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September 8, 2010

U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001
Attn: Mr. James P. Dwyer, Chief
Commercial and R&D Branch
Division of Nuclear Materials Safety

54-28275-02 MD
03030793

54-28275-01
03030788

RE: Clarification of 10 CFR 32.72

Dear Mr. Thompson,

MDS Nordion is seeking clarification on the interpretation of 10 CFR 32.72 as it relates to requirements for linearity testing of dose calibrators. The applicable sections of the regulation are as follows:

Regulation of 10 CFR 32.72 "Manufacture, preparation, or transfer for commercial distribution of radioactive drugs containing byproduct material medical use under part 35".

32.72 (c) A licensee shall possess and use instrumentation to measure the radioactivity of radioactive drugs...In addition the licensee shall:

- (1) Perform tests before initial use, periodically, and following repair, on each instrument for accuracy, linearity, geometry dependence, as appropriate for the use of the instrument; and make adjustments when necessary;

This regulation describes the requirements for the manufacture of radioisotope containing products for medical use. Requirements are given for the control of dose calibrators including requirements for linearity studies. The regulation appears to provide for flexibility in need for linearity studies based on the use of the device.

MDS Nordion is interested in eliminating linearity studies carried out on two categories of dose calibrators that are used in the manufacture of radiopharmaceutical products. The dose calibrators being considered have two functions (described below), neither of which is used for finished product release.

Dose Calibrator Functions

The first dose calibrator (dose calibrator #1) is used to measure the activity of a known volume of precursor product stock in order to determine the activity concentration prior to final dilution. This information allows operations personnel to calculate the quantity of diluent necessary to achieve the target activity concentration of the final product stock. Dose calibrator #1 is then used to measure the activity of a known quantity of the final product stock and to confirm that it falls within the target activity concentration range. A subsequent



sample of the final product stock is also analysed by QC in a NIST traceable GeLi Detector MCA, the output of which is used in the release of the finished product. Finished product release is determined based on the known volume dispensed (as verified by QC and Operations personnel) and the activity concentration (as determined with the NIST traceable GeLi Detector MCA).

The second dose calibrator (dose calibrator #2) is used as an in-process monitoring device to confirm the performance of the unit dose dispenser. The activity content of every 5th vial is measured in dose calibrator #2. Product volumes are subsequently 100% visually verified prior to release by the production personnel and on a sample basis by QC as a finished product release test.

Proposal

Currently, linearity studies are performed on both dose calibrators as an element of the ongoing performance monitoring of these devices. We propose that the specific uses of the devices do not warrant carrying out linearity studies and as a result, linearity studies can be eliminated. We can demonstrate that we are, in effect, carrying out dose calibrator accuracy checks in the precise activity range of the finished product for each use of the dose calibrator. In one case where the dose calibrator is also used for a precursor stock (in a different activity range), a measure of the linearity effect is determined each time the device is used.

Rationale:

Dose calibrator #1

Dose calibrator #1 is used to measure 5 ml quantities of product stock prior to dilution and again after dilution to final product activity concentration.

The activity concentration of the finished product stock is subsequently measured directly in a NIST traceable GeLi Detector MCA. This allows Operations personnel to confirm the accuracy of dose calibrator #1 at the final product activity concentration each time the device is used (this is an actual to actual comparison of finished product activity concentration using the two methods).

Dose calibrator # 1 is also used to measure the activity of a 5 ml sample of precursor stock. Measurement accuracy of dose calibrator #1 could potentially be influenced by a linearity effect over the range of use from the precursor measurement to the final activity concentration (this is nominally a 25% dilution range). However, Operations personnel can determine the combined effect of linearity and dilution variances by comparing the actual versus expected dose calibrator readings post dilution (where expected is calculated using the precursor activity concentration and the known volume of diluent). The difference between these two values represents the combined effect of linearity error and error in the dilution volume.

Control charts are used in both cases to improve our ability to detect a small shift in performance of the dose calibrator relative to the GeLi Detector MCA. Control charts allow us to detect statistically significant shifts in process performance before they are likely to result in out of specification product.



For these reasons MDS Nordion believes that further periodic linearity studies are not required for dose calibrator #1.

Dose calibrator #2

Dose calibrator #2 is used to for early detection of changes in the performance of the dispenser that could put the production run at risk. Dispenser accuracy is confirmed volumetrically prior to the start of each run. A 10% shift from the target dispensing volume would generate "out of specification" product. Actual performance, based on statistically determined control limits, shows dispenser variation less than +/- 2% (determined based on data from 10 production runs). Dose calibrator #2 is therefore used to detect a shift from nominal that exceeds 2%.

The accuracy of dose calibrator #2 is confirmed with each run by measuring the first vial of active product in the dose calibrator and then determining activity concentration using the same finished product unit dose in the NIST traceable GeLi Detector MCA. Subsequent vials (every 5th) are measured in dose calibrator #2 to detect a shift in performance of the dispenser that exceeds the control limits (+/- 2%). The effect of linearity on a measurement that is within 2% of the nominal measurement (that has already been demonstrated to be accurate) is not significant. Control charts again are used to evaluate historical trend data of the dose calibrator #2 relative to the GeLi detector MCA and detect minor changes requiring investigation prior to any possibility of producing "out of specification" material. As a result, MDS Nordion believes that periodic linearity studies are not required for dose calibrator #2.

Conclusion

MDS Nordion would like to confirm that the USNRC interpretation of "as appropriate", in the applicable this regulation, aligns with our interpretation, and that linearity studies are not necessary for these particular applications of dose calibrators. Your advice on this question is greatly appreciated.

Should further information be required related to this request, please feel free to contact me by phone at (613) 592-3400 ext. 2730, by fax (613) 592-2006 or by email at jackie.kavanagh@mdsinc.com.

Yours truly,

A handwritten signature in cursive script that reads "J. Kavanagh".

Jackie Kavanagh
Manager, Facility and Transportation Licensing and Compliance

cc: R. Beekmans - MDSN