March 15, 2020

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Division of Materials Safety, Security, State, and Tribal Programs
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: Request for Interpretation: Confirmation of Applicability of 10 CFR 20.2003(b) to Sanitary Sewerage Disposal for C-Scan

Mr. Einberg,

Following up from the March 3, 2020 teleconference meeting between Check-Cap Ltd. ("Check-Cap") and the U.S. Nuclear Regulatory Commission ("NRC") Office of Nuclear Materials Safety & Safeguards, Check-Cap seeks an informal interpretation of the NRC's regulations to confirm that its regulations at 10 CFR 20.2003(b) apply to disposal of the Check-Cap C-Scan® ("C-Scan") system in medical excreta. As described below, this interpretation aligns with the text and regulatory history of the 10 CFR 20.2003(b) sanitary sewerage disposal rule, and past NRC practice. Check-Cap respectfully requests this informal interpretation as soon as possible to support an upcoming U.S. Food and Drug Administration ("FDA") trial expected to commence towards the end of this year ("Pivotal Trial").

[redacted]

I. Overview of Check-Cap & C-Scan System.

Check-Cap is a clinical stage medical diagnostics company advancing the development of the C-Scan system, the first and only preparation-free ingestible scanning capsule-based system for the prevention of colorectal cancer through the detection of precancerous polyps. Check-Cap's goal is to redefine colorectal cancer prevention through this technique.[2]

[1] [redacted]

[2] For more information, please visit our website at www.check-cap.com. More about Check-Cap and C-Scan can also be found in the presentation provided to the NRC Staff accompanying the March 3, 2020 meeting.

A. Colorectal Cancer Detection Challenges & C-Scan Solution

Colorectal cancer is one of the most common cancers in the world, with 1.8 million cases a year—just short of the number of cases of breast cancer and lung cancer. Moreover, colorectal cancer is projected to grow 60% by 2030, making it potentially the leading cause of cancer in the world. Colorectal cancer kills over 880,000 people each year, and is the second leading cause of cancer death among men and women combined in the United States.[3]

The human costs of colorectal cancer can be much lower than they are now. There is a 10-year window for detecting colon polyps before they become serious. However, the discomfort and costs associated with the current diagnostic approaches—namely colonoscopies—keep screening rates impermissibly low. Colonoscopy rates for persons above 50 are just above 50% in the United States. Outside of the United States, screening rates even in the developed world are well below 50%—and elsewhere far lower or nonexistent. Based on currently-available technologies, however, there is no effective alternative to colonoscopies. Fecal immunochemical tests, currently being explored as a potential alternative to colonoscopies, have sub-30% detection rates for polyps before they become cancerous.

Check-Cap wants to change this, through an ingestible solution for colorectal cancer screening, the C-Scan. Utilizing innovative ultra-low dose X-ray and wireless communication technologies, the C-Scan capsule generates information on the contours of the inside of the colon as it passes naturally. This information is used to create a 3D map of the colon, which allows physicians to look for polyps and other abnormalities. Designed to improve the patient experience and increase the willingness of individuals to participate in recommended colorectal cancer screening, C-Scan removes many frequently-cited barriers, such as laxative bowel preparation, invasiveness and sedation.

The patient-friendly test has the potential to increase screening adherence and reduce the overall incidence of colorectal cancer. C-Scan is non-invasive and requires no preparation or sedation, allowing patients to continue their daily routine with no interruption as the capsule is passed through the gastrointestinal tract by natural motility.

The C-Scan has been demonstrated to detect 76% of polyps greater than or equal to 10mm, and 100% of all polyps greater than or equal to 40mm. For reference, polyps 30mm or greater in size have an approximately 38% likelihood of transforming in to cancer—meaning that Check-Cap can likely detect a large majority of pre-cancerous polyps, far outstripping the sub-30% detection rates for fecal immunochemical tests. The result is that the C-Scan has the potential to save tens or even hundreds of thousands of lives a year in the United States and around the world.

B. Radiological Safety Embedded in C-Scan Design

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[3] Facts and Stats, Fight Colorectal Cancer, https://fightcolorectalcancer.org/colorectal-cancer/facts-stats/.

[redacted]

[redacted]

[redacted]

C. Regulatory Engagement & FDA Pivotal Trial

Check-Cap has had a long history of engagement with regulators in the United States and abroad to ensure public safety. Engagement with the FDA began in 2008, with an initial Investigational Device Exemption submission and meeting.[6] Close coordination with FDA has continued since then, with a U.S. pilot study conducted in conjunction with our manufacturing partner, and with two broad-scope licensees at New York University and Mayo Clinic. That successful study, which involved 45 patients, has helped demonstrate the safe use of the device from a medical context.[7] In that test, the capsules were retrieved and did not enter the sanitary sewerage.

To advance FDA approval in the United States, Check-Cap plans to conduct the previously described Pivotal Trial in late 2020, involving approximately 800 patients across the United States and abroad. [redacted]

[4] [redacted]

[5] [redacted]

[6] Upon initial engagement with the FDA in 2008, Check-Cap at that time through counsel also reached out to the NRC to discuss the applicability of the 10 CFR 20.2003(b) sanitary sewage rule to a C-Scan-like product. The NRC staff at that time responded favorably in oral discussions to application of the rule to the C-Scan product, citing the health hazards with collecting medical excreta as the alternative.

[7] Outside of the United States, about 350 patients have been taken the C-Scan as part of clinical trials, and pilot sales are expected to begin in Israel this year.

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II. Sanitary Sewerage Disposal of Medical Use Radiological Material in Excreta

The NRC regulations set forth in 10 CFR 20.2003 provide two separate mechanisms by which licensees can dispose of radioactive waste by release in sanitary sewerage.

The first mechanism, found in 10 CFR 20.2003(a), permits a broad range of licensees to dispose of radioactive materials used in industrial and medical applications into sanitary sewerage, under certain specific conditions. A key requirement of the Section 20.2003(a) mechanism is that the radioactive material be dispersible—that is, "the material is readily soluble (or is readily dispersible biological material) in water." 10 CFR 20.2003(a)(1) [8] As explained in the regulatory history for this rule, issues had been identified in particular where radioactive metal shards were collecting in sanitary sewerage systems.[9] The Commission considered sewerage disposal for insoluble materials compared to "dispersible biological materials," and found that in the case of insoluble materials a "broad provision" allowing for sewerage disposal was not advantageous compared to alternative disposal options (such as disposal at a low-level radioactive waste disposal facility).[10]

The second mechanism, found in 10 CFR 20.2003(b), is a more specifically tailored—but otherwise unrestricted—exemption. It provides that "[e]xcreta from individuals undergoing medical diagnosis or therapy with radioactive material are not subject to the limitations contained in" Section 20.2003(a). This is because this second exemption has its roots in fundamentally different NRC policy considerations—including the health hazards involved with handling human excreta. Therefore, Section 20.2003(b) makes clear that unlike Section 20.2003(a), there are no additional limitations on the applicability of Section 20.2003(b), including any limitations that the material must be dispersible. Rather, as clearly set forth in Section 20.2003(b), if the radioactive material was used in individuals undergoing medical diagnosis or therapy, and is eliminated from the body in excreta, then it may be disposed of in the sanitary sewerage. Indeed, in the 1985-1991 Part 20 rulemaking, sanitary sewerage disposal in the general case was evaluated distinct from disposal of medical wastes—with the latter treated as a "medical exception."[11]

The fact that the two regulations were crafted at the same time, but in drastically different formats, highlights their different application—and that the requirements of one regime cannot be read into the other. The broad-based Section 20.2003(a) mechanism, and its consideration of quantity and cost, indicates the narrower cost-benefit analysis between disposal of wastes via alternative options (e.g., in sewerage versus on land).[12] The specifically tailored—and unqualified—disposal permission for medical excreta in Section 20.2003(b), on the other hand, recognizes the significant health cost associated with

[8] The conditions under 10 CFR 20.2003(a) also include certain restrictions on quantity of radioactive material released into the sewer per month and annually.
[9] *See* Final Rule for Standards for Protection Against Radiation, Nuclear Regulatory Commission, 56 Fed. Reg. 23,360, 23,381 (May 21, 1991) ("1991 Part 20 Final Rule").
[10] *See id.*; Disposal of Radioactive Material by Release Into Sanitary Sewer Systems; Withdrawal of Advance Notice of Proposed Rulemaking, 70 Fed. Reg. 68,350, 68,350 (Nov. 10, 2005) ("2005 Withdrawal of Sewerage Disposal ANOPR").
[11] Proposed Rule, Standards for Radiation Protection, Republished Corrected Version, 51 Fed. Reg. 1092, 1116-17 (January 9, 1986).
[12] *See* 2005 Withdrawal of Sewerage Disposal ANOPR at 68,351 (citing comments regarding the cost, burdens, and safety risks of implementing several options to modify the current restrictions on radioactive releases under 10 CFR 20.2003 as a reason for withdrawing the ANOPR).

handling excreta, and thus the clear instruction that when excreta is involved, public health is best served by allowing sanitary sewerage disposal. The NRC could have placed additional restrictions in Section 20.2003(b), including that the regulation only applied when the radioactive material involved was dispersible—as it did in Section 20.2003(a)—but the NRC did not. It is a standard canon of legal construction that where a requirement is placed in one element of a statute or regulation, the omission of that same requirement in an adjacent provision is intentional. If the NRC wanted to insert a solubility requirement when addressing medical excreta, "it presumably would have done so expressly as it did in the immediately" preceding provision.[13]

Ultimately, the foundation behind Section 20.2003(b) is the balance between biological and radiological harm.[14] The Commission has found that the human harm accompanying management of excreta outweighs the harms from release of medical excreta into the sanitary sewers. Thus, the disposal of medical waste into sanitary sewerage is preferred to "handling human excreta"—the latter of which would be necessary if the Check-Cap is to be recovered after release from the patient.[15]

Given the game-changing nature of the C-Scan system for colorectal screening, the capsule will likely still be used around the world, including in the United States, even if the sanitary sewerage exemption is not allowed. The health risks to every person handling excreta to remove the C-Scan—including radiological exposures to those removing the capsules—exceed radiological risks to sewage workers, especially considering that the dose to sewage workers is expected to be only 1% of background.[16]

This interpretation is also consistent with how the NRC treats the disposal of other insoluble wastes, such as brachytherapy seeds. The NRC is aware that certain radioactive materials used in medical procedures and released in excreta are insoluble.[17] The brachytherapy seeds, in particular, have a 60-day half-life and larger doses, and are sometimes excreted by the patient in urine in a form that does not disperse.[18]

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[13] *Sandoz Inc. v. Amgen Inc.*, 137 S.Ct. 1664 (2017) (citing *Russello v. United States*, 464 U.S. 16, 23 (1983) ("[W]here Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.")) (internal parentheticals and citations omitted). "Regulations, like statutes, are interpreted according to the canons of construction." *Black & Decker Corp. v. Comm'r*, 986 F.2d 60, 65 (4th Cir. 1993); *see also Resnik v. Swartz*, 303 F.3d 147, 152 (2nd Cir. 2002) (applying the *Russello* canon regarding intentional omissions to regulatory construction).

[14] *See, e.g.*, 2005 Withdrawal of Sewerage Disposal ANOPR at 68,359-68,361.

[15] 1991 Part 20 Final Rule at 23,381. Although in 1994 the Commission in an advance notice of proposed rulemaking sought feedback on the exemption of medical excreta given potential very low-level concentration of radioactive materials at treatment facilities, in 2005 it set aside this rulemaking and re-affirmed the current regulatory framework. *See* 2005 Withdrawal of Sewerage Disposal ANOPR (setting aside the 1994 ANOPR, found in 59 Fed. Reg. 9146 (Feb. 25, 1994)). Even in the 1994 ANOPR, the Commission concluded that use of the exemption for medical excreta was warranted when doses to individuals are "far below the NRC's dose limit for members of the public"—which is the case for the C-Scan. 1994 ANOPR at 9148.

[16] 2005 Withdrawal of Sewerage Disposal ANOPR at 68,352 (commenters resisting changes to the current medical use sanitary sewerage rule, given "the additional waste handling that would be required would cause doses to workers that would not be justified based on the minimal dose to members of the public or [publicly owned treatment works] workers that might be avoided").

[17] *See, e.g., id.* (commenters in response to the 1994 ANOPR informed the NRC that "insoluble radionuclides" may be present in excreta).

[18] *See* Bradley J. Stish et al., Low Dose Rate Prostate Brachytherapy, Translational Andrology and Urology, Vol. 7, No. 3, at 344-45 (June 2018) (discussing housing of the brachytherapy seeds in metal jackets, and doses to urethrae and rectum due to passage of the seeds out of the body), http://tau.amegroups.com/article/view/18019/18298.

III. [redacted]

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[20] [redacted]

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Sincerely,

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