



August 6, 2018

US Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Shortage of Germanium-68/Gallium-68 Generators for the Production of Gallium-68

Dear Dr. Marzella and Dr. Zadecky,

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) would like to provide the following information related to availability of GMP-grade germanium-68/gallium-68 generators in the United States.

SNMMI, composed of 15,000 members, works to set standards for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals, hosting meetings, and leading advocacy on key issues that affect molecular imaging and therapy research and practice.

Germanium-68/Gallium-68 generators ($^{68}\text{Ge}/^{68}\text{Ga}$)

Gallium-68 is currently milked from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator. Several manufacturers produce these table top generators including Eckert & Ziegler (Germany), IRE ELiT (Belgium), Isotopen Technologien Munchen (ITG) (Germany), and iThemba (South Africa). The Eckert & Ziegler GalliaPharm[®] and the IRE ELiT Galli Eo[®] generators are both GMP grade and have type II drug master files on file with FDA.

Use of Gallium-68 (^{68}Ga) in the U.S.

The radioisotope ^{68}Ga is used in the production of NETSPOT[™], a kit for the preparation of gallium ^{68}Ga dotatate injection, an FDA-approved radiopharmaceutical. NETSPOT was approved in June 2016 for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients using Positron Emission Tomography (PET). NETSPOT is currently approved for use only with the GalliaPharm ^{68}Ga generator from Eckert & Ziegler.

NETSPOT has experienced rapid adoption in the US. Advanced Accelerator Applications (AAA) has been expanding the network of pharmacies that distribute NETSPOT since its approval. As of June 2018, approximately 500 imaging sites were requesting doses of NETSPOT for their neuroendocrine tumor patients.

Currently, NETSPOT is the only FDA-approved radiopharmaceutical using the ^{68}Ga isotope however there are numerous ongoing clinical trials with agents labelled with ^{68}Ga , namely prostate specific membrane

antigen (PSMA) agents for imaging prostate cancer patients. In many of these trials, ⁶⁸Ga from non-GMP generators is being utilized.

GalliaPharm® generator availability

GalliaPharm generators are the only approved generator to be used in the manufacture or synthesis of ⁶⁸Ga-dotatate, or NETSPOT doses. The generator is approved for 400 elutions, or uses, or one year, whichever comes first. Due to NETSPOT demand, Eckert & Ziegler became unable to keep up with the demand for GalliaPharm generators starting in 2017. Some academic sites were informed that the wait time for a generator was 14 to 18 months.

The largest consumers of the GalliaPharm generators are the commercial pharmacies that prepare and deliver NETSPOT doses. AAA reports that pharmacies have self-imposed blackouts for NETSPOT doses to expand the lifespan of the generator until the replacement generator arrives, not wanting to risk a full shortage in an area. Cardinal in Las Vegas has been shut down completely since May 2018. The sites below have black-outed dates on their delivery schedules:

1. NDP Rockaway (New York metro area)
2. NDP Plainview (New York metro area)
3. Sofie Romeoville (Chicago area)
4. Cardinal Beltsville (Washington DC area)
5. Cardinal Pittsburgh
6. Cardinal Nashville
7. NDP Cherry Hill (Philadelphia area)
8. Washington University (St. Louis)
9. Triad Houston
10. Triad Commerce (Los Angeles area)
11. Cardinal New Orleans

Nine other major metropolitan areas, listed below, currently have insufficient supply meaning that >70% of the total capacity is in use; this typically results in a 3 week wait time for an appointment.

1. New York
2. Houston
3. Denver
4. Washington DC
5. St. Louis
6. Charlotte
7. Los Angeles
8. New Orleans
9. Pittsburgh

The sixteen additional cities listed below have yet to be supplied with doses due to the lack of generators.

1. Memphis, TN
2. Raleigh, NC and adjacent areas (outside of university hospitals)
3. Richmond, VA
4. Charleston, SC
5. Greenville, SC and adjacent areas
6. Palm Beach, FL
7. Grand Rapids, MI
8. Louisville, KY
9. Mobile, AL
10. Birmingham, AL and adjacent areas Huntsville and Montgomery (outside of university hospital)
11. Jackson, MS
12. Little Rock, AR
13. Tyler, TX and adjacent area Shreveport, LA
14. Colton, CA and inland Los Angeles area
15. Placentia, CA and Orange County
16. Honolulu, HI

In a brief survey of nine academic centers who are members of SNMMI's Gallium Users Group, 7 of 9 sites currently have a total of 11 generators (ITG = 3, IRE = 1, E&Z GalliaPharm = 3, E&Z non-GMP = 4). The remaining two sites do not have a generator because of "the lack of availability of and wait time for

GMP generators is too great". Of the 7 sites with generators, 6 have experienced delays with scheduled replacement of the generator. Two of the sites are currently waiting for a replacement generator from Eckert & Ziegler, one for 6 months, one for 2 months. Three sites reported delays in the recent past ranging from 2 to 6 months. Four sites reported that they have been directly affected by lack of availability of ^{68}Ga ; this has resulted in the need to cancel or reschedule patient scans at one site or cancel clinical trial scans. One academic site (Washington University St. Louis – noted above also) supplies NETSPOT doses to 6 area hospitals, they have cut production from 14 doses per week to 6 doses or less, and currently have a two-week blackout period during which no doses will be available.

Reason for shortage

Currently, the E&Z GalliaPharm generator is the only approved source of ^{68}Ga for production of NETSPOT (^{68}Ga -dotatate) doses. Thus, every dose of NETSPOT used in the U.S. since its approval in June 2016 has been made with these generators. NETSPOT has experienced rapid adoption since it is a first-of-its-kind agent, i.e., a somatostatin receptor PET tracer. This radiopharmaceutical quickly replaced its predecessor in markets where it is available due to superior performance and patient-friendly regimen, namely injection and imaging are completed in approximately three hours versus 72 hours. Additionally, the imaging test is covered by insurance in many cases which allows those who could not pay out-of-pocket for an expanded access scan to receive one.

To determine if lack of availability of germanium-68 (the source material in the generator) was contributing to the shortage of GalliaPharm generators, SNMMI contacted Jehanne Gillo, Director of Department of Energy (DOE) Isotope Program. Dr. Gillo stated on April 2, 2018 that availability of ^{68}Ge was not the cause of the shortage. The shortage is due to production capacity of GalliaPharma generators by the manufacturer Eckert & Ziegler. E&Z is expanding their manufacturing facility but is not anticipated to meet full capacity until mid-2019.

Potential remedies for shortage

There are several ways to alleviate the shortage and options would be effective by varying degrees. The GalliaPharm generator has a lifespan of 400 elutions or one year, whichever comes first. AAA reports that many generators reach the elution limit before the one-year mark. A temporary exemption to the 400-elution limit would have a major impact on NETSPOT capacity for patients, almost immediately.

The IRE ELIT manufacturer has filed a type II drug master file with the FDA. Using this generator for production of NETSPOT doses may be able to restore or extend access in some markets. These generators would have similar limitations as GalliaPharm generators.

A new technology for the production of ^{68}Ga – cyclotron-generated gallium using an aqueous target - has advanced rapidly and is ready for human trials. Both General Electric Healthcare (GEHC) and IBA have mature products. In Europe, IBA cyclotron and target-produced gallium chloride has been used to produce ^{68}Ga -dotatoc that meets the European monograph 01/2013 2482 parameters. Allowing NETSPOT kits to be produced with cyclotron-produced gallium chloride would increase production at mostly academic sites over the next 3 to 6 months. This would alleviate the need for a GMP-grade generator in that particular location. Further discussion with the manufacturers is necessary.

Summary

NETSPOT has proven to be a very important imaging agent for NET patients in the U.S. The demand has taxed the supply chain as it currently exists. With the January 2018 FDA approval of ¹⁷⁷Lu-dotatate (Lutathera®), the demand is further increasing due to the fact that a NETSPOT scan is required prior to receiving therapy.

SNMMI and its physician and scientist members stand ready to answer any questions or assist in the resolution of this issue. Please feel free to contact me or Bonnie Clarke, Director of Research and Discovery, at bclarke@snmmi.org or 703-667-5120.

Sincerely,



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