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Germanium 68/ Gallium 68 Generator Best Practices

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OBJECTIVES

- **The Basics: What is a Ge-68/Ga-68 Generator**
- **Learning the different methods to produce Gallium 68**
- **Describing the steps on how to elute a Gallium-68 generator**
- **Describing methods on measuring Germanium-68 breakthrough**
- **Describing best sterile techniques when eluting the Gallium-68 generator in an ISO 7/8 and ISO 5 environment**
- **Generators: What is next?**

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BIO

Jay Simon, RPh, ANP is a pharmacy graduate from the University of NewMexico (UNM) and the UNM Radiopharmacy program. Starting out as the Manager for Syncor,(now Cardinal Health) in Colombus Ohio right after graduation before transferring to Syncor in Phoenix eventually becoming the Southwest General, where he introduced the concept of PET to Gene McGrevin, then Syncor CEO and later CEO for PETNet. After a series of promotion, Mr. Simon left Cardinal Health in 2003 as the Vice President of International representing 55 business in 22 countries with over 500 employees to form Global Medical Solutions (GMS). At GMS, Mr. Simon was the President and COO responsible for the business in Asia Pac and Brazil consisting of more than 35 businesses including 20 radiopharmacies across nine countries.

In 2012, Mr. Simon moves to Sydney Australia to become the CEO of Axiom Molecular to establish radiopharmacies and PET Centers across Asia-Pac. In mid-2013, Mr. Simon returned to the US to help restart the UNM radiopharmacy program and then began consulting for other countries. In 2020 Mr. Simon accepted a position at Eckert & Ziegler Radiopharma (EZR) to establish a Y-90 production site near Boston and to manage the EZR business for all of North America where he currently is employed.

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DISCLOSURES:

Jay R. Simon is the Managing Director of Eckert & Ziegler Radiopharma, Inc.
There is no previous or existing relationship to iCARE Pharmacy Services, Inc other than to make this presentation.

The opinions expressed are that of the presenter as an ANP, industry veteran and are not as a representative of any other person or from any company.

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The Basic – What is a Ge-68/ Ga-68 Generator?

* A radionuclide generator that contains Ge-68 as the mother nuclide that decays to the daughter nuclide Ga-68 used for in vitro radiolabeling of various molecules and cold kits.

* In the US, Ga-68 generators are Type II DMF's as the Ga-68 is not intended for direct use in patients.

* In Europe, Ge-68/Ga-68 generators are registered drugs.

* Ga-68 has a half-life of 67.71 minutes while Ge-68 has a half-life of 270.95 days.

* Ga-68 emits 511 keV Gamma Rays ideal for PET camaras

* Uses sterile ultrapure 0.1mol/l HCL to wash the Titanium Dioxide Column

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As of January 2024, numerous Ga-68 radiopharmaceuticals and theranostic pairs utilizing novel ligands are currently under investigation for use in[1]:

• Brain and CNS tumors

Colorectal cancer

• Pancreatic cancer

Neuroendocrine tumors

• Esophageal cancer

Prostate cancer

• Head and neck cancers

Sarcomas

• Kidney cancer

Solid tumors

• Melanoma and other skin cancers

[1] **Source: NIH U.S. National Library of Medicine. Available at www.clinicaltrials.gov.**

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QUESTION #1: Why is ultrapure HCL used to wash the Ge-68 column?

1. It is readily available.

2. It is sterile.

3. Minimize metal that will interact with the Ga-68.

4. It does not make a difference as long as it is 0.1 mol/l

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Answer:

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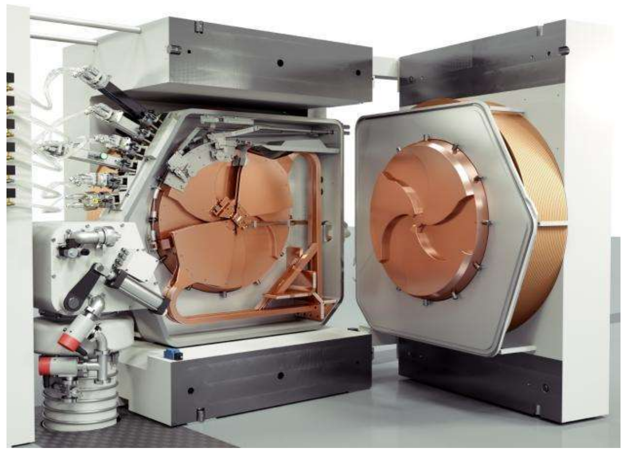
DIFFERENT WAYS TO PRODUCE Ga-68

Ge-68/Ga-68 Generator **Cyclotron**



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CYCLOTRONS:

Cyclotrons can produce 1 Curie or more amount of ^{68}Ga with solid targets and 100 mCi's or more with liquid targets.

Advantages:

- Production when needed without owning a generator
- Access to high activities for long distance transportation

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Cyclotron Disadvantages:

- Follows FDA GMP guidelines vs radiopharmacy guidelines
- Need to have a cyclotron! Not possible at small sitesCyclotron operation cost is considerable with up to 4 hours of cyclotron and target preparation per batch
- Cyclotron is engaged with ^{18}F and ^{11}C productions in the morning only making ^{68}Ga available later in the day
- Multistep purification needed before using with the kits
- The purity still varies from batch to batch
  Facilities typically do not rely completely on cyclotron and keep one generator as back up
- ^{68}Ge can be produced by different routes, including α-irradiation of zinc and irradiation of gallium with protons or deuterons
- A Ni/Ga target is irradiated at beam currents >250µA for many days

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- The main nuclear reactions at target irradiation are the following:
  $^{69}Ga(p,2n)^{68}Ge$ ($T_{1/2}$ = 270.82 d)
  $^{58}Ni(p,2p)^{57}Co$ ($T_{1/2}$ = 271.74 d)
  $^{58}Ni(p,2n)^{57}Cu \rightarrow {}^{57}Ni \rightarrow {}^{57}Co$
  $^{71}Ga(p,\alpha n)^{68}Zn$ (stable)
  $^{69}Ga(p,\alpha n)^{65}Zn$ ($T_{1/2}$ =243.93 d)
  $^{69}Ga(p,\alpha)^{66}Zn$ (stable)
  $^{69}Ga(p,n)^{69}Ge$ ($T_{1/2}$ =1.627 d)
  $^{71}Ga(p,n)^{71}Ge$ ($T_{1/2}$ =11.43 d)
- Before post irradiation processing the target is held for a minimum of 15 days (in most cases 20 - 25 days) to allow for decay of ^{69}Ge ($T_{1/2}$= 1.627 d) and other short-lived radionuclides.
- Sophisticated post-irradiation chemical separation produces a ^{68}Ge feedstock solution that is used to "load" the generator.
- ^{68}Ge Chloride is the loading solution
- Cyclotron produced ^{68}Ge has many metal impurities in it making it impractical for NET labeling.
- Because of reliabilty, downtime with cyclotrons, every Ga-68 producing cyclotron has a Ge68/Ga68 generator!

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Ge-68/G-68 GENERATORS

Eckert & Ziegler GalliaPharm™

IRE ELiT's Galli-EO™

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Ge-68/GA-67 GENERATORS

- The generator is a closed system consisting of a borosilicate glass column containing a titanium dioxide bed on which ^{68}Ge is absorbed
- ^{68}Ga is continuously produced by decay of its radioactive parent ^{68}Ge and is eluted with sterile, ultra-pure 0.1M HCl
- The useful shelf-life of the generator has been investigated in a long-term study that confirmed compliance with the specification over a 12-month period
- The FDA has approved Ga-68 generators to be used with NETSPOT™, Illuccix™ and Locametz™

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Major differences between the two GMP generators

(IRE ELiT's Galli-EO™ andEckert & Ziegler GalliaPharm™)

- Elution volume
- Enclosed HCL versus external HCL
- Number of elution's
- Efficiency

OTHER Ge68/Ga68 GENERATORS – research generators

ITM No longer on the market

IGG 100 Research generator

Monrol Not available in the US

iThemba Research generator

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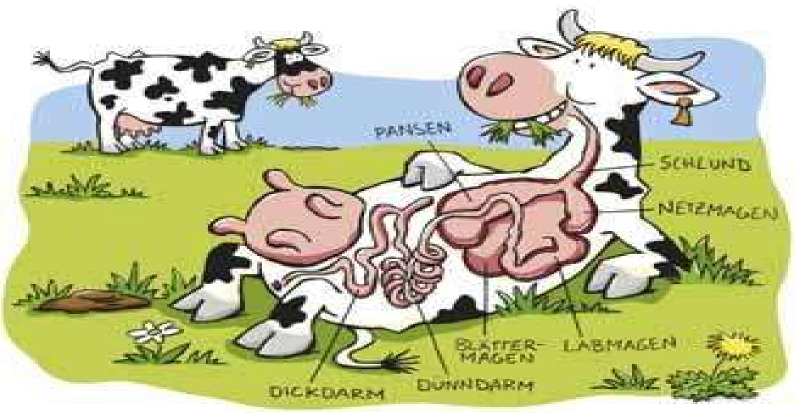
What is inside the cow?



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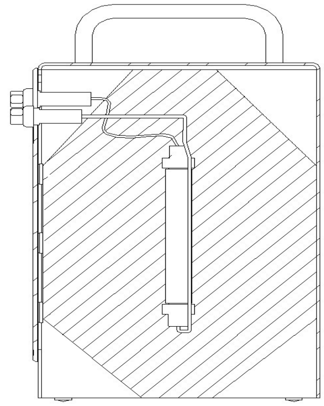

Borosilicate glass column

Titanium dioxide bed which the Ge-68 is absorbed

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QUESTION # 2

Why are generators commonly called “cows?”

1. Because they are large
2. They give off eluants called milk
3. Short from Mallinckrodt’s Ultrakow(TM) generator
4. They go along with lead pigs

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ANSWER:

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Ge-68 BREAKTHROUGH

^{68}Ge-Breakthrough testing = Once a week

Test basic setup:

- Measure ^{68}Ga at the elution time in a MCA or similar
- Let the sample decay for at least 48 hours
- Count with MCA for de novo Ga-68 emissions coming from ^{68}Ge breakthrough
- Use ^{68}Ge NIST reference vial standard for gamma well efficiency determination
- Note the limit of $<0.001\%$ (typically $<0.0001\%$)

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There are a few ways to measure Ge-68 breakthrough. The one I used at the University of New Mexico was suggested by AAA:

- Use fresh eluate from a generator that was eluted no more than 24 hours earlier. If the generator had not been eluted for 24 hours, you should do a 10ml flush and then a 5 ml elution a few hours, up to 24 hours later.
- From the eluate, take about 0.05 to 0.1 ml (depending on the age of the generator) and place it in a sealed serum vial, tube or similar depending on your MCA configuration.
- Take a one-minute background count on your MCA and then a one-minute count of the sample. You should get between 2-3 million counts. Don't over saturate your crystal. Difficulties with low counts of 1 million counts or lower.
- Measure again 48 hours later both the background and counts from eluate and then you can determine how much Ge68 if any (usually the counts are at or near background) is in the sample and then divide it from the original counts less background, and you should have <0.001%
- Do this weekly and of course - **record the results!**

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Alternative method to determine Ge68 Breakthrough:

1. Elution of the generator:

- Elute the Ge-68/Ga-68 generator following the manufacturer's instructions.

- Collect the entire eluate (typically 5-10 mL) in a shielded vial.

2. Initial activity measurement:

- Measure the initial activity of the eluate using a **dose calibrator set for Ga-68.**

- Record this value as A_0 and the time of measurement.

3. Sample preparation:

- Take a small aliquot (e.g., 0.1-0.5 mL) of the eluate for testing.

- Place this aliquot in a suitable container for long-term measurement (e.g., a plastic scintillation vial).

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4. Decay period:

- Allow the sample to decay for at least 24 hours (preferably 48 hours) to ensure complete decay of Ga-68.

- Ga-68 has a half-life of 67.71 minutes, so after 24 hours, less than 0.00001% of the initial Ga-68 remains.

5. Residual activity measurement:

- After the decay period, measure the residual activity of the sample using a highly sensitive detector.

- Options include:

  a) A low-background gamma counter

  b) A well-type NaI(Tl) scintillation detector

  c) A high-purity germanium (HPGe) detector

- **Record this value as A_1 and the time of measurement**.

  Ge-68 breakthrough (%) = (A_1 / A_0') × 100

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6. Background measurement:

- Measure the background activity of the detector using a blank sample.

- Subtract this background from the residual activity measurement.

7. Calculation of Ge-68 breakthrough:

- Calculate the decay-corrected initial Ga-68 activity (A_0') at the time of the residual activity measurement:

  $A_0' = A_0 \times e^{(-\ln(2) \times t / T_1/_2)}$

  where t is the time elapsed between measurements and $T_1/_2$ is the half-life of Ga-68 (67.71 minutes)

- Calculate the Ge-68 breakthrough as a percentage:

  Ge-68 breakthrough (%) = (A_1 / A_0') × 100

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8. Evaluation:

- Compare the calculated Ge-68 breakthrough to the specified limit (typically 0.001% or 1E-5).

- If the breakthrough exceeds the limit, the generator may need to be replaced or **additional purification steps may be required before using the eluate.**

9. Documentation:

- Record all measurements, calculations, and results in the appropriate quality control log.

- Include the date, time, generator details, and operator name.

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Note: This method assumes secular equilibrium between Ge-68 and Ga-68 in the generator. For more precise measurements, especially for new or recently eluted generators, multiple measurements over time may be necessary to account for potential disequilibrium.

This method provides a reliable way to quantify the amount of Ge-68 breakthrough in the Ga-68 elution. It's important to note that both the GalliaPharm and Galli-Eo generators specify a maximum Ge-68 breakthrough of 0.001% (1E-5) of the eluted Ga-68 activity.

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A few additional points to consider:

1. Frequency of testing: Both generators recommend weekly testing for Ge-68 breakthrough. However, more frequent testing might be necessary if there are concerns about generator performance or if required by local regulations.

2. Sensitivity: The method described requires a sensitive detector due to the very low levels of Ge-68 expected. A high-purity germanium (HPGe) detector would provide the best sensitivity and specificity but might not be available in all facilities.

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3. Alternative methods: Some facilities may use gamma spectroscopy to directly measure the 511 keV peak from Ge-68/Ga-68 (in equilibrium) after the Ga-68 has decayed. This method can provide additional information about other potential radionuclidic impurities.

4. Pre-elution effects: Both generators mention that Ge-68 breakthrough can increase if the generator isn't used for several days. The GalliaPharm instructions specifically state that breakthrough can increase above 0.001% if not eluted for several days. This underscores the importance of regular elutions and testing, especially after periods of non-use.

5. Record-keeping: Maintaining accurate records of breakthrough testing is crucial for quality control and regulatory compliance. These records can also help identify trends in generator performance over time.

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Gamma Counter Procedure:

1. Prepare the Gamma Counter:

- Ensure the gamma counter is calibrated and functioning correctly.

- Set the energy window to encompass the 511 keV peak of Ge-68/Ga-68.

2. Background Measurements:

- Prepare at least 10 blank samples identical to those used in your Ge-68 breakthrough tests.

- Count each blank sample for the same duration you use in your breakthrough tests (e.g., 300 seconds).

- Record the counts for each sample.

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3. Calculate Mean Background:

- Sum all background counts and divide by the number of samples to get the mean background count.

- Calculate the standard deviation of the background counts.

4. Determine Critical Level (LC):

- Calculate LC using the formula: $LC = 2.33 \times \sqrt{(\text{mean background count})}$

- This means multiply 2.33 by the square root of the mean background count

- This represents the count level above which you can be 95% confident that a signal is present.

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5. Calculate Minimal Detectable Count (MDC):

- Use the formula: MDC = 2.71 + 4.65 × √(mean background count)

- This means: add 2.71 to the product of 4.65 and the square root of the mean background count

- This represents the count level at which you can be 95% confident in detecting a signal 95% of the time.

It's important to note that taking the square root is a way to account for the statistical nature of radioactive decay and background radiation in these calculations. The square root is used because the standard deviation of counts in radioactive decay follows a Poisson distribution, where the variance is equal to the mean

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6. Convert MDC to Activity:

- Determine the counter efficiency (ε) for Ge-68 using a calibrated Ge-68 source.

- Calculate the Minimal Detectable Activity (MDA) using:

MDA = MDC / (ε × t)

where t is the counting time in seconds.

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7. Evaluate MDA:

- Compare the calculated MDA to the required detection limit for Ge-68 breakthrough (typically 0.001% of the expected Ga-68 activity).
- If the MDA is significantly lower than the required detection limit, your system is suitable for breakthrough testing.
- If the MDA is close to or higher than the required detection limit, you may need to optimize your counting conditions (e.g., longer counting time, different detector, or lower background environment).

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8. Document Results:

- Record all calculations and the final MDA value in your laboratory notebook.
- Include the date, equipment details, and any relevant environmental conditions.

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9. Periodic Verification:

- Repeat this MDA determination periodically (e.g., annually) or after any significant changes to the gamma counter system.
- Monitor for any trends in the MDA over time, which could indicate changes in system performance.

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10. Quality Control:

- Incorporate regular blank and background measurements into your routine Ge-68 breakthrough testing protocol.
- Use control charts to monitor the stability of your background measurements over time.

Note: This procedure provides a general approach to MDA determination. Always consult your equipment manual and local regulatory guidelines for specific requirements or recommended practices.

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This second method of measuring Ge-68 breakthrough and preparation of the gamma counter is courtesy of:

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QUESTION #3:

What are the advantages of a Ge68/Ga68 generator compared to a cyclotron?

1. Easly obtainable
2. Practice of Pharmacy versus FDA manufacturing
3. All commercial kits have been have been approved for use with generators
4. Cost
5. All of the above

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ANSWER:

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USP 825

ISO 8, ISO 7, ISO 5: The controversy, the questions

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Table 7. Preparation Conditions for Sterile Radiopharmaceuticals

Preparation Conditions			
Manipulation	PEC	SEC	BUD (hours)
Immediate use	—	—	1
Direct infusion system, one puncture only (e.g., PET patient infusion system, Rb-82 generator)	—	—	10
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	SRPA	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	SRPA with ISO Class 8 total airborne particle count	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
		ISO Class 7 or better buffer area	

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ISO 5 compounding, dose preparation:
– how to shield the 15 kg generator with enough lead to get from 100 mR/hr to 2 mr/hr at elution and not collapse the ISO 5 Hood.

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ISO 8 eluting – the best alternative with critical aseptic techniques and media fill at the end of the generator life?

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Sterility of the eluant - .22 micron filters?

Should we use a 0.22 micron filter-No you can't filter out spores, just decrease the bioburden. Bubble testing of the filters?

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NETSpot's (TM) – what to do? ISO 5 preparation, ISO 8 elution?

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Sterility of the lines- Can we use SIPA on the critical sites with each change?

"Aseptic working technique must be maintained during the assembly process, especially when handling the ports. This is critical for the maintenance of sterility."

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If not in an ISO 5 when changing solvent when is the BUD of the 250 mL bag? 2 weeks? One year? Or?
Should it be assessed in the worst-case environment MEDIA FILL once a year? An ISO 7 or 8 for an aseptic transfer of saline through similar tubing with then further routine manipulation in the ISO 5 Hood?

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When you compare the most similar generator system, Mo99/Tc99m, each port has a cover. When replacing a cover, the septum is wiped with sterile 70% IPA.

When the generator is not in use, one port is covered with a vial with antimicrobials.
The biggest difference is that the Moly generator will not be used past 2 weeks.

Ga68 generator expiration is 12-months.

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The only thing that should touch the ports are freshly unwrapped, sterile needles after the ports are aseptically wiped with sterile, 70% IPA in between elutions.

Remember that 0.1 mol/L HCl is not sporicidal.

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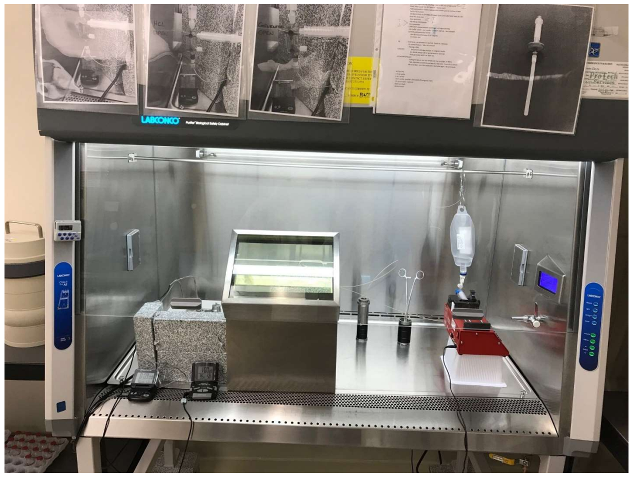

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GENERATORS – WHAT IS NEXT?

Mobile Generators – the risks

Larger generators

Extended expiration

Lastly: Current NRC thinking on Financial Assurance, decommissioning bond

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THANK YOU!

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