Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Use of Isotopes (ACMUI)

Subcommittee on

NorthStar Molybdenum-99 / Technetium-99m Generator (RadioGenix™) Licensing Guidance

***Draft* Report**
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I. Introduction

There were multiple presentations to the ACMUI over the past several years on a new molybdenum-99 (Mo-99)/technetium-99m (Tc-99m) generator system, the RadioGenix™, developed by NorthStar Medical Radioisotopes, LLC. This novel generator system provides a practical alternative to the conventional and widely used column-based Mo-99/Tc-99m generator. Since the column-based generator utilizes exclusively fission (i.e., reactor)-produced Mo-99 and since the foreign reactors which produce Mo-99 are aging and increasingly unreliable, there is an urgent need for a reliable, domestic supply of Mo-99 to avoid potential shortages of Tc-99m for clinical studies, such as those which occurred several years ago. The RadioGenix™ generator system utilizes linear-accelerator rather than fission-produced Mo-99 and thus should address this important unmet need[1]. A joint NRC/Agreement States working group was formed to review, evaluate, and determine how this generator should be licensed. Through their evaluations, it was decided that this particular generator needs to be licensed under 10 CFR 35.1000 and is intended for both 1) medical-use licensees and 2) commercial radiopharmacies (nuclear pharmacies).

Unlike the conventional Mo-99/Tc-99m generator using fission-produced Mo-99, the NorthStar device is designed as a closed system to contain, move, and shield all Mo-99 (as a solution of a mixture of radioactive Mo-99 and Mo-98 or Mo-100) during the computer-driven process of isolating Tc-99m from molybdenum before delivering Tc-99m for injection into a patient. However, individual users of the system do interact with several shielded doors, by opening and closing them, in order to insert new and remove used source vessels from the system. As a result,

[1] According to the NorthStar Medical Radioisotopes, LLC web site, it is projected that when fully operational its manufacturing facility in Benot, WI will be able to supply 50% of the Mo-99 needs required by the US market, http://www.northstarnm.com/advanced-production, Accessed 9/7/2016.

there are specific training and experience and administrative requirements that are unique to the system. These include 1) training individuals to perform the individual tasks within the protocol, 2) identifying a system administrator and designee, 3) identifying the radiation safety officer responsible for radiation safety oversight of the system, and 4) identifying an authorized medical-use licensee or nuclear pharmacist responsible for the system. In addition, there is specific vendor training for changes to hardware and software related to the operation and safety of the RadioGenix™. Design specifications of the components are necessary to maintain the device's integrity as a closed system and to ensure that the radioactive material is adequately shielded with all doors closed and with supplemental shielding in place and that safety features are designed so that the device fails in a shielded (or fail-safe) manner.

II. Authorized User and Training Requirements

The RadioGenix™ System protocols will generally be performed by individuals who are working under the supervision of Authorized Users (AUs) or Authorized Nuclear Pharmacists (ANPs). Since there may be a large number of such individuals at a medical facility or a commercial nuclear pharmacy, arranging for the manufacturer to train all of them in the protocols may be impractical. On the other hand, given the gradual shift of nuclear medicine imaging centers from on-site Mo-99/Tc-99m generators to unit doses, the subcommittee estimates that perhaps less than 10% of all clinical imaging programs in the United States may have one of these generators on site. Moreover, given the complexity of use of the RadioGenix™ System, it is more likely that this generator will be used almost exclusively by commercial radiopharmacies.

The training will initially be provided by a NorthStar representative (or an individual certified by NorthStar to provide the training) and the AU, the System Administrator or the System Administrator designee who have successfully fulfilled the requisite NorthStar training and experience and who will subsequently train other individuals responsible for performing the specific tasks within the protocol. The subject of whether the NorthStar training course should be reviewed and approved by the NRC was considered. *Given the unique design and operation of the NorthStar system, the subcommittee agreed that NorthStar should have sole responsibility for the content of the training course and certification.*

The requirement for three (3) proctored "cases" in all aspects of the operation of the NorthStar generator system is reasonable and consistent with other "35.1000" agents. However, the Draft Guidance (page 10, lines 29-32) states that the training for users of the NorthStar system must include the following, "Perform each of the protocol tasks (i.e., initialize system, produce Tc-99m, add/change reagent kit, exchange used reagent container, add source vessel, remove source vessel, and sterilization) at least three times in the physical presence of a NorthStar representative or an individual certified by NorthStar to proctor all the protocol tasks." The subcommittee questions if this requirement is practically compatible with the "lifespan" of the Mo-99/Tc-99m source vessel. Specifically, if the lifespan is of the order of several days or longer, the foregoing requirement would require the trainer to return to or otherwise be present at the applicant facility on three separate occasions that are days apart in order to satisfy the "add-source-vessel" training requirement. On the other hand, if there are multiple RadioGenix™ Systems at the NorthStar training site, and each of the generators are at various operational stages (including the several days

lifespan of the Mo-99/Tc-99m source vessel), then the training can be expedited and accomplished during that same training period. *This part of the training requires further clarification. Alternatively, could training be performed and therefore expedited using a "dummy" (ie non-radioactive) source vessel?*

Further Clarifications for the Use of "Protocol" and "Software" Applications: It is stated in the document (bottom of page 7) that "The RadioGenix™ System is fully computer-driven with specific protocols that must be performed in a set sequence and by individuals with specific radiation safety training and experience for each protocol". Similarly, on page 8, item 1, the applicant must commit to the following: "To use the accounts and roles structure of the RadioGenix™ System's software to limit what protocol can be initiated by an individual." The use of the term "protocol" in these sentences is a bit confusing. A protocol usually connotes a series of tasks and not an individual task. The most common meaning of protocol is "a system of rules that explain the correct conduct and procedures to be followed in formal situations." This was made clear under the subheading of "Protocol tasks" which was placed before the body of the narrative of the Licensing Guidance, where all the individual "tasks" were listed: 1) initialize system, 2) add/change reagent kit, 3) produce (i.e., separate) Tc-99m, 4) remove source vessel, 5) sterilization, and 6) exchange used reagent container. However, within the body of the narrative the terms "protocol" and "software" are used rather than the term "individual tasks." It is confusing because the reader may be left with the (unintended) impression that there may in fact be several protocols and software programs that could be applied with the RadioGenix™ System, with each protocol and program having a unique set of individual tasks. *Accordingly, the subcommittee recommends using the term, "individual tasks," throughout the document for consistency and to clarify that there is only one protocol and software program with this system.*

The System Administrator (or administrator designee) is responsible for ensuring that an individual initiating a protocol task meets the training and experience for that protocol outlined in this Guidance. The sequence of tasks and training was felt to be more analogous to chemistry modules for preparing cyclotron-produced radiopharmaceuticals rather than generator-produced radiopharmaceuticals. The applicant's name is apparently added to the "software" after the training of individual "protocol tasks" is completed. *This entire sequence of training for individual tasks within a "protocol" and then adding the applicant's name to the "software" should be clarified in the document.*

Additional Training as a Result of Changes to the RadioGenix™ System: The Guidance states that if there are software, hardware or procedure changes to the RadioGenix™ System, the applicant shall commit to successful completion of the training on the "changes" prior to first operation of any component or first handling of licensed material associated with the system. The subcommittee felt that this section was rather vague. For example, what is the responsibility of the vendor/manufacturer to inform and train the applicants on changes in a timely manner? What is the appropriate time period allotted for training on the "changes"? Will the generator be "non-operational" until ALL individuals handling the generator are trained in the changes, including the AU, RSO, system administrator, etc. or does it require only the AU to be trained on the "changes"? If the latter, once the AU is trained on the "changes", is the AU then solely responsible for training all others on these changes?

III. Safety Precautions

The subcommittee understands that the NorthStar system utilizes a Mo-99/Tc-99m solution in a source vessel and that the activity in this vessel (which is on the order of Curies) can be very high relative to typical "nuclear medicine" clinical activities. Such a large quantity of activity in liquid form raises the possibility, at least in theory, of a very significant spill (more so than for a conventional Mo-99/Tc-99m generator in which the activity is bound to a column). The Draft Licensing Guidance is largely silent on emergency response other than to defer to the procedures of the manufacturer. *While the subcommittee appreciates that NRC endeavors to be non-prescriptive, given the potential severity of a spill with such large quantities of radioactivity in liquid form, perhaps the manufacturer's procedures should be reviewed and incorporated into the Licensing Guidance itself.*

Surveys/Survey meters/monitors: Given the complexity of the entire system with the potential for increased exposure of the workers to radiation fields higher than those associated with conventional fission Mo-99/Tc-99 generators, "it is necessary for the licensee to routinely perform additional surveys to identify higher than expected radiation fields and system failures". *The term "higher than expected" should be defined in terms of a maximum specific exposure or exposure-rate limit which a survey meter should be capable of measuring.*

IV. Other Recommendations and Specific Comments

Annotated figure and/or video clip of the generator system: The inclusion of an annotated figure of the NorthStar generator system and a summary of its operation is very helpful but the subcommittee felt that it is confusing to insert it before the body of the narrative of the Draft Licensing Guidance, that is, without some introductory description of what the figure depicts. The use of color-coded contours to identify the various components of the generator system was also felt to be confusing. *The subcommittee recommends the use of labeled arrows to identify each component by name directly on the photograph. For the training module, the subcommittee recommends that NorthStar provide a video clip of how the system operates.*

"System Administrator": Given the unique role of the "System Administrator", will that individual be named on the license? It is also important to clarify that a system administrator can be any individual assigned by the AU without a specifically defined educational or training background.

"System Administrator Designee": Regarding "System Administrator Designee", although it may not have been intended, one could infer from the description of the System Administrator designee that there can be only one designee (as the term, "designee," is used exclusively in the singular). Presumably, there can, and should, be multiple System Administrator designees. This should be stated explicitly.

"Sensitive Security Related Information": The section on "Sensitive Security Related Information" may be unnecessary as Mo-99 and Tc-99m are not covered by the guidance for sensitive security-related information.

Specific Comments (page numbers refer to the file page numbers)

Pg 2 Line 14 The phrase, "…for the…," is repeated.

Pg 3 Lines 19-20 The phrase, "…opening shielded door, handling and disposal of radioactive materials and potentially contaminated components," should be changed to, "…opening the shielded door and handling and disposal of radioactive materials and potentially contaminated components."

Pg 16 Lines 18-19 The Draft Guidance states that applicants must commit, "Having radiation monitor(s)/meter(s) (in addition to the radiation monitor in the RadioGenix™ System) with the ability to monitor and detect expected transients." As noted above, this seems ambiguous; the maximum exposure or dose rate value measurable for a compliant radiation monitor, for example, should be specified.

Pg 17 Lines 17-18 The Draft Guidance states that the licensee will commit to the following, "To confirm that individuals will not stand near the system during the protocol due to elevated dose rates that will occur during portions of the protocol." This, too, seems ambiguous, as the term, "near," is not precisely defined. Should a minimum specific distance away from the generator be used instead? Further, should the system operator visually monitor the system during the elution procedures and would that require the operator being near the system?

V. Concluding Remarks

The subcommittee agrees with the remainder of the Licensing Guidance. The subcommittee felt that the draft Licensing Guidance is, overall, reasonable and not particularly onerous for prospective users and, given the new and novel features of the NorthStar generator system, licensing under 10CFR 35.1000 is reasonable.

Respectfully submitted, September 08, 2016
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