to approve any neutron capture Tc-99m generators using conventional generator technology.

III. ENVIRONMENTAL IMPACT

The undersigned claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

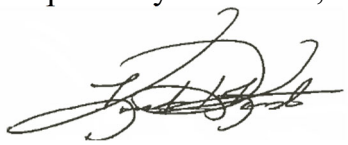
IV. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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