Received 12/22/17
1 p.m.

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E-RIDS= ADM-03
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December 21, 2017

Re: **BTG comments on proposed licensing guidance 'Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance, Revision 10' (NRC-2017-0215)**

Dear May Ma,

This letter outlines BTG's comments on the proposed licensing guidance 'Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance, Revision 10' that was posted in the Federal Register on Nov. 7, 2017 (NRC-2017-0215).

Comments on the Proposal to Remove Alternate Training Pathway 2

BTG believes that well-trained clinicians are essential to ensure the safety of patients receiving Yttrium-90 microsphere treatment, as well as the medical staff performing the treatments, and is responsible according to ISO 13485 for determining the user training needed to ensure safe use of the medical device. BTG is committed to working with the US NRC to ensure that the training requirements for Authorized Users (AU) are appropriate, comprehensive and in the best interest of patients.

TheraSphere® is manufactured by Nordion (Canada) Inc. (named on the Sealed Source and Device Registry) for Biocompatibles UK Ltd, a BTG International group company. BTG is responsible for the TheraSphere® training program which has been intentionally designed to match the educational needs of the AU for licensing purposes as well as the needs of the treating team, while addressing the evolving use of TheraSphere® for its approved indication.

BTG believes that the removal of Pathway 2 in the experience and training section of the Y-90 Microsphere Brachytherapy Licensing guidance would not be in the best interests of physicians seeking AU designation for Y-90 Microsphere Brachytherapy, and ultimately is not in the best interests of potential patients who may need this therapy. Removal of Pathway 2 could have a negative effect on quality of physician training, as well as patient safety and access to quality of care. We further believe that eliminating Pathway 2 would create a hindrance and an additional hurdle in training for physicians seeking AU status, and as a result could limit physician access to training.

Removal of Pathway 2 will have an adverse effect on quality of physician training

BTG is concerned the proposed change in training requirements will have an adverse effect on quality of physican training in the following ways:

- The TheraSphere® administration system has been specifically engineered by BTG to safely and efficiently transfer the TheraSphere® dose to the treatment site. A major benefit of Pathway 2 is the three simulated (in-vitro) hands-on cases which include troubleshooting and mitigation measures unique to the administration system. BTG medical employees convey a comprehensive understanding of the administration system features, benefits and limitations at every training session.

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- Although AUs are familiar with the use of the TheraSphere® administration system, BTG medical employees engage in Quality System post-market surveillance activities (e.g. complaints, AEs, medical events) of the device use. BTG has the capability to adapt the training in a timely and standardized manner for continuous education and enhanced product knowledge.

- There is concern with the removal of Pathway 2 of BTG's ability to control the training information provided. Candidate AUs would need to rely on independent AUs to complete the three supervised hands-on cases. The training for both the supervised hands-on in-vitro simulated cases and the three supervised patient administrations is currently provided by BTG medical employees who present comprehensive, standardized information so all AUs receive the same information. The absence of this standardized training platform would create a gap in training.
- The experience of the BTG medical team spans thousands of TheraSphere® cases, far more than the inherently limited experience of an individual AU.
    - For example, an AU performing training may only have experience from 4 clinical cases or has not had recent experience with the product within the past 5 years. The proposed licencing guidance provides no guardrails on competency or training experience for existing AUs.
- BTG is concerned that the absence of a standardized training platform could result in a risk of higher incidence of gastrointestinal ulcer adverse events. The gastrointestinal ulcer rate associated with TheraSphere® treatment has decreased since the implementation of BTG's comprehensive training program in 2004 (4% before 2004 vs. <0.5% currently) based on comprehensive published literature review of over 1600 hepatocellular carcinoma (HCC) patients.
- The comprehensive BTG training program is delivered in partnership with physicians in clinical practice as follows:
    - Clinical use experience and literature training is provided by multidisciplinary teams at the TheraSphere® Center of Excellence (CoE) and supported by field-based physician advisors. The multidisciplinary CoE training team typically includes representatives from radiation safety, nuclear medicine, interventional radiology, nursing, surgical and/or radiation oncology. The interventional radiologists and nuclear medicine physicians are AUs for TheraSphere®.

    - BTG has a medical team dedicated to supporting and training AUs and their medical teams including Radiation Safety Officers (RSO). BTG periodically adapts the training to integrate changes to TheraSphere® clinical practice nationally, with global awareness, versus independent institution-based AUs who may be unfamiliar with evolving clinical practice.

- Independent AUs who are currently providing training on Y-90 microspheres typically only train the prospective AU and not the entire multidisciplinary treatment team. This lack of comprehensive training for the whole treatment team would lead to a gap in knowledge for the safe and efficient handling of TheraSphere®, and could create a risk to patient safety.
- Brachytherapy medical training is standard curriculum in medical schools due to the prevalence of prostate cancer whereas TheraSphere® administration training is provided to Interventional Radiology fellows in limited, select institutions with existing TheraSphere® treatment programs. As of September 2017, there were 69 accredited IR residency programs in the US (https://www.sirweb.org/learning-center/ir-residency/integrated/). The residency curriculum is concentrated on diagnostic radiology in the first three years and interventional radiology in the last two years with no commitment to incorporate Y90 microsphere use in the curriculum. Of the 69 residency programs, 38 (55%) were actively using TheraSphere® Y90 microspheres, which represents approximately 13% of the overall TheraSphere® treatment sites. Alignment of the licensing guidance in keeping with brachytherapy medical training is premature relative to radioembolization training and a majority of institutions would not have the skills to deliver this product specific training resulting in a less robust training program.
    - In addition, brachytherapy treatment involves the selected placement of a 50-100 radioactive seeds with percutaneous needle placement into the prostate or other target tissue under imaging guidance. Whereas with TheraSphere®, millions of microspheres are implanted in the liver tumoral area while taking into consideration catheter navigation, hemodynamics, perfusion volume for dosing, non-target deposition, arteriovascular shunting and other relevant primary and secondary liver cancer treatment considerations to ensure fundamental liver function is maintained to sustain bodily functions. The absence of this standardized training currently stated within the Licensing Guidance for the administration of a unique, implanted radioactive device could create a negative impact to patients.

Removal of Pathway 2 will create a hindrance/delay for physicians seeking AU status

Elimination of Pathway 2 would hinder physician AU training and patient access to TheraSphere® as follows:

- Liver oncology patients require immediate and timely access to Y-90 microsphere treatment. This would be restricted in hospitals that are new to microsphere therapy, where there are no trained AUs. Patient access would be restricted if treating physicians have to first identify external AUs and rely on their availability to coordinate training and subsequent documentation-related requirements for a license amendment. Existing healthcare networks may limit identification or access to AUs from other healthcare networks. Hence, patient treatment may be delayed or a less suitable alternative therapy could be chosen as a consequence of AU unavailability. Therefore, the patient may not get the best treatment available for their liver cancer. Under Pathway 2, the vendor training team is adequately staffed to meet the training demands across the country. They have inherently more flexibility, are easily available to the treating physician, resulting in more seamless patient care. As well, the vendor medical team creates enduring training materials for future reference and

documents training events as well as when training requirements are or are not met by the AU in training.

- Existing AUs have active clinical practices and are managing a multitude of needs for their liver oncology patients. An AU with sufficient expertise and experience with TheraSphere® providing high-quality training to candidate AUs would also be regularly treating patients. Taking time away from their own clinical practices to train candidate AUs would therefore reduce their ability to treat their current patients, further negatively impacting their patient access to radioembolization therapy. As well, approximately 10-20% of Y90 patient cases are cancelled due to changes in patient health status; most are cancelled within days or day of scheduled treatment. This inefficiency is built into BTG's resource model, whereas it is not possible for AU trainers to accommodate it. In totality, the AU trainer model results in treating fewer patients thereby hindering patients access to the best clinical care. In the current training approach, BTG provides the candidate AU ample training to ensure TheraSphere® use is safe and effective. The BTG trainers are full-time trainers, primarily responsible for delivering high-quality training.

- Outsourcing external physicians to provide training to staff can be burdensome with internal barriers and political issues within hospital administrations. This can delay or restrict the ability of a candidate AU to receive Pathway 1 training. Training of additional AUs within a single institution is expected to be far easier than bringing in an external AU to provide training at an institution.

    - BTG has the flexibility to address the needs of various institutions and their teams in a timely manner, including the ability and willingness to train multiple AUs at the same time. If Pathway 2 is eliminated, physician and patient access would be affected due to the limited availability of AUs for training.

- It is also important to recognize the difference in clinical indication and FDA approval status of the Y-90 microsphere products and how this might hinder the training of candidate AUs. In the US, TheraSphere® has specific FDA approval for hepatocellular carcinoma (HCC, a sub-set of liver cancer patients) while SIR-Spheres is indicated for metastatic colorectal cancer within the liver. Metastatic colorectal cancer has a significantly higher incidence than HCC. Consequently, there is currently a larger number of SIR-Spheres AUs compared to TheraSphere® AUs. Removal of Pathway 2 training would result in an imbalance due to the limited availability of existing AUs with TheraSphere® experience, which would hinder the training of candidate AUs. The difference in product indication and approval status creates a disadvantage for TheraSphere® with respect to the number of existing AUs, which then would cause a physician and patient access hindrance to hospitals starting a TheraSphere® treatment program or replacing an AU who is no longer at that hospital. As well, the AU shortage in turn could result in more off label use of SIR-Spheres for treatment of patients with HCC, an indication where there is limited data on dosing, safety and efficacy.

The robustness of BTG's Pathway 2 training program is described further in Appendix A.

BTG is committed to ensuring that the training requirements for Authorized Users (AU) are appropriate and comprehensive and in the best interests of patients. As stated above, BTG believes that eliminating Pathway 2 of the Y-90 Microsphere Brachytherapy training program could have a negative impact on the quality of training, patient safety and access to quality care.

Comments on specific NRC questions:

1) Recommended Minimum Clinical Experience: BTG agrees that three patient cases provides adequate technical experience for a physician to gain AU status for Y-90 microspheres. Adequate clinical experience comes with fellowship and is developed over time.

2) Adding Authorization for Other Microsphere Type: BTG agrees that training on three additional cases for the other type of microspheres is necessary for the AU to gain the knowledge to safely administer the new microsphere, as there are many differences between the dosimetry and techniques used to administer the two products.

3) Written Attestation from Preceptor: BTG believes that there will be issues with obtaining written attestations from preceptors. Specifically, one cannot attest that a physician is competent in performing a procedure with limited observation. Physician training programs require a substantially greater procedural experience before the training physician will attest that the trainee is competent. As microsphere training only occurs in few residency programs, and an external preceptor does not know the trainee's overall competence, the preceptor will be reluctant to sign a written attestation. BTG believes that there are still too few AUs in the US to implement a written attestation since only approximately 13% of TheraSphere® user sites have an active residency program and have the AU relevant experience to assess competency for TheraSphere® use.

4) Clinical experience under the Supervision of a Manufacturer Representative: As outlined in pages 1-4 of this letter, BTG strongly disagrees with the removal of the alternate training pathway (Pathway 2).

5) Timeliness for Completion of In-Vivo Cases: BTG agrees that it is appropriate for a physician in training to complete one in-vivo case prior to treating patients as an AU if six months has passed since their previous training case, to ensure recentness of training. BTG is concerned about who will oversee this requirement. If Pathway 2 is maintained, it would be straight forward for the manufacturer to ensure compliance with, and to be available for required training sessions because of its strict record keeping, documentation and standard operating procedures.

6) Medical Event Definition: The delivery of TheraSphere® can be controlled to a specific lobe or location as described in the written directive. Flexibility in the written directive is not required.

Other comments on the proposed licensing guidance:

In the section 'Radionuclides, Form, Possession Limits, and Purpose of Use', we recommend that the maximum possession limit be increased to 4 Ci, or be set by how much the user anticipates using. We recommend the addition of a comment stating that the user can request the amount that they require.

In the section 'Medical Device Reporting', fourth bullet, we recommend the following wording changes (marked in strikethrough and bold):

> For the purpose of this document, shunting is defined as ~~an unexpected~~ blood flow (i.e. due to patient vasculature) causing the Y-90 microspheres to flow to an unwanted location. Unexpected dose to an organ or tissue other than the treatment site that is caused by catheter placement, **or by blood flow not previously evaluated or observed (e.g. vasospasm),** during delivery of the Y-90 microspheres is not considered shunting.

In the section 'Waste Disposal Issues', BTG has provided USNRC updated impurities data for TheraSphere® and requests that the referenced Information Notice be updated to reflect the current data.

We welcome further discussion on the comments provided in this letter.

Sincerely,

Francis Facchini, MD FSIR
Chief Medical Officer

Mira Leiwant, RAC
VP, Regulatory Affairs

Appendix A

BTG Multidisciplinary Center of Excellence (CoE)

The BTG Center of Excellence program is a one day course that provides the multidisciplinary treatment team with information on implementing a TheraSphere® program. The Center of Excellence Program began in September 2004 and since that time has trained Authorized Users (AU) which include Interventional Radiologists (IR), Nuclear Medicine physicians and Radiation Oncologists.

The program agenda consists of the following:

- Y90 Physics, Nuclear Medicine, Radiation Safety, Regulatory Information
- Clinical Care of the Patient
- Angiography Considerations
- Hepatocellular Carcinoma and Treatment Considerations
- Comprehensive Review of TheraSphere® Clinical Data
- Administration Accessory Kit Set Up
- TheraSphere® Dosimetry with Practice Dosimetry Questions

The CoE course is held approximately every six weeks at one of three sites nationally: Northwestern Hospital in Chicago, Mt. Sinai Medical Center in New York and Banner University Medical Center in Phoenix.

On-site training

The BTG AU training program includes face to face training that takes place with the physician seeking AU status. During this training session the physician is trained on the TheraSphere® Y-90 Glass Microsphere System with three mock infusions, including reviewing issues that may be encountered during a TheraSphere® administration. At the conclusion of this training for IR's seeking AU status a) – g) training is covered as outlined below.

a) Ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys; (Includes ordering, receipt and storage of dose vial; removal of dose vial from box and using the TheraSphere® measurement template.)

b) Performing quality control procedures on instruments used to determine the activity of TheraSphere® and performing checks for proper operation of survey meters; (Includes demonstration of dose calibrator checks; discussion of reference standard and dose vial measurement; and performance checks on contamination detection equipment.)

c) Evaluation of each patient or human research subject for the dose/activity of TheraSphere® to be administered to each treatment site; (Includes discussion of recommended dose as per the Package Insert (80-150 Gy) and dose vial size options for perfused liver volumes.)

d) Calculating and measuring the activity and safely preparing TheraSphere® to be delivered to the patient or human research subject; (Includes demonstration of dose calculation to treatment volume and infusion system setup as per the Package Insert checklist.)

e) Using administrative controls to prevent a medical event involving the use of byproduct material; (Includes reviewing administration system assembly, infusion flow rate, dose vial preparation, and pinch clamp use; demonstration of percent delivery calculation.)

f) Using procedures to control and to contain spilled byproduct material, including TheraSphere®, safely and using proper decontamination procedures; (Includes identifying potential spill or contamination risks; how to mitigate risks; and decontamination principles and techniques for TheraSphere®.)

g) Follow up and review of each patient's or human research subject's case history for Y-90 microspheres; (Includes reviewing typical follow-up regimens; identifying typical treatment response periods, and typical and atypical adverse events, as per the Package Insert and TheraSphere® Reference Manual.)

On-Site Multidisciplinary Training

BTG provides a multidisciplinary Vendor Training session for each new site. This session typically includes the following staff: Interventional Radiology and Nuclear Medicine technologists; radiation safety; medical physics; nursing staff and AU's and IR's if not the AU. During this session a review of TheraSphere® takes place including dosimetry calculations, kit set up and roles and responsibilities of everyone involved in the Y-90 TheraSphere® treatment.

Supervised Cases

For at least the first three cases, prior to the treatment day, usually the day of or the day after the mapping angiogram, BTG medical employees consult with the physician seeking AU status to assist in proper patient selection and review the calculations. At this time the correct TheraSphere® dose vial for the patient treatment is identified and ordered.

On the treatment day BTG meets with Nuclear Medicine prior to the case and walks through all of the pre-treatment measurements necessary for the TheraSphere® Written Directive. During the case, BTG guides all staff so a safe administration takes place and all radiation safety monitoring is performed properly. Following the case BTG medical works with the AU/ nuclear medicine staff to complete the TheraSphere® written directive.

BTG Preceptor (Physician Advisor) Program

BTG also works closely with physicians seeking AU status through the TheraSphere® Preceptor Program. This program consists of two highly respected Interventional Radiologists with extensive Y-90 TheraSphere® experience who assist AUs with cases that are technically challenging or in cases that require a second opinion relating to clinical practice and appropriate use or constraints for Therasphere® use. Typically a phone call takes place where the case is discussed and a medical response is generated by the TheraSphere® Preceptor.