FDA-NRC Workshop on Novel Technologies – Radiopharmaceuticals and Radiological Devices (October 14, 2020) Additional Questions from the Participants at the Workshop with Post-meeting Answers Provided by the Speakers and Panelists[1]

	SESSIONS I AND II	
1	What about a radioactive drug and a software program to inform the appropriate administered activity? If there is 510K for the software, I assume this would not be a combination product.	Whether something is a combination product depends on the configuration/packaging as well as labeling. If there is a separate 510(k) for the software, then it may not be a combination product, and the software is meant for use with an identified radioactive drug. However, if uses of the drug and device are limited for use only with each other, then these may be considered a combination product. In considering whether the proposed products are combination products the Agency will consider the configuration and labeling to ensure the safe and effective use of the products together.
2	I have heard of Phase 1a and 1b studies, and Phase 2a and 2b studies. What are the differences?	**Phase 1 a** studies are usually conducted in a small number of participants and typically involve single ascending dose studies of a drug to evaluate safety. Participants are dosed with a particular dose. If no adverse reactions are observed, the dose is escalated with a new group of subjects. **Phase 1b** studies involve the assessment of pharmacokinetic and pharmacodynamics of a drug with multiple doses in groups of subjects evaluated sequentially starting with multiple lower doses followed by multiple higher doses in other groups of subjects. Biological samples are collected at various time points and analyzed to examine safety and tolerability. **Phase 2 a** studies are usually proof of concept studies designed to evaluate clinical activity of a drug. **Phase 2 b** studies are dose-finding studies designed to establish the safe and optimal dose for efficacy studies.

3	I have a proton therapy system at my hospital. It was mentioned that the accelerator is not regulated by the NRC but the activation in the walls are, does the activation in the system (energy degraders, Dee's, or activated water) also fall under the NRC? Would a NRC license need to list these?	The accelerators discussed by the NRC are those used to produce radioactive materials. A cyclotron used to irradiate a target (e.g. O-18 to produce F-18 produces a radionuclide and NRC/Agreement States regulate the production of the radionuclide used for producing a radioactive drug, the activation products in the cyclotron and shielded walls. The NRC does not regulate the cyclotron itself. If a linear accelerator is used to produce a radionuclide, the NRC would regulate the production of the radionuclide but not the linear accelerator itself. The NRC does not regulate the medical use of an accelerator to directly treat patients.
4	The issue of the update to Appendix B in Part 20 identified over a decade ago, when accelerator produced became by product material. Fix identified then, but when is this regulation going to get updated?	The NRC is initiating a rulemaking on Decommissioning Financial Assurance Requirements for Sealed and Unsealed Radioactive Material.
5	Regarding licensing of I-125 RSL seeds: I have seen these licensed on a couple different broad scope licenses under 35.400 and included in the 1-83 sealed source authorization but not listed separately as a 35.1000 line-item. Does I-125 RSL need to be listed specifically as a 35.1000 authorization on broad scope licenses?	Depending on jurisdiction there may be local differences on how the regulator adds RSL to specific and broad scope licenses. The RSL procedure, low activity radioactive seeds, including but not limited to iodine-125 (I-125) and palladium-103 (Pd-103), are implanted for localization and are not intended to deliver a therapeutic dose to tissue. RSL procedures are localization procedures and not therapeutic; therefore, 10 CFR Part 35.400 does not apply for this use. The use of byproduct material for localization procedures is regulated under 10 CFR Part 35.200 but does not apply to this use because it uses sealed byproduct material. Because RSL procedures are not regulated under these parts, 10 CFR Part 35.1000 “Other Medical Uses of Byproduct Material or Radiation from Byproduct Material” applies. Broad scope licensees are exempted under 35.15 from the requirements to apply for an amendment for 35.1000 uses because their license medical use authorization is broad enough (diagnosis, therapy and research involving human subjects) to cover 35.1000 uses. The broad scope licensee may have to get an amendment, if their license does not

		include authorization for the radionuclide or the quantities needed for the RSL procedure.
6	Has NIST developed a calibration source for Cu-64?	The NIST primary standard for Cu-64 activity is described in Applied Radiation and Isotopes (Bergeron et al., v. 139, pp 266-273 (2018). Because of the short half-life, NIST does not issue a Standard Reference Material, but calibrations can be arranged.
7	With the advent of SUV SPECT and dosimetry-based radiopharmaceutical treatment planning based on imaging, is NIST developing standards for dose calibrator calibration (and perhaps imaging) for Tc-99m (for quantitative SPECT), Lu-177 and/or I-131?	NIST has developed activity standards for Tc-99m, Lu-177, and I-131. NIST-determined settings for radionuclide calibrators ("dose calibrators") for these and other nuclides were recently summarized by Bergeron & Cessna in Nuclear Medicine Communications (v. 39, pp. 500-504 (2018)). Moreover, I-131 and Tc-99m sources are issued as Standard Reference Materials annually by the Measurement Assurance Program (https://www.us-rma.org).
8	Has NIST developed a calibration source for Cu-64? If not, could a Ge68/Ga68 calibration source be used as equivalent considering some variable emissions between the two isotopes?	The NIST primary standard for Cu-64 activity is described in Applied Radiation and Isotopes (Bergeron et al., v. 139, pp 266-273 (2018). Because of the short half-life, NIST does not issue a Standard Reference Material, but calibrations can be arranged. NIST has not established response ratios for Ge-68/Ga-68 sources, but this should be possible.
9	How about Ac-225-radiopharmaceuticals and the "cold" standards or reference standards?	The long-lived Ac-227 isotope (21.8 yrs) complexed with the ligand (pharmacophore) may serve as reference standard(s) for Ac-225. "Cold" reference standards may or may not be applicable to actinides. However, for characterization, a surrogate metal ion with similar chemistry, e.g., La3+ may be considered. In general, a reference standard should be developed from a GMP batch or a highest purity batch
10	I seem to recall reading not too long ago about the disposal of depleted uranium (U-233) versus preserving it for radionuclide production (e.g., medical). What is the status of that?	Please see the link below for information about the status of the U-233 for the provision of medical isotopes: https://oakridgetoday.com/2019/11/22/company-that-bill-gates-helped-launch-oak-ridge-contractor-making-cancer-treatment-materials/
11	Can you discuss the status of direct cyclotron production of Ga-68, which, I have read, has the potential to make a much larger amount of Ga-68 available than that using generators.	The method for production involves either a solid or liquid Zn-68 target. Several irradiation parameters could be exploited and optimized for the production. Overall the cyclotron yield published in the scientific literature indicates higher Ga-68 yield compared to the 50 mCi limit

		for the currently available generator-derived material. The FDA approval route will require that applicants establish a consistent, high quality product via associated automated synthesis and cassette systems that will be linked to specific drug products.
12	If a sponsor of an on-going clinical trial desires to switch from generator produced Ac-225 to accelerator produced Ac-225 containing a small quantity of a longer-lived impurity Ac-227, what bridging studies or data might be expected by FDA and would NRC need to address disposition of waste prior to use in the clinic?	Before the change can be implemented the sponsor needs to amend their IND with the following data and other information. • Complete CMC information for the accelerator produced Ac-225. • Radionuclide impurity specifications to include "Specified radionuclide impurity (Ac-227) specification" in the Ac-225 raw material and for the final Ac-225 radiopharmaceutical drug product. Ac-225 raw material exceeding the Ac-227 limit should not be used in drug product production and the Ac-225 radiopharmaceutical should meet the radionuclidic impurity specification throughout its shelf life. • Impact of impurity on human health and justification of the level of Ac-227 impurity in the Ac-225 radiopharmaceutical dose for safety (e.g., dosimetry, impurity level qualification). With regard to disposition of waste we have the following comments. • Medical licensees dispose of radioactive waste by one or both of the following methods: Decay-in-Storage or transfer to an authorized recipient. The regulation at 10 CFR 35.92, "Decay-in-storage" was revised in 2002. It permits licensees to hold byproduct material for decay in storage (DIS) with a half-life of less than or equal to 120 days. Prior to 2002, waste held for decay in storage

		was held for a minimum of ten half-lives. The 2002 regulation is performance-based and does not specify a holding period. The waste held for DIS can be disposed of as ordinary trash once it is no longer distinguishable from background radiation. • Some short half-life radionuclide medical use products (e.g., samarium-153, Tc-99m/Mo-99 generator columns and Y-90 microspheres) may contain long half-life contaminants that may preclude disposal by decay-in-storage. Long-lived contaminants need not be listed on an NRC license; however, licensees need to perform surveys and dispose of the material in accordance with Part 35 or Part 20 requirements. • The NRC is initiating a rulemaking on Decommissioning Financial Assurance Requirements for Sealed and Unsealed Radioactive Material which may provide an opportunity to address long-lived contaminants that result from accelerator production in regulation in a risk informed performance-based manner.
13	Having only previously had NRC regulatory interactions, would it be prudent to formally engage the FDA with a Type C Meeting to review proposed DMF content and its adequacy.	We strongly encourage requesting a Type C meeting to discuss content of a DMF for a proprietary manufacturing process of radionuclides and other components of radiopharmaceuticals.
14	If target irradiation occurs upstream and this NRC facility is responsible for processing, purifying, analyzing and certifying, does target irradiation need to be detailed in the DMF ?	Yes, the irradiation parameters may be included in the DMF or cross-referenced to a secondary DMF if the companies are different and do not share information.
15	Would formatting the DMF for a radioisotope API best be provided using eCTD formatting found in Module 3.2.S for Drug Substance	Yes, this is appropriate.

16	How would the NRC respond to a Y-90 procedure where the facility requests to skip the lung shunting pre-evaluation which was required during licensing?	The NRC does not require pre-evaluation for lung shunting if an AU plans to omit it based on their medical judgement. However, a licensee is required to report a medical event caused by shunting if the potential for shunting is not evaluated prior to treatment in accordance with manufacturer procedures.
17	Please comment on the need for 3 validation runs on NDA product when there is a change in the source of Ga-68.	The current protocol operated by the FDA requires that the Ge-68/Ga-68 generator has well characterized feedstock Ge-68, as submitted in the generator's Type II DMF. The generator must be proven to stably produce Ga-68 chloride that satisfactorily radiolabels the NDA owners imaging kit – via the NDA owner submitting a supplement to their NDA showing satisfactory radiolabeling in 3 radiolabeling kits. Each generator manufacturer is approved by the FDA for the specific NDA owner's kit. There is no "universal" generator producing Ga-68. If a new supplier of Ge-68 is utilized in a generator then the manufacturer has to submit an amendment to their Type II DMF and then have the NDA owner conduct 3 radiolabeling kit runs to prove radiolabeling equivalency. The NDA owner then has to submit a supplement to their NDA for FDA approval.
18	Can you please provide an explanation about the level of information that is required regarding isotope production for inclusion in an IND?	For IND submissions a certificate of analysis (COA) or a DMF from the commercial vendor is adequate. However, for in-house produced radionuclide CMC information required includes irradiation source (e.g.cyclotron,) target material and fabrication, irradiation parameters, isolation of the radionuclide, acceptable specifications (e.g. radionuclide purity and identity, impurity limits)
	SESSION III	
1	Should absorbed dose to extravasation site be calculated?	Dosimetry assessments will be helpful for clinically important extravasations of radiopharmaceuticals.
2	What is the policy for 227Ac contaminated waste, and how does this affect disposal route (compared to 225Ac waste only) and licensing requirements? This is a concern if we are to use the accelerator produced material for pre-clinical studies.	Medical licenses dispose of radioactive waste by one or both of the following methods: Decay-in-Storage or transfer to an authorized recipient. The regulation at 10 CFR 35.92, "Decay-in-storage" was revised in 2002. It permits licensees to hold byproduct material for decay in storage (DIS) with a half-life of less than or equal to 120 days. Prior to 2002, waste held for decay in storage was held for a minimum of ten half-lives. The 2002 regulation

		is performance-based in that it does not specify a holding period. The waste held for DIS can be disposed of as ordinary trash once it is no longer distinguishable from background radiation. Some short half-life radionuclide medical use products (e.g., samarium-153, Tc-99m/Mo-99 generator columns and Y-90 microspheres) may contain long half-life contaminants that may preclude disposal by decay-in-storage. Long-lived contaminants need not be listed on an NRC license; however, licensees need to perform surveys and dispose of the material in accordance with Part 35 or Part 20 requirements. The NRC is initiating a rulemaking on Decommissioning Financial Assurance Requirements for Sealed and Unsealed Radioactive Material which may provide an opportunity to address long-lived contaminants that result from accelerator production in regulation in a risk-informed performance-based manner.
3	What role does/can personalized dosimetry play in FDA approval or clinical dosing?	Currently personalized dosimetry is not mandated for FDA approval. However, more work in this field is encouraged to establish dose-response relationships for both tumor and normal tissues in order to enable clinicians to move from activity-based prescribing to absorbed dose prescribing.
4	Dr. Chakrabarti. Thank you for the great presentation on extravasations. It was most informative. You cited the van der Pol et al. article and noted that 3 of the 3,016 reported diagnostic extravasations had dosimetry performed and were followed and all three resulted in adverse tissue reactions. You pointed out that these injuries were delayed	Yes, dosimetry assessments will be helpful for clinically important extravasations of radiopharmaceuticals.

	up to three years. Many people have drawn the conclusion that with only 3 out of 3,016 patients injured therefore diagnostic extravasations are not truly harmful. However, the authors point out that none of the remaining 3,013 diagnostic extravasation cases described "dosimetric parameters or follow-up." So, we don't know what happened to those 3,013 patients. I would welcome your comments on whether significant extravasations should have dosimetry performed and the patients be followed to check for delayed radiation injury? Thank you.	
5	The 23Gy limit to the kidney is based on external beam radiation therapy, high dose rate data. As Dose rate does clearly impact cell kill in both tumor and normal tissue, how does FDA recommend the field collect data to support higher kidney doses?	Well-conducted animal studies should be performed to address this question and help establish a dose modification factor reflective of dose-rate based normal tissue tolerance differences. Also, the ongoing VISION trial, which was mentioned at the conference, may help to address this question, as the study permits up to 6 doses of Lu177 at 7.4 GBq/dose. Patients receiving this dose will receive a renal dose >23 Gy and long-term follow-up of these patients may help shed light on whether the renal tolerance dose in humans is different for conventionally fractionated external beam vs. this radiopharmaceutical.
6	Regarding alpha emitting radiopharmaceuticals, at what point during the drug development process is the binding efficiency/chelation evaluated for the recoil effect during decay ?	The alpha recoil energy effect should be investigated early in the drug development process preferably in animal studies or in in-vitro stability monitoring is plasma.
7	For alpha isotopes, how does one use clinical dosimetry with an agent such as Gallium or Lutetium to estimate appropriate thresholds for Ac225 administration? For example, if you have a radiopharmaceutical drug labeled	As noted, there remains uncertainty in the renal tolerance from radioisotopes and the reference dose used is based on standard external beam fractionation. In addition, for alpha particles, there remains uncertainty in the exact RBE relative to beta and gamma irradiation. Thus, the approach taken for the alpha emitter Ra-223, which is approved for the treatment of

	with Lu-177 and from dosimetry you identify 4 Gy absorbance per dose (let's say 1 unit of drug) to the kidney and knowing that for kidney the max tolerable absorbed dose is ~22Gy, what would be the max dosing you could give in drug units of Actinium225?	selected patients with metastatic prostate cancer, may provide some guidance in estimating the absorbed radiation dose to various organs per unit of administered activity for other alpha emitters.
8	Is there some type of document that indicates a drug has been approved by the FDA? For instance, for a drug in clinical trials should licensing entities look to ensure the drug has a DMF. If so is there a location where the approval can be verified and specific guidance be observed?	Approved drugs can be found at "Drugs@fda". Drugs in clinical trials may or may not include a DMF to reference CMC information. Alternatively the CMC information may be included in the application. Refer to "Clinicaltrials.gov" for drugs in clinical trials.
9	For alpha-emitter based radiopharmaceuticals in particular, technical challenges arise with clinical verification of the activity to be administered -- partly due to dosing levels in the microcurie range, and partly due to limitations of the dose calibrator. In addition, with the typical administration ranges in the microCurie levels, exceeding the threshold for a medical eventwill additional guidance be developed?	For radium-223 a NIST-traceable reference standard was used to obtain a dial setting for a standard dose calibrator. Standard dose calibrators can accurately measure kBq quantities of radium-223. Similar assessments may be needed for other alpha-emitter based radiopharmaceuticals.
10	How does the NRC view the term "localized" as proposed by the petitioner.: "(iv) An extravasation that leads to an irradiation resulting in a localized dose equivalent exceeding 0.5 Sv (50 rem)", as the volume of distribution of an extravasated RP and of the resulting dose equivalent are indeterminable.	The NRC Medical Event reporting regulation does not use the term localized dose, but rather (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin. The NRC is evaluating the merits of the petition. 75-day public comment period announced on September 15. Comment period closes 11/30/2020 (https://www.federalregister.gov/documents/2020/09/15/2020-19903/reporting-nuclear-medicine-injection-extravasations-as-medical-events).
11	Can some ADME/PK tests be done using non-radioactive version of the radiotracer? For	We recommend ADME/PK with radioactive drug instead of using stable element.

	instance using 19F instead of 18F.	
12	Will the FDA go the way of Europe and require personalized dosimetry for every patient?	Currently this is not an FDA requirement. The Agency continuously evaluates the state of the science to determine the need to alter guidance provided to sponsors.
13	I am a radiopharmacist and am aware of the petition regarding extravasations. I have seen that the ACMUI position states that extravasations are frequent events and that several medical societies have affirmed the ACMUI position. As a radiopharmacist, we are committed to providing the right dose to the right patient at the right time. It would seem to me that for any radiopharmaceutical to work effectively it needs to be administered as intended. I know that most diagnostic radiopharmaceuticals have to be injected as a bolus to ensure the highest quality of image and to provide repeatable quantitative results. Additionally, it is critical that therapeutics be delivered without any extravasation for safety and efficacy reasons. In the approval of radiopharamaceuticals, can't the FDA mandate that manufacturers and clinicians ensure/document that the prescribed dose is actually delivered as intended? It would be helpful to the radiopharmacy team when evaluating reported abnormal bio-distributions and I believe the patient would certainly want to know that has happened.	A drug product's labeling contains information on adverse drug reactions. On a case by case basis FDA may mandate a risk evaluation and mitigation strategy for a specific drug with serious potential risks. Extravasation events associated with the intravenous administration of drug products are a measure of the quality of healthcare and as such are the concern of various medical practice professionals. Health-care systems and organizations and medical professionals are involved in the development of standards that affect the quality of healthcare.
	Session IV	
1	Does Ga68 from different type of generator from what it has been validated for a NDA on PET drug for NON-KIT product also need	Introduction of a new source of Ga-68 to an approved product will require a prior approval supplement. Similarly, a change to a new brand

	validation when changing generator? If a conventional radio-labeling is done with Full PET QC do we still need to validate the NDA approved drug using a new brand of Ga68 generator?	of generator will require validation/qualification and submission of a prior approval supplement.
2	Is there any consideration on revising Part 35 ME criteria for Y90, as you have made specific exemptions for 35.400 seeds. We feel that using MIMS is beneficial for the patient, but problematic since it ties into QM program.	There is no on-going revision of the Y-90 microsphere licensing guidance. However, if the Commission directs the staff to add Y-90 microspheres into part 35 as part of the emerging technology rulemaking effort, medical event criteria would be evaluated at that time.
3	Use of the Ge-68/Ga-68 generators has been hampered for some medical end-users because of the need to submit (to NRC or Agreement States) either a decommissioning funding plan or an exemption request (along with a legal agreement with the manufacturer/distributor for generator take back) due to 10 CFR 30.35. The issue arises because there is no value for Ge-68 in Appendix B to 10 CFR 30. There are values in Appendix B for other long-lived, gamma-emitting radionuclides (e.g., Cs-137; natural thorium—which has several gamma-emitters in equilibrium). Does NRC have any plans to update 10 CFR 30, Appendix B, and list a value for Ge-68 so that a decommissioning funding plan (or exemption) is not required to possess these generators?	The NRC is initiating a rulemaking on Decommissioning Financial Assurance Requirements for Sealed and Unsealed Radioactive Material.