AVANIR PHARMACEUTICALS

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Thursday, July 16, 2020

Janice Owens
International Operations Branch
Office of International Programs
US Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: Letter in Support of NRC Rulemaking: Updates and Clarifications on the Export of Deuterium

Ref: Letter from Avanir to US NRC, Revisions to definition of deuterium under 10 CFR §110.2 to mitigate regulatory burden for safe and effective pharmaceutical therapies containing deuterium (Sept. 25, 2018).

Dear Ms. Owens,

Avanir Pharmaceuticals, Inc. ("Avanir") writes to support the important rulemaking currently under consideration by the U.S. Nuclear Regulatory Commission ("NRC") Office of International Programs ("OIP"), *Updates and Clarifications on the Export of Deuterium* (Docket NRC-2014-0201).

I. SUMMARY

The medical community is rapidly moving towards the use of deuterium across a range of medical applications. Deuterated pharmaceuticals[1] present significant patient benefits in the treatment of chorea associated with Huntington's disease and tardive dyskinesia, and are in clinical trials for treatment of conditions such as agitation in Alzheimer's dementia, negative symptoms of schizophrenia, cystic fibrosis, and neurobehavioral disinhibition in traumatic brain injury. Deuterated pharmaceuticals can potentially provide longer medical effectiveness while reducing potential side effects. A significant number of deuterated pharmaceuticals are in various stages of clinical development, and many of these drugs are in the later stages of the U.S. Food and Drug Administration ("FDA") approval processes.

Avanir is a pharmaceutical company focused on acquiring, developing and commercializing novel therapeutic products for the treatment of central nervous system ("CNS") disorders. Avanir is developing medicines in areas of significant unmet need for which there are no currently approved treatments on the market—including Alzheimer's dementia, negative

[1] In this letter, "deuterated pharmaceuticals" refers specifically to pharmaceutical compounds which contain deuterium at greater than its natural abundance.

symptoms of schizophrenia, neurobehavioral disinhibition in traumatic brain injury, and intermittent explosive disorder. In particular, Avanir's pipeline product, AVP-786, is a combination drug product containing deuterated dextromethorphan hydrobromide (duedextromethorphan or d6-DM), and is in development for several important unmet medical needs.[2] As described in greater detail below, however, Avanir is not alone in developing deuterated compounds for a variety of medical applications.

The existing NRC export control framework regulates deuterium for its non-proliferation concerns, but it does not contemplate that deuterium could be used in pharmaceuticals. This leaves a framework where the use of deuterium in pharmaceuticals is lumped in with the use of deuterium for nuclear end uses—an unnecessary burden for the medical community, including the pharmaceutical companies that manufacture the drugs as well as the doctors and patients that need access to these important medicines. Given the NRC's already ongoing 10 CFR Part 110 rulemaking to address the non-nuclear uses of deuterium, and the increasing trend towards using deuterated compounds for medical purposes, now is an ideal time for the NRC to adapt its export licensing framework to align with this growing medical trend.

From a regulatory and safety perspective, there is no reason to regulate deuterated pharmaceuticals under the NRC export control framework. Deuterium is not a radioactive material, and it is clear that deuterated pharmaceuticals do not present a proliferation concern. There is a reason that the global non-proliferation regime only polices exports of deuterium for *nuclear* end uses. While nuclear reactors require metric tons of deuterium to operate, deuterated pharmaceuticals carry just milligrams of the isotope per pill. Moreover, there is no concern that the deuterium used in pharmaceutics could be used for nuclear end uses. The total amount of deuterium in pharmaceuticals is trivial, and to extract meaningful amounts of deuterium from deuterated pharmaceuticals would be so expensive and time consuming, compared to other options, that it is not realistic or practically feasible. Additionally, as prescription drugs, the supply of such drugs is already monitored by the medical community and medical regulators.

At the same time, the current NRC export licensing framework, which extends to commercial exports of deuterated pharmaceuticals, risks entrapping the medical community and NRC in a licensing nightmare if no action is taken. The NRC's export licensing framework is geared towards bulk exports of large nuclear equipment to limited recipients, not a worldwide distribution chain involving milligrams of deuterium shipped to thousands of pharmacies and millions of patients. Current licensing requirements are unclear as to how they would extend to deuterium—but in the worst case could lead to hundreds of exports licenses with thousands of consignees for each *type* of pharmaceutical exported. Including deuterated medicine in an export licensing regime designed for nuclear reactors also brings other burdens, such as intervention opportunities that could be abused by competitors and unfairly harm U.S.-based innovators, and unclear and onerous reporting obligations (*see, e.g.,* 10 CFR 110.54).

[2] More about Avanir can be found on our website, https://www.avanir.com/, as well as in past correspondence to the NRC (Reference).

To address this issue, Avanir suggests that the NRC OIP, as part of its deuterium export licensing rulemaking, either exempt exports of deuterated pharmaceuticals from its export licensing framework; or in the alternative extend the 10 CFR 110.24 general license for exports of deuterium to deuterated pharmaceuticals, and further clarify that the reporting requirements of 10 CFR 110.54 do not apply.[3] Avanir strongly supports NRC completion of the rulemaking by January 2022, in advance of the wave of deuterated pharmaceuticals anticipated to enter the market.

II. THE DEUTERATED MEDICINE MARKET IS ANTICIPATED TO GROW RAPIDLY IN THE COMING DECADE

Deuterated medicine—in which certain locations of hydrogen atoms in the active compound contain deuterium at a level higher than its natural abundance—has the potential to bring significant advancements to medical treatment. In short, as a result of the "kinetic isotope effect,"[4] certain pharmaceuticals using deuterium instead of protium are able to resist metabolization in the liver or otherwise act differently in the human body. This can result in drugs that have, among other benefits, a longer lifetime in patients and reduced side effects.[5]

As a result of these benefits, deuterated medicine is being explored across a spectrum of applications. As earlier noted, a number of deuterated pharmaceuticals are in various stages of FDA review. The following chart provides a sample of deuterated pharmaceuticals currently undergoing FDA trials.

Sampling of Deuterated Pharmaceuticals Currently in FDA Trials

Compound	Proposed Medical Use	FDA Stage
Austedo (deutetrabenazine)	Huntington's Chorea and Tardive Dyskenesia	Approved & In Market
AVP-786[6] (d6-dextromethorphan)	Agitation in Alzheimer's Disease (AAD), Negative Symptoms of Schizophrenia (NSS), and Neurobehavioral Disinhibition in Traumatic Brain Injury (TBI)	Phase 3 Trials (AAD) Phase 2 Trials (NSS & TBI)
VX-561 (d9-ivacaftor)	Cystic Fibrosis	Phase 2 Trials
VX-984	Enhance Cancer Treatments	Phase 1 Trials
DRX-065 (d1-(R)-pioglitazone)	Liver Diseases	Phase 1 Trials
RT001 (d2-linoleic acid ethyl ester)	Progressive SupraNuclear Palsy	Phase 1 Trials

[3] As is discussed further below, this new exemption or general license could be limited to those deuterated pharmaceuticals that have received approval by the relevant medical regulator.
[4] Sarah Cargnin *et al.*, *A Primer of Deuterium in Drug Design*, Future Medicinal Chemistry, https://www.future-science.com/doi/pdf/10.4155/fmc-2019-0183.
[5] *DCE Technology*, CoNCERT Pharmaceuticals, https://www.concertpharma.com/platform/platform/dce-technology/.
[6] As mentioned above, Avanir is developing AVP-786.

It would not be unreasonable to expect that over time, however, deuterium could find application in everyday medical products. The global market size for deuterated medicines is expected to be considerable. Life sciences companies have already invested *billions* of dollars to research, develop, and commercialize deuterated pharmaceuticals.

The accompanying supply chain for deuterated medicine and deuterated pharmaceuticals will be equally complex. Although the supply chain has yet to be fully developed, deuterated pharmaceuticals are likely to be manufactured in several locations—both in the United States as well as outside (e.g., South Korea and Europe)—and from there sent to many pharmaceutical distribution outlets in other countries, and from there to pharmacies and eventually doctors and patients. The intermediate parties in the distribution of deuterated pharmaceuticals could reach into the thousands; and the ultimate recipients / end users of the medicine—the patients—will reach into the millions. As the potential market for deuterated medicine is likely to be extensive, it is incumbent on the NRC to revisit its export licensing framework to ensure that it adapts to this new medical opportunity.

Pharmaceutical Supply Chain

III. DEUTERATED MEDICINE DOES NOT PRESENT A PROLIFERATION CONCERN

Exports of deuterium have traditionally been controlled for *nuclear* end uses. Deuterium can be used as a moderator in certain "heavy water" reactor designs, with a prime example being the Canada Deuterium Uranium ("CANDU") reactor. Heavy water serves as an additional mechanism to sustain a critical fissile reaction in the reactor, mitigating the need for enriched uranium. CANDU reactors, for example, can run on deuterium and *un*-enriched uranium.[7]

On the other hand, the global non-proliferation regime has generally exempted control of exports of deuterium for *non-nuclear* end uses. The Additional Protocol for the Application of Safeguards, for example, which sets much of the framework for regulation of the global nuclear trade, only requires the tracking of deuterium "for use in a nuclear reactor."[8] The same is true

[7] *CANDU Technology*, Canadian Nuclear Association, https://cna.ca/technology/energy/candu-technology/.
[8] *See* United States Additional Protocol Agreement (entry into force 2009), Annex II § 2.1, https://www.bis.doc.gov/index.php/component/docman/?task=doc_download&gid=153&Itemid=182; INFCIRC/540, Model Additional Protocol Agreement, Annex II § 2.1, https://www.iaea.org/sites/default/files/infcirc540c.pdf.

for the Nuclear Suppliers Group Trigger List.[9] When it comes to imports, the U.S. Department of Commerce again only regulates imports of deuterium for use in nuclear reactors.[10] Similarly, Avanir has been advised by the NRC that it does not need to provide the required reports of deuterium exports under 10 CFR 110.54(a) because such reports are not required under the Additional Protocol.[11]

It is easy to see why this differentiation exists. The use of deuterium for nuclear end use is very different than for non-nuclear end uses, particularly medical use. Among other reasons, the quantities involved are vastly different. The amount of deuterium required for use in reactors is often measured in tons. For example, about *500 metric tons (i.e., 500,000,000 grams)* of deuterium is required for a CANDU nuclear reactor.[12] The amount of deuterium used in a pill of deuterated medicine, however, is measured in milligrams. A typical pill of AVP-786, for example, only contains 1.36 milligrams of deuterium. At its highest dose, a one-month supply of 60 capsules of AVP-786 contains only 81.6 mg of deuterium. As a result, many orders of magnitude separate the quantities of deuterium that would typically be sold to a patient in the form of deuterated pharmaceuticals, and what would be useful in a nuclear reactor.

Beyond this, many barriers remain if a bad actor were to try to divert deuterated pharmaceuticals for a nuclear end-use. First, that person would have to have a technology to extract the deuterium bound to the pharmaceutical, without losing the deuterium or introducing more unenriched water into the process—a complex task. Second, that same person would have to acquire an incredible number of pills to accumulate a significant amount of deuterium—pills which are priced according their valuable medical benefits. Even at wholesale prices, it would be practically infeasible on cost alone for any bad actor to acquire a quantity of deuterated pharmaceuticals for a concerning use.

Neither would any effort to accumulate so many pills go unnoticed. Even without NRC involvement, the sale and consumption of prescription medicine is heavily monitored and controlled, including by medical regulators, border regulators, and distributors and pharmacies—not to mention the doctors themselves. Similarly, production of deuterated pharmaceuticals at contract manufacturing sites is controlled by pharmaceutical company representatives and manufactured strictly based on demand for the required medicine. It would not be practically feasible to divert the millions or more pills required to establish a nuclear end use.

In contrast, producing deuterium from other methods is a far more straightforward process. Deuterium can be readily distilled from seawater using common industrial methods. The price of deuterated water extracted from seawater, for example, is estimated by one source to be

[9] *Documents*, Nuclear Suppliers Group, https://www.nuclearsuppliersgroup.org/en/nsg-documents.
[10] *See* 15 CFR Part 873 Appendix, Supplement No. 3 § 2.1.
[11] *See* Letter from the Peter Habighorst, NRC to Linda MacDonald, Avanir (Nov. 7, 2018).
[12] Robert Nanis, H*eavy Water Cycle in the CANDU Reactor*, Nuclear Energy in Central Europe 2000 Conference Paper, https://inis.iaea.org/collection/NCLCollectionStore/_Public/34/087/34087588.pdf.

roughly $300 per kilogram of D_20.[13] It would cost many orders of magnitude more to acquire an equivalent quantity of deuterium from deuterated pharmaceuticals, even ignoring the extraction and oversight challenges mentioned above.

As a result, the global trade of deuterated pharmaceuticals does not present a practical proliferation concern.

IV. NRC EXPORT LICENSING OF COMMERCIAL DEUTERATED PHARMACEUTICAL DISTRIBUTION WOULD URNEASONABLY BURDEN PATIENT ACCESS

The burgeoning market for deuterated pharmaceuticals is starting to run up against the NRC's nuclear export licensing framework in 10 CFR Part 110. The NRC's export licensing regime is geared towards bulk exports of large nuclear equipment to limited recipients, not a worldwide distribution chain involving milligrams of deuterium shipped to thousands of pharmacies and millions of patients.

So far, exports of deuterated medicine have largely not encountered this regime, as exports have fallen within the general license for the export of deuterium available in 10 CFR 110.24, which allows annual exports of up to 200kg of deuterium per country per year (and reporting of exports is not required[14]). However, at commercial scale these limitations on the general license will be surpassed, and specific licenses will be required for exports of deuterated pharmaceuticals. Controlling commercial exports of deuterated pharmaceuticals under the Part 110 regime raises many questions and potential barriers to patient access.

A primary challenge is the potentially unmanageable burden—from both the commercial side and the NRC side—associated with licensing the movement of deuterated pharmaceuticals around the world. Among other things, the apparent scale of information on the medical supply chain alone required to obtain an NRC export license would be immensely burdensome and unworkable. NRC Form 7, the NRC's export license application form, requires each "ultimate foreign consignee" to be listed on an application. According to the NRC's export licensing FAQ, this is the akin to the "end user" or person whom "ultimately uses the exported/imported items/materials."[15] In medical terms, this may well mean the *patient*—who procures and finally uses the deuterated pharmaceutical from a pharmacy or doctor—would be the end user that must be named in the export license. A direct reading of the regulations and application form would thus indicate that individual patients would have to be listed on specific export license

[13] Alistair I. Miller, H*eavy Water: A Manufacturers' Guide for the Hydrogen Century*, Canadian Nuclear Society Bulletin (Feb. 2001), https://cns-snc.ca/media/Bulletin/A_Miller_Heavy_Water.pdf ("[S]eparation of deuterium from protium is easy compared to some separations of different elements."). Indeed, the process of modifying the concertation of deuterium in water is increasingly commonplace, such that some entities have even started marketing deuterium-depleted water as a retail product. *See, e.g.,* Litewater, https://www.drinklitewater.com/; DIVINIA Water, https://www.diviniawater.com/.

[14] *See supra* note 11.

[15] *Frequently Asked Questions (FAQ) About Export-Import Licensing*, NRC (last updated Aug. 18, 2017), https://www.nrc.gov/about-nrc/ip/faq.html (Question "Who is the end-user?"; Question "What is an Intermediate Foreign Consignee?").

applications when known, an impossible task.

Even if the NRC were to try to take a different reading of its export licensing requirements to accommodate the industry—for example, by treating the ultimate foreign consignee as a pharmacy (or an aggregate pharmaceutical wholesale distributor) the challenges posed by the NRC's regime would not necessarily be avoided. For starters, raising the ultimate consignee requirement to the pharmacy level would still leave thousands of pharmacies and other distribution entities listed on NRC licenses, per drug, per country. The end result would still be that each US manufacturer and exporter of deuterated medicine would potentially have to obtain hundreds of licenses,[16] each with hundreds or thousands of consignees on each license. The end result would be an administrative nightmare unsupported by any true risk associated with the drug involved.

In addition, it is unclear such an approach is possible. In the past when the NRC has licensed specific exports of deuterium, the agency has treated manufacturing sites in the recipient countries that use the deuterium to create other products as the ultimate consignees[17]—in the medical context, however, there is no clear analog. After a deuterated pharmaceutical is manufactured and shipped from the United States, it is essentially unchanged as it passes through the distribution network to the pharmacy or hospital, and finally to the doctor and patient. The pharmaceutical supply chain has evolved, and in a Covid-19 impacted world, direct "Site to Patient" shipments are not uncommon and have already been initiated by Avanir in Europe.

Moreover, beyond the work to obtain an export license in the first instance, licensees would have to frequently update their licenses to align with a dynamic medical marketplace. The addition of new consignees, such as pharmacies or new distribution networks, cannot wait the months normally required for processing of amendments to export licenses without impacting patient access to important medicines. The NRC also cannot afford this level of licensing activity, which risks turning OIP into a mill for processing deuterated medicine licenses, incapable of tackling issues far more relevant to global safety and nuclear non-proliferation.

Beyond the licensing burdens, treating deuterated medicine the same as deuterium destined for nuclear reactors adds other unnecessary burdens to patient access. For example:

- **Supply Chain Disclosure:** Avanir and others may be required to publicly disclose many aspects of their planned exports as part of each export license application. While some of this material can be protected from public disclosure, in the end competitors may be

[16] From a review of issued licenses, NRC practice in this area also appears to be to issue licenses per country for exports of deuterium.

[17] Specific License XMAT445 Granted to Sigma Aldrich (June 13, 2018) (ADAMS Accession No. ML18165A110) (permitting exports of up to 5,000 kilograms of deuterium per year for non-nuclear end uses, including medical uses, to recipients in Spain).

able to use the NRC database and process to unfairly learn more about Avanir's and U.S. peer companies' deuterated medicine supply chains and market strategies.

- **Hearings on Applications:** The NRC regulations at 10 CFR Part 110, Subpart H provide the public a right to petition to intervene in NRC export licensing actions. This may allow competitors to try to seek information on exports or delay these license applications. These harmful disclosure and intervention requirements would not be in furtherance of public safety benefit, and would particularly benefit non-U.S. competitors who do not face similar requirements.

In short, the NRC has never intended to license the global trade in medicine, nor should it serve in this role. Bucketing deuterated medicine in the same regime that licenses exports of nuclear reactors risks creating significant burdens on the medical community—and the uncertainly alone associated with the applying the NRC licensing process to this field risks creating a chilling effect on the industry. The NRC has already recognized this issue by initiating a rulemaking to address commercial exports of deuterium for non-nuclear end uses (Docket NRC-2014-0201), and Avanir strongly advocates that the NRC bring this rulemaking to completion.

V. SUGGESTED REFORMS

To assist the agency rulemaking effort, Avanir suggests potential reforms the NRC could implement regarding exports of deuterated pharmaceuticals, and proposes next steps to align its efforts with the needs of the medical community.

Suggested Reform: Revised Definition of Deuterium

The simplest and most effective reform is to clarify the definition of deuterium in 10 CFR Part 110, to exempt deuterium exported for the specific medical uses described above. This would bring the NRC's export control framework more in line with global norms.

To help ensure public safety and avoid potential abuse of the revised definition, the exemption could potentially be restricted to exports of deuterated pharmaceuticals approved for sale and marketing by the FDA or the analogous regulator where the medicine is to be ultimately used. An example revised definition of deuterium, exempting deuterated pharmaceuticals, could state:

> "*Deuterium* means deuterium and any deuterium compound, including heavy water, in which the ratio of deuterium atoms to hydrogen atoms exceeds 1:5000, excluding deuterium in the form of deuterated pharmaceuticals approved for sale and marketing by the United States Food & Drug Administration or equivalent foreign regulator where the deuterated pharmaceutical will be ultimately used."

Alternative Approach: New General License

An alternative to amending the definition of deuterium in Part 110 could be to extend the general license for the export of deuterium to exports of deuterated pharmaceuticals. An example new general license in 10 CFR 110.24(c) could state:

> "A general license is issued to any person to export to any country deuterium in the form of deuterated pharmaceuticals approved for sale and marketing by the United States Food & Drug Administration or equivalent foreign regulator where the deuterated pharmaceutical will be ultimately used."

If the general license approach is pursued, the NRC should also codify that exports of deuterated pharmaceuticals under this new general license do not need to be reported under 10 CFR 110.54. This would align the text of the NRC's reporting regulation with current agency practice.[18] This can be accomplished for example by adding a new clause, 10 CFR 110.54(a)(3), stating: "Exports made pursuant to the general license in 10 CFR 110.24(c) are exempt from the reporting requirements in this section."

Neither the proposed revised definition of deuterium, nor the proposed new general license, would interfere with the NRC's ongoing jurisdiction over exports of deuterium for nuclear end uses. As before, the NRC and U.S. Department of Commerce (along with the International Atomic Energy Agency) would continue to strictly monitor exports and imports of deuterium for nuclear end uses per its regulations, such as in 10 CFR Part 110 and 15 CFR Part 783.

Suggested Next Steps

To support the anticipated commercial sale of deuterated pharmaceuticals, the NRC should resolve its planned rulemaking on this topic and institute the reforms recommended above by January of 2022, with a proposed rule issued in early 2021.

If helpful, a direct final rulemaking could be considered as part of the NRC's rulemaking plan in the event the NRC's planned Part 110 rulemaking might not be completed in the next few years. In any event, a rulemaking pertaining to the deuterium exports as described herein is likely to be noncontroversial and is unlikely to attract negative public attention. Shipments of deuterated medicine under the NRC's general license have been proceeding for a long time with no issue, and the rulemaking only serves to bring the NRC into alignment with the global non-proliferation regime (which monitors exports of deuterium for nuclear-specific end uses). At the same time, delaying this rulemaking past the above date risks creating the burdens discussed above on commercial distribution of deuterated medicine, and thus patient access to these important compounds.

To the extent that additional information is required by the NRC to complete the rulemaking, the NRC wishes to take a significantly different approach to resolve this issue, or the NRC wishes to act on a different timeline, Avanir strongly suggests that the agency consult with the deuterated medicine community for additional input, including through a meeting with the NRC staff.

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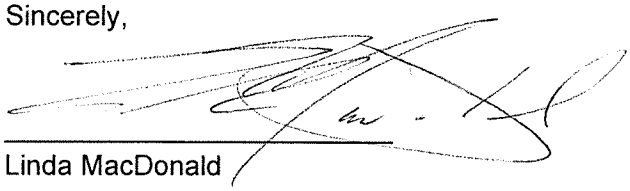
[18] *See supra* note 11 (explaining that "the reporting requirements in section 10 CFR Part 110.54(a)(1), only apply to deuterium exported for use in a reactor; i.e., for use as a moderator and/or a coolant in a nuclear reactor").

Avanir appreciates the opportunity to weigh in on this important issue. Please contact Avanir's counsel for nuclear regulatory matters, Amy Roma, at Hogan Lovells US LLP (202-637-6831/amy.roma@hoganlovells.com), if you have any questions or require additional information.

Sincerely,



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