Cardinal Health
Nuclear Pharmacy Services
Quality & Regulatory
7000 Cardinal Place
Dublin, OH 43017
tel 614.757.4120
fax 614.652.4598

www.cardinal.com

CardinalHealth

December 8th, 2017

Bryan Parker, Licensing
U.S. Nuclear Regulatory Commission
Region III – Division of Nuclear Materials Safety
2443 Warrenville Rd, Suite 210
Lisle, IL 60532-4352

Re: Amendment Request for Radioactive Materials License 34-31473-03MD, Cardinal Health Nuclear Pharmacy Services, Dublin, OH.

Mr. Parker:

Cardinal Health 414, LLC (Nuclear Pharmacy Services and Radium-223 Manufacturing Services, hereafter Cardinal Health) is requesting permission to modify the existing bioassay monitoring procedure to the following.

Employees at this location will perform bioassays under the following conditions:

- Upon hire and prior to working with material to establish a baseline
- When two of the three events occur:
  - Portable Air Monitoring Alarm
  - Personal Contamination Event
  - A spill occurs outside of the hot cell.

This change to the bioassay monitoring procedure is justified by data collected for 15 individuals over the past two years shown in Attachment A. An analysis of this data has determined that, under routine operations, there is negligible risk for an internal exposure. Every bioassay measurement for the past two years was significantly below the action level 1 (100 mRem). This indicates that the routine bioassays required for individuals at this facility are overly conservative and do not provide a significant benefit.

It is proposed that bioassays only be conducted when two of the three possible events listed above occur. When these conditions are met, it was determined that the risk for an internal exposure would be significant and warrants a bioassay.

If you have any questions regarding this request, please contact me at 614.757.9586.

RECEIVED DEC 11 2017

Sincerely,

Glenn Sullivan, CRSO
Corporate Radiation Safety Officer
Director, Health Physics
Nuclear Pharmacy Services

/tc

Enclosure: Bioassay Data

cc: License File, Loc. 7220 (3)
David Pellicciarini, VP Pharmacy Safety, Practice and Technical Operations
Katherine Benson

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Attachment A
Bioassay Trending Data

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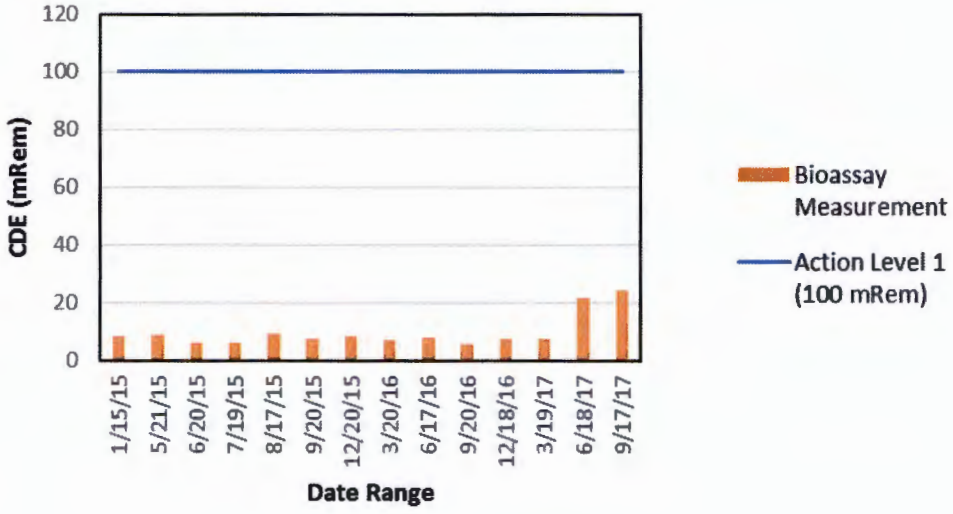
Employee 1 Bioassay



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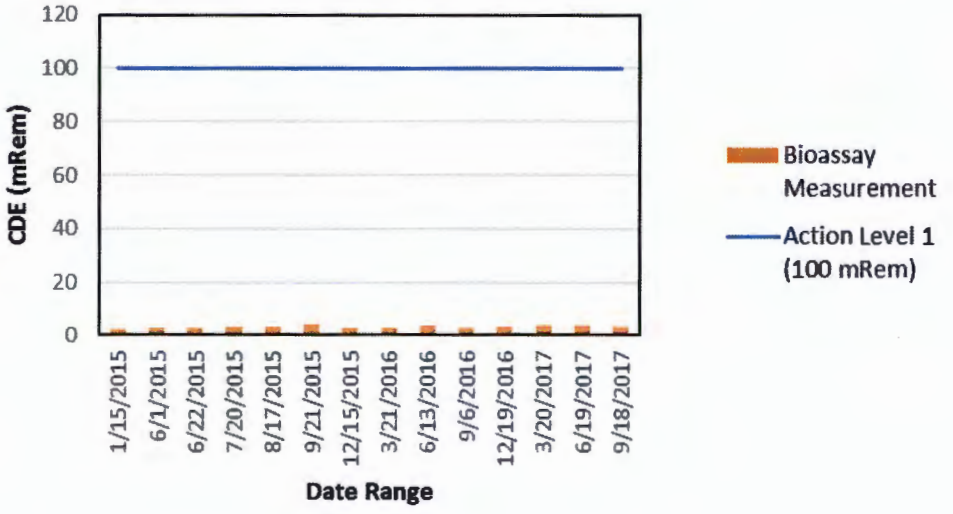

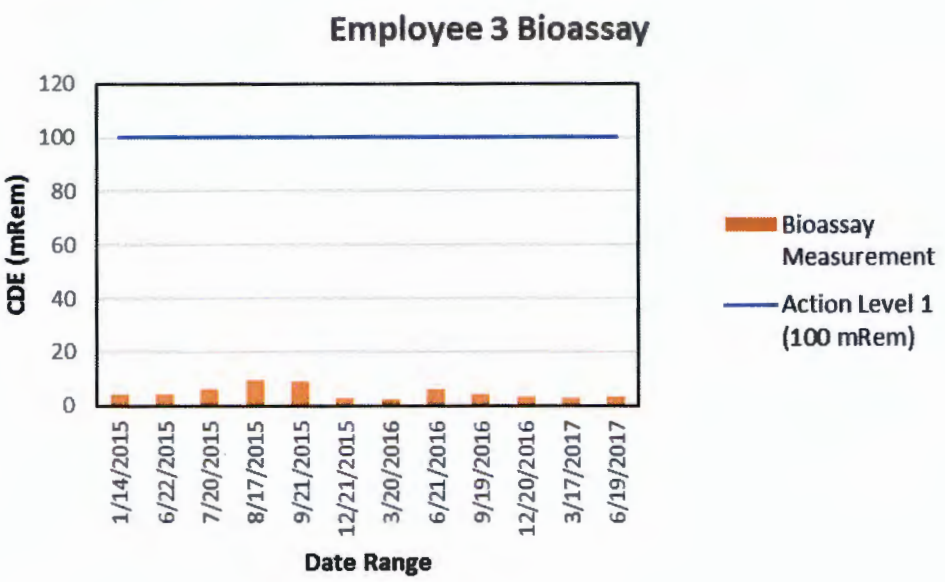
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CDE (mRem)
120
100
80
60
40
20
0
1/14/2015
6/22/2015
7/20/2015
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9/21/2015
12/21/2015
3/20/2016
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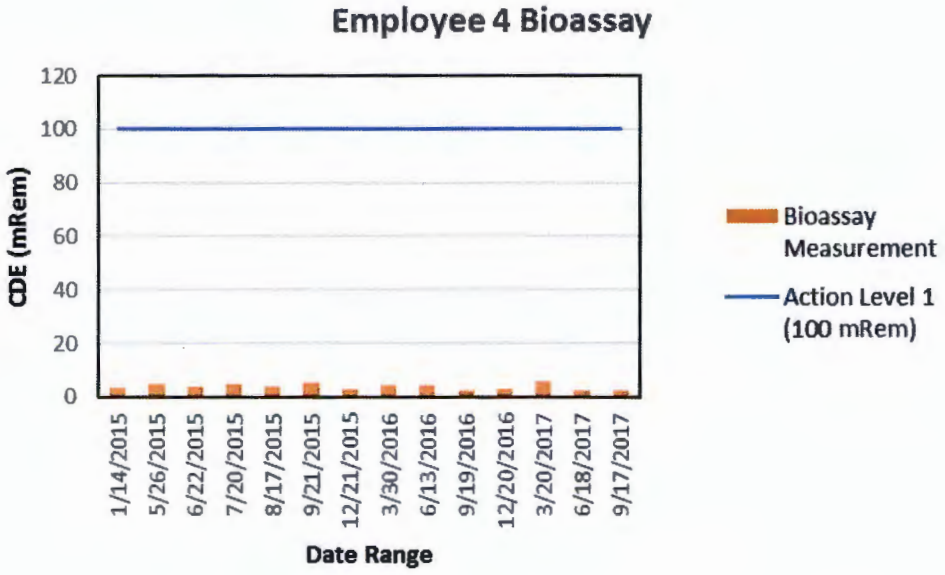
9/19/2016
12/20/2016
3/17/2017
6/19/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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80
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8/17/2015
9/21/2015
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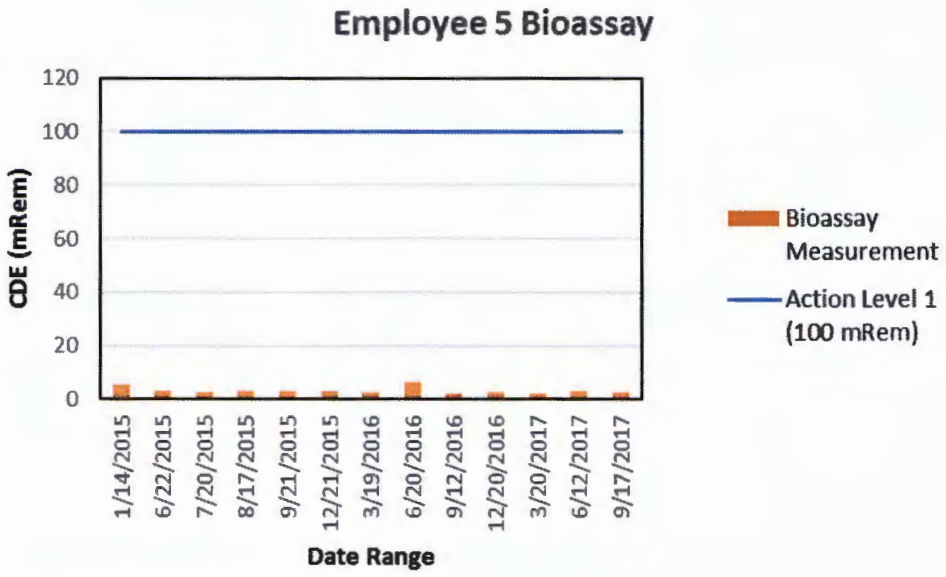
9/17/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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6/22/2015
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3/19/2016
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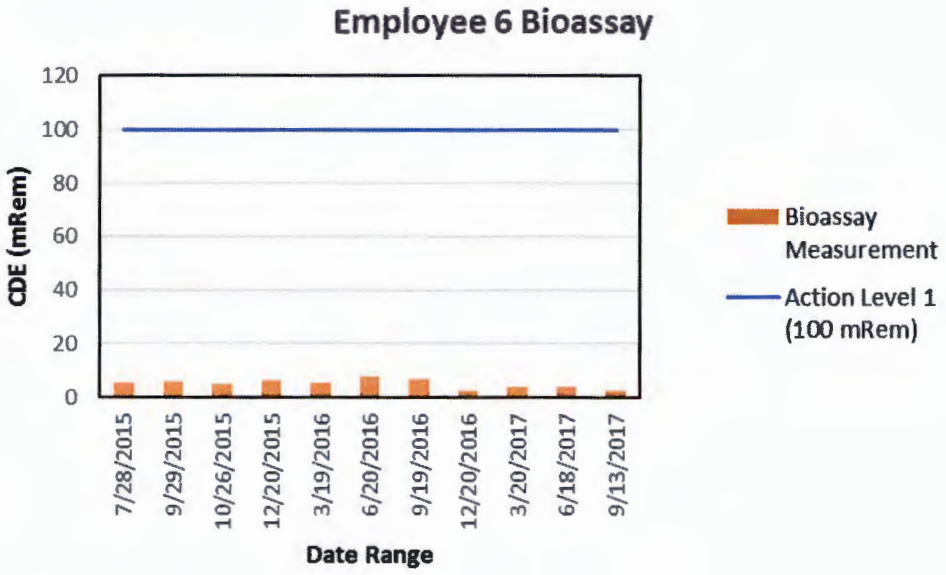
9/17/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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100
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60
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9/29/2015
10/26/2015
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3/19/2016
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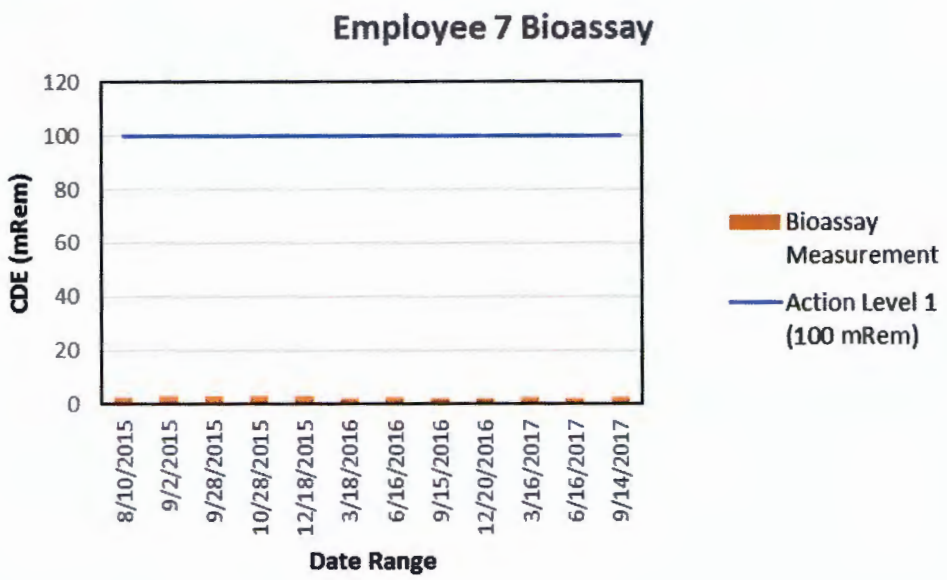
3/20/2017
6/18/2017
9/13/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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20
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CDE (mRem)
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9/2/2015
9/28/2015
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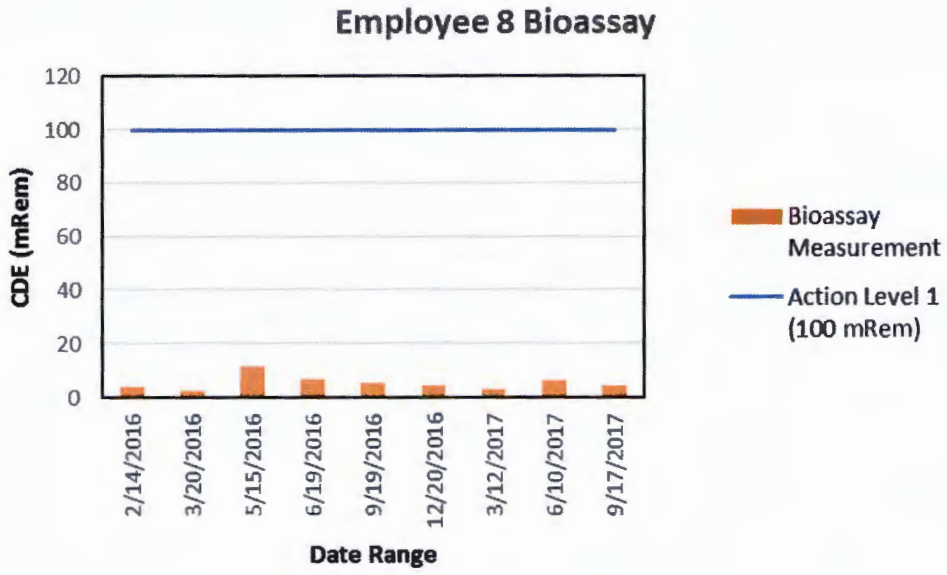
12/18/2015
3/18/2016
6/16/2016
9/15/2016
12/20/2016
3/16/2017
6/16/2017
9/14/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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80
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0
CDE (mRem)
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3/20/2016
5/15/2016
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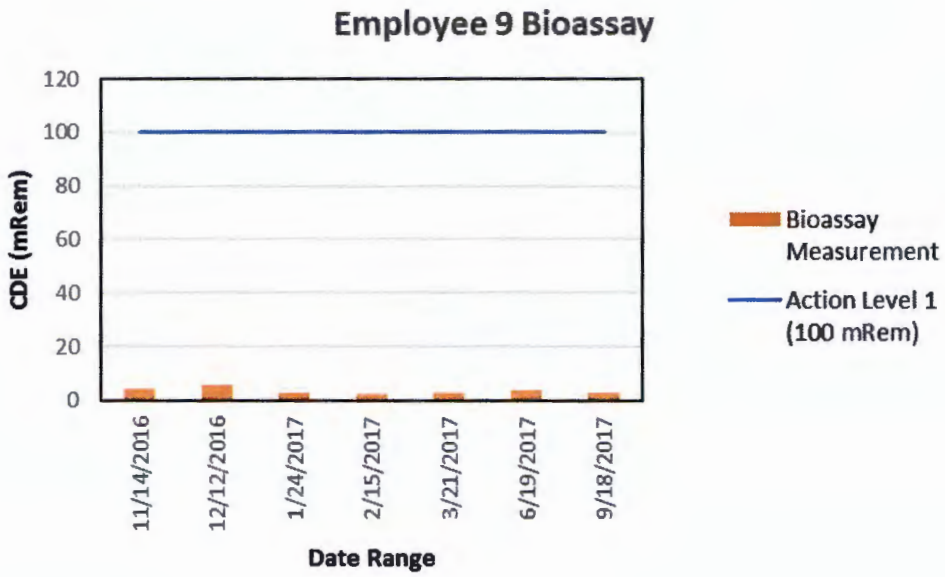
9/17/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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100
80
60
40
20
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CDE (mRem)
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12/12/2016
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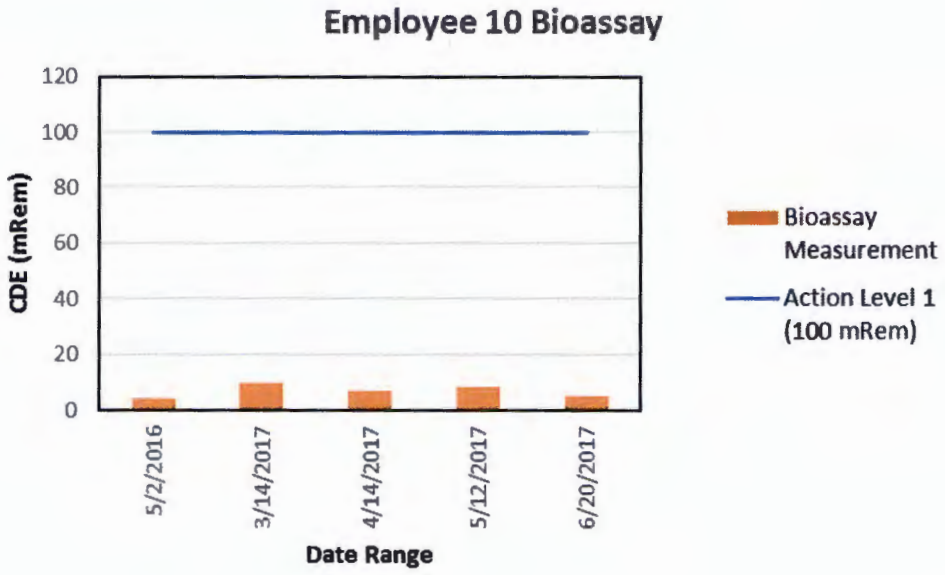
9/18/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)


Employee 10 Bioassay
120
100
80
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40
20
0
CDE (mRem)
5/2/2016
3/14/2017
4/14/2017
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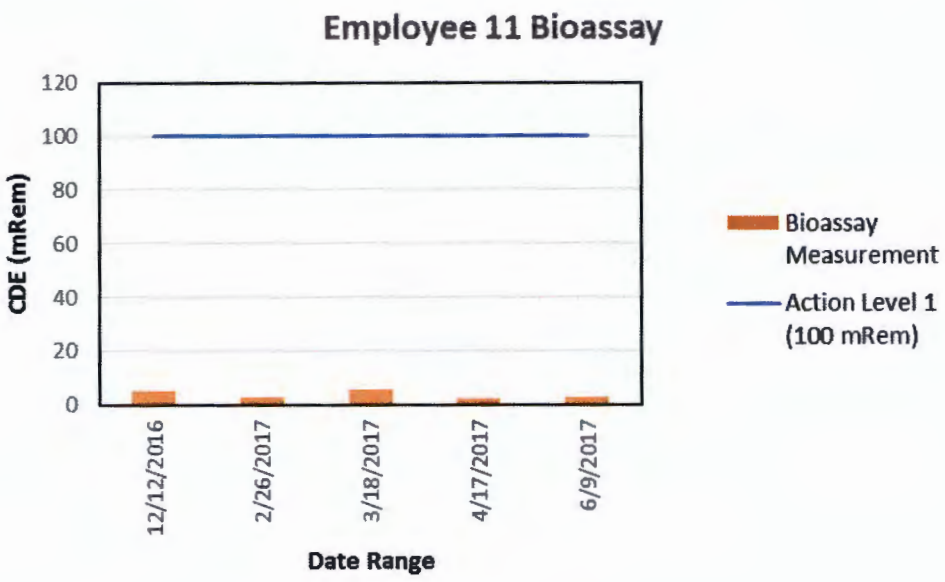
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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100
80
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CDE (mRem)
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2/26/2017
3/18/2017
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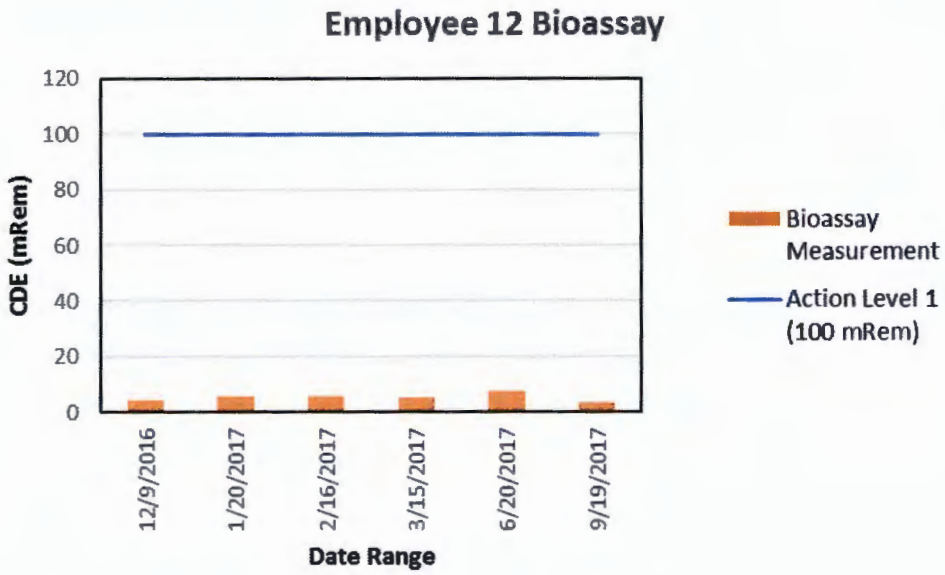
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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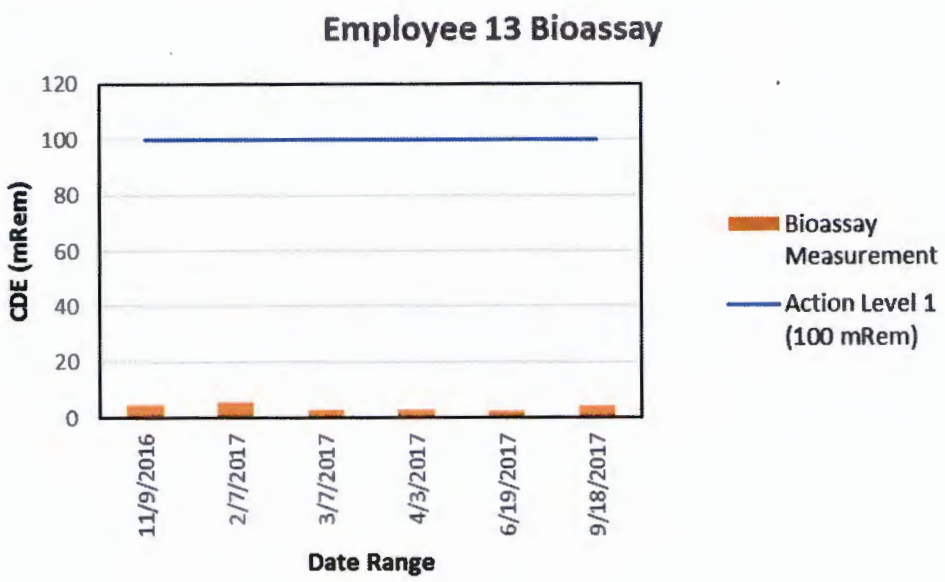
100
80
60
40
20
0
CDE (mRem)
12/9/2016
1/20/2017
2/16/2017
3/15/2017
6/20/2017
9/19/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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0
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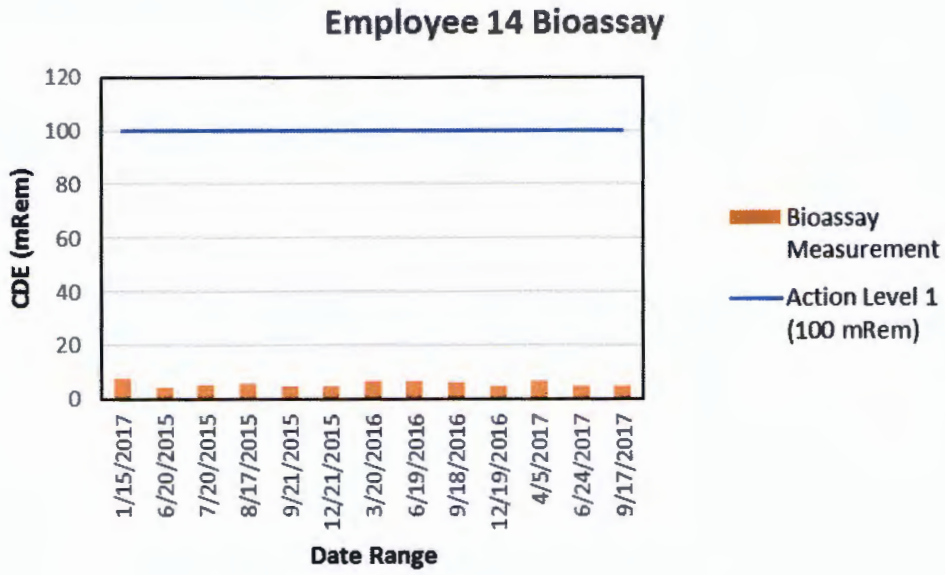
Bioassay Measurement
Action Level 1 (100 mRem)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80
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CDE (mRem)
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7/20/2015
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9/21/2015
12/21/2015
3/20/2016
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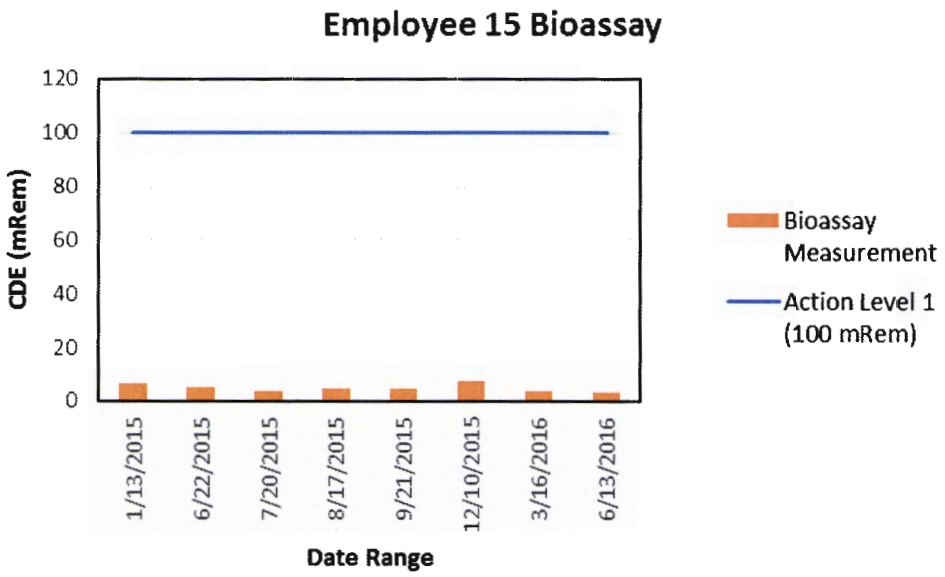
4/5/2017
6/24/2017
9/17/2017
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)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100
80
60
40
20
0
CDE (mRem)
1/13/2015
6/22/2015
7/20/2015
8/17/2015
9/21/2015
12/10/2015
3/16/2016
6/13/2016
Date Range
Bioassay Measurement
Action Level 1 (100 mRem)

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CardinalHealth

www.cardinalhealth.com/nps

December 8th, 2017

U.S. NRC - Region III
Radioactive Material Licensing
2443 Warrenville Road, Suite 210
Lisle, IL 60532-4352

Re: Amendment Request for Radioactive Materials License 34-31473-03MD, Cardinal Health Nuclear Pharmacy Services, Dublin, OH

Licensing:

Cardinal Health 414, LLC (Nuclear Pharmacy Services, hereafter Cardinal Health), requests the addition of 1000 millicuries for IRE Galli-Eo® (50 mCi) Germanium-68 / Gallium-68 generators and 1000 millicuries of Ga-68 as explained below, for the above referenced radioactive materials license, Indianapolis, Indiana pharmacy.

The IRE Galli-Eo® (50 mCi) Germanium-68 / Gallium-68 generators are being made commercially available under a Drug Master File (DMF) number 03171 Type II.filed with the U.S. FDA. The generators will be utilized in accordance with the manufacturer's instructions for use. The Ga-68 trichloride is not intended for direct patient administration. All radiopharmaceuticals prepared with the 68.3 minute half-life Ga-68 trichloride eluate from the Ge-68 generator will be either U.S. FDA approved kits, or research compounded that are part of a U.S. FDA approved IND drug study.

Cardinal Health is the sole distributor for IRE Galli-Eo® Germanium-68 / Gallium-68 generators in the United States. In addition to preparing radiopharmaceuticals with the use of this generator, Cardinal Health also requests the ability to distribute new, unused generators to Cardinal Health customers on the behalf of IRE. Cardinal Health will maintain a return agreement with each customer receiving this generator.

Cardinal Health commits to the return of the generator(s) to IRE for disposal when each unit is no longer used. There will be no decay in storage of the Ge-68. Cardinal Health's legally binding agreement with the manufacturer, IRE, for the return of the generators is enclosed in Attachment C. Cardinal Health requests an exemption from the 10 CFR Part 30.35 Decommissioning Funding Plan (DFP) requirements for the Ge-68/Ga-68 generators per the NRC guidance document ML17075A487 dated July 13, 2017.

Cardinal Health will meet the requirements in U.S. NRC license guidance for 10 CFR 35.1000 and Authorized Nuclear Pharmacist training. Cardinal Health commits to following U.S. NRC license guidance dated July 13, 2017. Documentation concerning the manufacturer design and specifications of the Ge-68/Ga-68 generator is enclosed.

If you have any questions regarding this request, please contact me at 614.757.9586.

Sincerely,

Glenn Sullivan.
Corporate Radiation Safety Officer
Director, Pharmacy Safety and Practice
Nuclear Pharmacy Services

Encl: Attachment A – IRE Galli-Eo® Germanium-68/Gallium-68 Generator Instructions for Use
Attachment B – Ge-68/Ga-68 License Commitments
Attachment C – Cardinal Health Legally Binding Agreement with IRE

cc: License File, Loc. 7220 (3)
Benjamin Ellert
Kathi Benson
Roger Hackett

ATTACHMENT A

IRE Galli-Eo® (18.5 GBq) Germanium-68 / Gallium-68 Generator Instructions for Use

Galli Eo

^{68}Ge/^{68}Ga generator

INSTRUCTIONS FOR USE (TECHNICAL PART)

1. INTRODUCTION

The purpose of this document is to provide the information required for optimal operation (elution) of the *Galli Eo*™ Gallium-68 generator.

2. INSTRUCTIONS FOR USE

A. Unpacking of the generator

Before opening the case, please refer to the arrow signs to make sure the shipping box is placed **in the right orientation**. Then cut the shipping security seal and open the shipping box. (Check that the seals are not be broken before.)
Please carefully remove generator and **perform radiation survey**.

CAUTION: The generator weighs approximately 16 kg. Handle with care and firmly to avoid potential injuries or drop hazards.

Check the whole hull and **outlet port** for damage. Do not remove the port plug before installing the generator nor before being ready for elution.

B. Installation of the generator

Please install the generator at its site of use only in a **vertical position** i.e. so that the green control button faces upwards (as depicted in fig. 1). **The generator is not intended to be placed, used or stored in any other position (f.ex. horizontally).**

Elution of the generator must be performed in premises complying with the national regulations concerning the safety of use of radioactive products.
Aseptic working technique must be applied when using the generator, especially when handling the elution port. This is critical for maintaining the sterility.

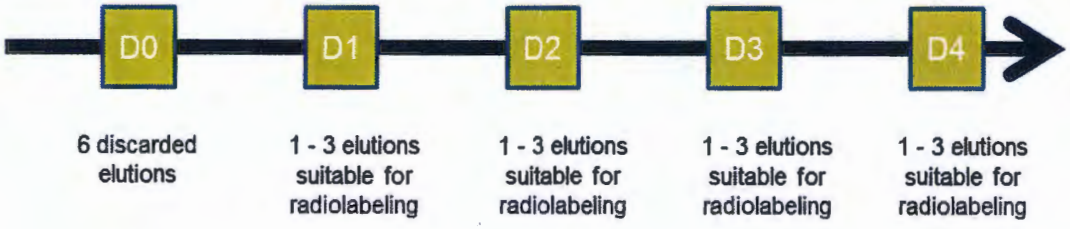
Local shielding is recommended when performing an elution and personal protective equipment, eye and hand protection, must be used.

C. First use of the generator and use during the first week or first 4 elutions

IMPORTANT: When using the generator for the first time, **a conditioning procedure must be performed** once before using it for radiolabeling purposes.

It consists of **six consecutive discarded elutions to be carried-out within 24 hours.** These elutions can be performed in a row (one directly after the other) if desired.

After that, the next generator eluates are suitable for radiolabeling purposes provided that they come from an elution performed within 24 hours since the last elution. **This conditions only applies to the first eluates intended for radiolabeling during the first four days (i.e. typically only during the first week of use of the generator).**



D. Elution process of the generator

A complete elution procedure of the *Galli Eo*^{TM} Gallium-68 generator by mean of a **sterile evacuated vial** is described in the following steps :

1) Unscrew manually the cap from the luer lock connector (fig. 1).

Fig.1

2) Connect manually a **sterile tubing** (extension line) to the luer lock connector (fig. 2). *For example, product number 1155.03 or 1155.05 from Vygon are suitable.*

Fig.2

3) Connect a **sterile needle** to the other end of the tubing using **a male/male luer lock adapter** (fig. 3).
For example, product number L10107 0.9 X 70mm 20G 2 ¾ from Neopoint and product number 893.00 from Vygon are suitable.

Fig.3

4) Turn the green button by 90° to the **loading position** and wait for **at least 10 seconds** (fig.4).

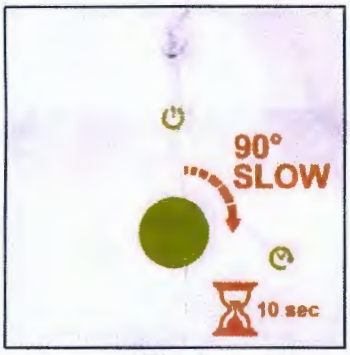


Fig.4

5) Then, turn back the button by 90° to its **initial position** (fig. 5).

Fig.5

6) Remove the cap from the needle and **quickly pierce vertically right in the center of the septum of a shielded sterile evacuated elution vial** (fig.6).

Wait for **at least 3 minutes** for the elution process to take place and for the line to be drained by air. Please use **local shielding** or **radioprotection mean** as the activity will be transferred from the generator to the vial

CAUTION :10 ml capacity sterile evacuated vials are suitable but it is recommended **to avoid contact of the eluate with uncoated halobutyl stoppers** as they may contain important amounts of zinc that might prevent a subsequent radiolabelling step

Fig.6

NB: Alternatively, the elution process can be carried out similarily by mean of **an automatic radiosynthesis unit.** In that case, it is recommended to place a single-use sterile check-valve between the male/male luer lock adapter and the automatic radiosynthesis unit. *For example, product number MX745-01 from Smiths Medical is suitable.*

7) Remove the needle from the vial and **place the cap** (fig. 7 and 8).

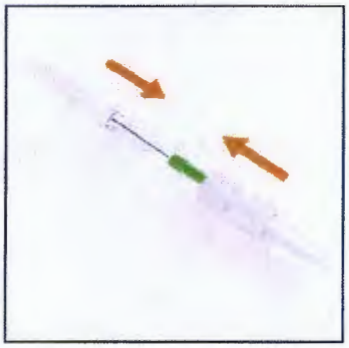


Fig.7 **Fig.8**

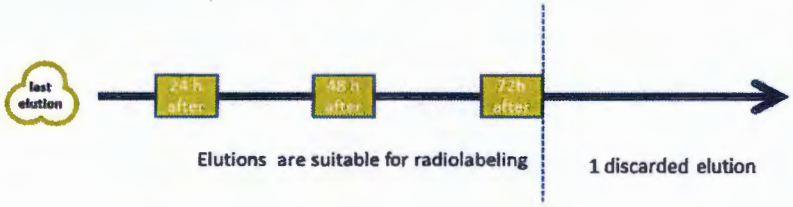
8) Disconnect manually the tubing from the luer lock connector and **place the cap in order to obturate the generator outlet** (fig. 9 and 10).

Fig.9

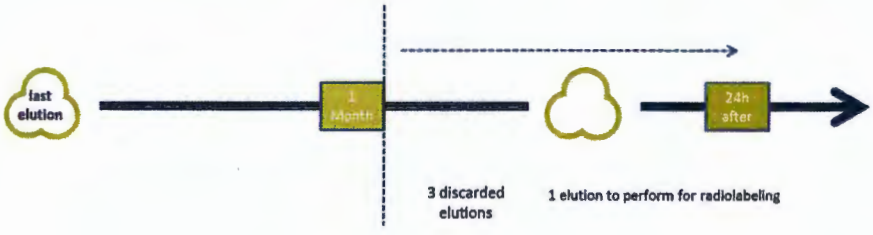
Fig.10

E. Normal (routine) use of the generator

Then, during the shelf life of the generator, the following eluates are suitable for direct radiolabeling provided that a previous elution has been performed **within the last 72 hours**. In case a radiolabeling is intended and the generator has not been eluted within that interval, it is recommended to perform one discardable elution beforehand.



If the generator is not eluted for **more than a month, three consecutive discarded elution are to be performed** and the first eluate intended for radiolabeling should be extracted within the next 24 hours.



F. General Remark

The generator must not be dismantled for any reason; such action will be considered as IP infringement.

ATTACHMENT B

License Commitments per U.S. NRC License Guidance July 13, 2017

General License Commitments for Ge-68 / Ga-68 Generators:

Cardinal Health commits to the following items for the IRE Galli-Eo® generators:

[X] Provide instructions and/or training on the manufacturer's procedures to all individuals involved in Ge-68/Ga-68 generator use, commensurate with the individual's duties to be performed.

[X] Not to open, breach, or physically modify the IRE Galli-Eo® generator in any way.

[X] Follow the manufacturer's procedures, including: generator set-up; generator elution; drug preparation; Ge-68 breakthrough testing; and final disposition.

[X] To elute the generator in accordance with the manufacturer's stated frequency and procedures to minimize the concentration of Ge-68 in the eluate.

[X] Not use an expired generator for preparation of materials that will be administered to patients or human research subjects.

[X] Only use a generator that has a clearly marked expiration date.

[X] After installation, elute the generator and properly dispose of the eluate prior to the first use of eluate for testing or human use.

[X] Develop and implement written procedures for the determination of breakthrough that will detect whether the eluate exceeds the manufacturer's breakthrough limit.

[X] Not knowingly dispense to an authorized recipient to administer a prepared dosage to a patient or human research subject any material containing Ga-68 which is determined to exceed the manufacturer's breakthrough limit.

[X] If the generator has not been eluted within 48 hours, then discard the first eluate prior to use (e.g., if the generator is used Friday and the next elution is not until Monday morning then the first eluate shall be discarded).

[X] Measure the breakthrough of the generator at least once per every 7 calendar days when in use.

[X] To remove a generator from use if the measured Ge-68 breakthrough exceeds the manufacturer's stated breakthrough limit.

[X] Not return a generator to service until the breakthrough has been measured again in a new elution and determined to be below the manufacturer's stated breakthrough limit.

[X] Maintain a record of the breakthrough tests for at least 3 years. These tests include the ratio of the measured activity of Ge-68 per Ga-68 corrected for the time of elution, time and date of the elution, time and date of the measurement, and the name of the individual who made the measurement.

[X] Use manufacturer instructions to develop and implement written emergency procedures for leaking or damaged generators.

[X] Notify by telephone the U.S. NRC Region and Operations Center; and the manufacturer/distributor of the generator within 7 calendar days after discovery of an eluate (excluding eluates from flushing the generator in accordance with manufacturer procedures) that exceeded the manufacturer's stated breakthrough limits of Ge-68.

Include in the report to NRC Operations Center the manufacturer, model number, and serial number (or lot number) of the generator; the results of the measurement; the date of the measurement; whether dosages were administered to patients or human research subjects; when the manufacturer/distributor was notified; and the action taken.

[X] Report, in writing, based on notification to and from our customers with medical use licenses, within 30 days, any doses to humans prior to the results of a failed breakthrough calculation in accordance with the rules for medical events, and reportable events as applicable for our customer medical use licenses.

[X] Send a written report to the NRC Operations Center and appropriate NRC Regional Office within 30 days after discovery of an eluate, excluding eluates from flushing the generator in accordance with manufacturer procedures that exceeded the manufacturer's stated breakthrough limits of Ge-68. We will include in the written report the action taken by the licensee; the patient dose assessment; the methodology used to make this dose assessment if the eluate was administered to patients or human research subjects; probable cause and assessment of failure in the licensee's equipment, procedures or training that contributed to the excessive readings if an error occurred in the licensee's breakthrough determination, and the information in the telephone report made as described above.

[X] Wipe test all areas of licensed material use, including the generator storage and kit preparation areas, for contamination using a survey instrument each day of use.

[X] Wipe test the generator casing quarterly for expired or unused generators in storage for more than three months.

ATTACHMENT C

Legally Binding Agreement
Cardinal Health and IRE

Return Agreement for Germanium-68/Gallium-68 Generators

This Return Agreement IRE ELIT, S.A. Germanium-68/Gallium-68 Generators (Return Agreement) is entered into by and between IRE ElIT, S.A. (IRE) and Cardinal Health 414, LLC (Cardinal Health), effective 10/1/2017 (Effective Date).

Background

1. Cardinal Health is purchasing Galli Eo Gemanium-68/Gallium-68 generator (Generator) from IRE ElIT. The Generator is a radioactive substance, the possession and use of which are subject to several regulatory requirements.

2. The July 29, 2016, U.S. NRC Memorandum entitled ***Authorization for Granting Specific Exemption from Decommissioning Funding Plan Requirement for Germanium-68/Gallium-68 Generators*** (NRC Memorandum) authorizes NRC regions to issue decommissioning exemptions to licensees when requested if a licensee has a binding agreement in place to return the generators to the manufacturer, including a commitment from the manufacturer to take generators back when the generators are expired or are no longer used to prepare Gallium-68 radiopharmceutical for patients, or the licensee ceases its prepartion of Gallium-68 radiopharmaceutical.

3. This Return Agreement documents a commitment between the parties to a standard return procedure for the Generator as referenced in the NRC Memorandum.

NOW THEREFORE, the parties agree as follows:

Agreement

1. Return Commitment: For each Cardinal Health radiopharmacy that possesses a Generator, Cardinal Health commits to return each Generator and IRE commits to accept the return of each Generator by Cardinal Health, subject to the terms and conditions of this Return Agreement and in compliance with all applicable laws. Such commitment by each party above applies upon expiration of the Generator or in the event Cardinal Health no longer uses the Generator to prepare Gallium-68 radiopharmceuticals for patients, or Cardinal Health ceases its prepartion of Gallium-68 radiopharmaceuticals.

2. Return Process:

2.1 Cardinal Health will contact IRE to obtain a returned materials authorization (RMA).

2.2 Any Generator returns shall be accomplished in accordance with IRE's reasonable instructions as mutually agreed upon by Cardinal Health. In the case of the Generator's shelf-life expiry, return must take place at the latest sixty (60) days following the expiry date; provided that IRE will accept the return of the Generator at any earlier date as may be requested by Cardinal Health.

3. Term. This Return Agreement commences on the Effective Date and will continue until Cardinal Health returns the final Generator and Cardinal Health confirms to IRE in writing that it no longer intends to possess any Generator.

4. Miscellaneous: The terms herein represent the entire agreement between with parties regarding the subject matter herein. This Return Agreement supersedes all previous communications, representations or agreements, whether oral or written, between the parties regarding the subject matter herein. This Return Agreement will not be amended except by mutual written agreement between the parties. Notices required

herein will be provided by each party to the other via overnight courier, hand delivery or certified mail/return receipt, directed to the address under the signature lines below.

Signature for accepting the above:

Cardinal Health 414, LLC:	**IRE EliT, S.A.**
Name: Tiffany Olson	**Name:** VANDERHOFSTADT
Title: President	**Title:** CEO
Signature:	**Signature:**
Address: 7200 Cardinal Place	**Address:** Av. ESPERANCE, 1
Dublin OH 43017	B-6220 FLEURUS
	BELGIUM

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1. Use the 'Print' button on this page to print your label to your laser or inkjet printer.
2. Fold the printed page along the horizontal line.
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