CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214793Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214793
PDUFA Goal Date	May 28, 2021
OSE RCM #	2020-2026; 2020-2027; 2020-2028
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Doris Auth, Pharm.D.
Review Completion Date	April 30, 2021
Subject	Review to determine if a REMS is necessary
Established Name	piflufolastat 18F
Trade Name	Pylarify
Name of Applicant	Progenics Pharmaceuticals, Inc.
Therapeutic Class	radiopharmaceutical
Formulation(s)	Injection: 37 MBq/mL to 2960 MBq/mL (1 mCi/mL to 80 mCi/mL) of piflufolastat 18F in a multiple-dose vial
Dosing Regimen	The recommended amount of radioactivity to be administered for PET imaging is (b) (4) administered as a single bolus intravenous injection (b) (4)

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Pylarify (piflufolastat 18F/18F-DCFPyL) is necessary to ensure the benefits outweigh its risks. Progenics Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 214793 for piflufolastat 18F with the proposed indication as a radioactive diagnostic agent indiated for positron emission tomography (PET) imaging in prostate cancer patients (b) (4) The serious risks associated with the use of piflufolastat 18F is image misinterpretation, hypersensitivity reactions and radiation exposure. The applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

The Division of Risk Management (DRM) and the Division of Imaging and Radiation Medicine (DIRM) have determined that if approved, a REMS is not necessary to ensure the benefits of piflufolastat 18F outweigh its risks. Piflufolastat 18F appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewers stated that piflufolastat 18F shows clinically meaningful benefit, and recommend approval of piflufolastat 18F as a radioactive diagnostic agent indicated for PET of PSMA positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

The most concerning adverse reactions observed with the use of piflufolastat 18F are risk of image misinterpretation, hypersensitivity reaction and radiation exposure. If piflufolastat 18F is approved, labeling, including information in Warnings and Precautions and Patient Counseling Information, will be used to communicate the safety issues and management of toxicities associated with piflufolastat 18F.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) piflufolastat 18F is necessary to ensure the benefits outweigh its risks. Progenics Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 214793 for piflufolastat 18F with the proposed indication as a radioactive diagnostic agent indiated for positron emission tomography (PET) imaging in prostate cancer patients (b) (4) The applicant did not submit a REMS with this application but proposed describing the risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

2 Background

2.1 PRODUCT INFORMATION

Piflufolastat 18F is a NME NDA type 505(b)(1) pathway application.[a] It is a radioactive diagnostic agent that binds to cells that express prostate-specific membrane antigen (PSMA), including malignant

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

prostate cancer cells, which usually overexpress PSMA. Fluorine 18 (F 18) is a β+ emitting radionuclide that allows PET.[1] Piflufolastat 18F is prepared as multiple-dose injection vials containing 37 MBq/mL to 2960 MBq/mL (1 mCi/mL to 80 mCi/mL) of piflufolastat 18F (b) (4) at calibration date and time. The recommended amount of radioactivity to be administered for PET imaging is (b) (4) MBq (b) (4) mCi), administered as a single bolus intravenous injection (b) (4) .[b] Piflufolastat 18F is not currently marketed in the United States. But it has been evaluated as a PET radiopharmaceutical diagnostic agent in other clinical trials and compassionate use clinical settings globally.[2]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for piflufolastat 18F (NDA 214793) relevant to this review:

- 10/19/2016: Investigation New Drug (IND) 129952 submission for [F-18] DCFPyL.
- 09/29/2020: NDA 214793 submission for piflufolastat 18F with the proposed indication as a radioactive diagnostic agent indiated for positron emission tomography (PET) imaging in prostate cancer patients (b) (4)

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Prostate cancer is the most common cancer among men in the United States, representing the second most common cause of cancer-related death in men.[3] Malignant transformation of the prostate follows a multistep process, initiating as prostatic intraepithelial neoplasia (PIN) followed by localized prostate cancer and then advanced prostate adenocarcinoma with local invasion, culminating in metastatic prostate cancer.[4] Its greater prevalence in the west and migrant population data implicate lifestyle and environmental risk factors. Aside from age and race, the only established risk factor for prostate cancer is a family history of the disease. The risk for first-degree relatives of men with prostate cancer is about twice that for men in the general population. This familial risk is more than four times higher than that for the general population for first-degree relatives of men with prostate cancer diagnosed younger than 60 years.[5] The expected number of new cases of prostate cancer in the United States in 2021 is 248,530[c], with 34,130 expected deaths due to the disease[d].[6] Five-year survival for patients diagnosed with prostate cancer is approximately 97.8%.[7] Guidelines for advanced prostate cancer from the American Urological Association (AUA), American Society of Radiation Oncology (ASTRO), and Society of Urologic Oncology (SUO) define advanced prostate cancer by disease states including biochemical

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

recurrence without metastatic disease after exhaustion of local treatment options, metastatic hormone-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, and metastatic castration-resistant prostate cancer.[8,9]

3.2 DESCRIPTION OF CURRENT DIAGNOSTIC AGENTS

Early detection and precise staging of prostate cancer are vital because the survival rate decreases dramatically when cancer has migrated beyond the prostate organ. Prostate-specific antigen (PSA)-based screening is one of the most common method of prostate cancer diagnosis. Expression of PSA has also been reported in other tissues such as normal epithelium of prostate, small intestine, kidney cells and salivary organs; however, the expression level in these parts is ~100–1000 folds lower than in prostate cancer.[10] After local therapy including surgery or radiation, the first sign of recurrence is typically a rising prostate specific antigen (PSA) in the absence of visible metastases. Currently, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) along with 99mTc-methylene diphosphonate bone scintigraphy remain the standard imaging approaches for post-treatment biochemical recurrence, although this is an evolving space. Clinicians may utilize novel positron emission tomography (PET)-CT scans (eg, fluciclovine, choline, PSMA) in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging.[8] Advances in prostate cancer–specific (pcPET) have demonstrated new insights into patterns of disease recurrence. Emerging pcPET radiotracers including carbon 11 (C-11) choline, gallium 68 (Ga-68) PSMA, C-11 acetate, and 18F-fluorocyclobutane-1-carboxylic acid fluciclovine (FACBC) [fluciclovine F 18] provide opportunities to localize prostate cancer recurrence at an earlier state in the disease course when the PSA level is low, to inform medical decision-making, and to study PET-directed local therapy.[11] Currently there are three prostate cancer–specific PET (pcPET) radiotracers that have gained FDA approval in the United States for the indication of identifying recurrent prostate cancer. C-11 choline received FDA approval on September 12, 2012, for the indication of PET imaging of patients with suspected prostate cancer recurrence.[12] Fluciclovine F 18 received FDA approval on May 27, 2016, for prostate cancer patients with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment.[13] Ga-68 PSMA received FDA approval on December 1, 2020, for the indication of PET imaging of patients with suspected metastasis who are candidates for initial definitive therapy and with suspected recurrence based on elevated serum PSA level.[14] The serious risks associated with C-11 choline and Ga-68 PSMA are image misinterpretation and radiation exposure and the serious risks associated with fluciclovine F 18 include image misinterpretation, hypersensitivity reaction and radiation exposure and none of these products have a boxed warning in their labels, nor was a REMS required for approval.[12,13,14] Please refer to DIRM's Multi-disciplinary Review and Evaluation for a detailed analysis of current treatment options.[15] Not all patients presenting to the treating oncologist fall into this relatively common clinical scenario of a rising PSA early after prostatectomy, however. Indeed, some patients present with rising PSA after definitive radiation therapy, whereas others present after they have received postprostatectomy radiation therapy, and others still after a late PSA rise years after initial surgery. Imaging with both a pcPET scan and a multiparametric MRI scan can provide complementary insight as to the location of recurrence.[11] Although the imaging of prostate cancer has made tremendous advances in recent years, due to tissue heterogeneity in prostate cancer, and the lack of specificity of conventional imaging techniques, difficulty remains in identifying small volumes of prostate cancer both in the gland and metastatic sites and no universally approved imaging methods exist for the early detection of prostate cancer.[10,16] There is a clear need for imaging strategies with new alternative modalities that target the extracellular domain of PSMA with high affinity and longer half-life, which allows for wider product distribution and accessibility to patients.

4 Benefit Assessment

The efficacy and safety of piflufolastat 18F were evaluated in two prospective, open label, multi-center clinical studies in men with prostate cancer: CONDOR (NCT03739684) and OSPREY (NCT02981368).[1] At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for piflufolastat 18F.

4.1 OSPREY

In OSPREY, 268 men with biopsy-proven prostate cancer were enrolled for radical prostatectomy and pelvic lymph node dissection. These patients were all considered to have high risk disease based on criteria such as Gleason score, PSA level, and tumor stage. Each patient received a single piflufolastat 18F PET/CT from mid-thigh to skull vertex. Three central readers independently interpreted each PET scan for the presence of abnormal piflufolastat 18F uptake in pelvic lymph nodes in multiple subregions including the common iliac lymph nodes. The readers were blinded to all clinical information.
A total of 252 patients (94%) underwent standard-of-care prostatectomy and template pelvic lymph node dissection and had sufficient histopathology data for evaluation of the pelvic lymph nodes. Surgical specimens were separated into three regions: left hemipelvis, right hemipelvis, and other. For each patient, piflufolastat 18F PET results and histopathology results obtained from dissected pelvic lymph nodes were compared by surgical region. PET results in locations that were not dissected were excluded from analysis. The median serum PSA was 9.3 ng/mL. The total Gleason score was 7 for 19%, 8 for 46%, and 9 for 34% of the patients, with the remainder of the patients having Gleason scores of 6 or 10.[1]

Efficacy was established on the basis of the patient-level specificity and sensitivity of piflufolastat 18F imaging for detection of pelvic lymph node prostate cancer metastases against a histopathology results. Other efficacy analyses in the setting of high risk prostate cancer included positive predictive value (PPV), defined as the percentage of patients with a one-to-one correspondence between localization of at least one lesion identified on piflufolastat 18F imaging and the composite standard of truth (SOT) and negative predictive value (NPV) for detecting pelvic lymph node metastasis, performance for pelvic nodal staging relative to conventional imaging, diagnostic performance for the primary tumor within the prostate gland, detection of distant metastasis, and change in intended clinical management plans. Piflufolastat 18F imaging demonstrated very high specificity (95% - 98%), with the lower bound of the 95% CI for all three readers exceeding the pre-specified 80% success criterion are shown in Table 1.[1,15,17,e]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

Table 1: Patient-Level, Region-Matched Performance of piflufolastat 18F for Detection of Pelvic Lymph Node Metastasis in OSPREY (n=252) [1,15,17,e]

	Reader 1	Reader 2	Reader 3
True Positive	23	17	23
False Positive	7	4	9
False Negative	36	43	37
True Negative	186	188	183
Sensitivity, % (95% CI)	39 (27, 51)	28 (17, 40)	38 (26, 51)
Specificity, % (95% CI)	96 (94, 99)	98 (95, 99)	95 (92, 98)
PPV, % (95% CI)	77 (62, 92)	81 (59, 93)	72 (56, 87)
NPV, % (95% CI)	84 (79, 89)	81 (76, 86)	83 (78, 88)

Abbreviations: CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value.

While a lower than expected sensitivity was observed (28% to 39%), with the lower bound of the 95% CI not exceeding the pre-specified 40% success criterion, specificity far exceeded (95% to 98%) the pre-specified threshold of 80% for all three readers.[15] The clinical reviewer noted that although pre-specified sensitivity goals of the OSPREY trial was not met, the observed diagnostic performance supports the clinical utility in this patient population. While the low sensitivity means that pelvic nodal disease will be missed in certain patients, a similar limitation applies to current standard-of-care imaging and it is not expected to negatively impact traditional patient management. A positive scan may sometimes need to be confirmed by other means, but could ultimately impact treatment strategy. Because piflufolastat 18F PET does not rely strictly on size for identification of abnormal lymph nodes, it can be considered a complementary test to CT and MR.[15] Approximately 24% of the patients studied were found to have pelvic lymph node metastases based on histopathology (95% confidence interval: 19%, 29%). In exploratory analyses, there were numerical trends to more true positive results among patients with total Gleason score of 8 or higher and among patients with tumor stage of T2c[f] or higher than in those patients with lower Gleason score or tumor stage.[1]

4.2 CONDOR

In CONDOR, 208 patients were enrolled with biochemical evidence of recurrent prostate cancer after definitive therapy, defined by serum PSA of at least 0.2 ng/mL after radical prostatectomy (with confirmatory PSA level also at least 0.2 ng/mL) or by an increase in serum PSA of at least 2 ng/mL above the post-therapy nadir after other therapies. All patients had some form of conventional imaging evaluation (for most patients, CT or MRI) within 60 days prior to the piflufolastat 18F PET, and this evaluation was negative or equivocal for prostate cancer. All patients received a single piflufolastat 18F PET/CT from mid-thigh to skull vertex with optional imaging of the lower extremities. Three central readers independently evaluated each PET scan for the presence and location of piflufolastat 18F-

[f] Cancer has invaded both sides of the prostate. American Cancer Society. Prostate Cancer. Early detection, diagnosis, and staging. https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/staging.html. Accessed on April 1, 2021.

positive lesions. Location of each lesion was categorized as one of 19 subregions that were grouped into 5 regions (prostate/prostate bed, pelvic lymph nodes, other lymph nodes, soft tissue, bone). The readers were blinded to all clinical information. Depending on the reader, a total of 123 to 137 patients (59% to 66%) had at least one lesion that was identified as piflufolastat 18F PET-positive. The region most commonly observed to have a piflufolastat 18F PET-positive finding was pelvic lymph node (40% to 42% of all PET-positive regions) and the least common region was soft tissue (6% to 7%). Depending on the reader, 99 to 104 patients with a piflufolastat 18F PET-positive region had composite reference information available that consisted of histopathology, imaging (CT, MRI, ultrasound, fluciclovine PET, choline PET, or bone scan) obtained within 60 days of the PET scan, or response of serum PSA level to targeted radiotherapy. Reference standard information for PET negative regions was not systematically collected in this study. The median serum PSA was 1.98 mg/mL. Prior treatment included radical prostatectomy in 76% of this group.

Efficacy was established on the basis of the PPV, (true positive / true positive + false positive) and and correct detection rate (CDR), defined as the fraction of true positive patients among all patients scanned and evaluated by the central readers as shown in Table 2. [1,15,17,e] For these results, a patient was considered true positive if they had at least one true positive region. [1]

Table 2: Patient-Level piflufolastat 18F PET Results in the CONDOR Study (n=208) [1,15,17,e]

	Reader 1	Reader 2	Reader 3
True Positive	89	87	84
False Positive	15	13	15
PET Positive Without Reference	33	24	24
PET Negative	71	84	85
PPV, % (95% CI)	86 (79, 92)	87 (80, 94)	85 (78, 92)
CDR, % (95% CI)	43 (36, 50)	42 (35, 49)	40 (34, 47)

Abbreviations: CDR = correct detection rate (number of true positive patients who have at least one true positive location matched region out of total number of patients scanned), CI = confidence interval, PPV = positive predictive value (number of true positive patients who have at least one true positive location matched region out of total number of scanned positive patients).

An exploratory analysis of region-level positive predictive value gave results of 67% to 70% with lower bound of the 95% confidence interval ranging from 59% to 63% depending on the reader. The likelihood of a patient having at least one piflufolastat 18F PET-positive lesion generally increased with higher serum PSA level.

The clinical reviewer stated that the performance of piflufolastat 18F PET in these two trials demonstrates the clinical usefulness of this imaging test in the studied patient populations. In summary, the Applicant has provided substantial evidence of effectiveness of piflufolastat 18F PET. [15] Please refer to DIRM's Multi-disciplinary Review and Evaluation for a detailed clinical review of efficacy. [15,17]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for piflufolastat 18F. The safety of piflufolastat 18F was evaluated in two prospective, open label, multi-center clinical studies: CONDOR (NCT03739684) and OSPREY (NCT02981368) (see Section 4: Benefit Assessment). In OSPREY and CONDOR, 593 patients diagnosed with various stages of prostate cancer were exposed to a single dose of piflufolastat 18F. The average injected activity was 340 ± 26 MBq (9.2 ± 0.7 mCi).[1]

The most common (>5%) adverse reactions reported were headache (n=13; 2%), dysgeusia (n=10; 2%) and fatigue(n=7; 1%).[1]

Deaths

No deaths were reported in OSPREY or CONDOR.[2,15]

Serious Adverse Events (SAE)

No significant adverse events were reported. No study dropouts or discontinuations due to adverse events were reported. One patient with a history of multiple allergies experienced a serious adverse reaction of hypersensitivity, which was assessed as unrelated by the Applicant. The clinical reviewer noted that upon review of the narrative summaries for these events, the assessment appears appropriate.[15]

If approved, labeling will include the following risks in the Warnings and Precautions section. Similar to other pcPE radiotracers such as fluciclovine F 18[13], labeling will include the risk of image misinterpretation, hypersensitivity reaction and radiation exposure.

5.1 Risk of Image Misinterpretation

Labeling will note that image misinterpretation errors can occur with piflufolastat 18F imaging. The Warnings and Precautions section of the label communicates that a negative image does not rule out the presence of metastatic prostate cancer and a positive image does not confirm the presence of recurrent prostate cancer.[1]

5.2 Hypersensitivity Reactions

Hypersensitivity reaction was reported in one patient (0.2%; n=1) with a significant history of allergic reactions.[17] Labeling recommends to monitor patients for hypersensitivity or anaphylactic reactions, particularly patients with an allergic history to other drugs and foods. Reactions may not be immediate. Labeling also instructs that emergency resuscitation equipment and personnel should be immediately available.[1]

5.3 RADIATION RISKS

Labeling will note that diagnostic radiopharmaceuticals, including piflufolastat 18F, expose patients to radiation and also note that the radiation exposure is associated with a dose-dependent increased risk of cancer. Labeling instructs to ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. The risk from radiation exposure will be communicated in the Warnings and Precautions section of the label, (b) (4) .[1] At the Federal level, the Nuclear Regulatory Commission (NRC) has established rules to protect the general public, patients, and radiation workers from unnecessary exposure to radiation.[18,19]

6 Expected Postmarket Use

According to the current proposed indication, if approved, piflufolastat 18F will be administered by health care professionals with experience in managing radiolabeled products in inpatient and outpatient licensed settings where these products are handled and administered routinely.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for piflufolastat 18F beyond routine pharmacovigilance and labeling. The applicant proposed describing these risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for piflufolastat 18F, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Piflufolastat 18F is a radioactive diagnostic agent, with the proposed indication for PET imaging in prostate cancer patients (b) (4) . Based on the efficacy and safety information currently available, the clinical reviewers stated that piflufolastat 18F shows clinically meaningful benefit, and recommend approval of piflufolastat 18F as a radioactive diagnostic agent indicated for PET of PSMA positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.[1,15,17g]

Prostate cancer is the most common cancer among men in the United States, representing the second most common cause of cancer-related death in men. Early detection and precise staging of prostate

[g] Labeling negotiations were ongoing at the time of completion of this review. Indication statement is likely to be updated and significant changes to the proposed label likely to be made by FDA prior to negotiations.

cancer are vital because the survival rate decreases dramatically when cancer has migrated beyond the prostate organ. Although the imaging of prostate cancer has made tremendous advances in recent years, due to tissue heterogeneity in prostate cancer and the lack of specificity of conventional imaging techniques, difficulty remains in identifying small volumes of prostate cancer both in the gland and metastatic sites and no universally approved imaging methods exist for the early detection of prostate cancer. There is a clear need for imaging strategies with new alternative modalities that targets the extracellular domain of PSMA with high affinity and longer half-life, which allows for wider product distribution and accessibility to patients. Piflufolastat 18F appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.[1,15,17] Piflufolastat 18F will be administered by health care professionals with experience in managing radiolabeled products in a licensed settings where these products are handled and administered routinely.

DRM and DIRM have determined that if approved, a REMS is not necessary to ensure the benefits of piflufolastat 18F outweigh its risks. The most concerning adverse reactions observed with the use of piflufolastat 18F are risk of image misinterpretation, hypersensitivity reaction and radiation exposure. The serious risks associated with previously approved C-11 choline, Ga-68 PSMA are image misinterpretation and radiation exposure and the serious risks associated with fluciclovine F 18 include image misinterpretation, hypersensitivity reaction and radiation exposure, and none of these products does not have a boxed warning in its label and a REMS was not required for approval. At the time this review was completed , none of these risks will receive a boxed warning in the label, labeling negotiations were still ongoing with the Applicant; if piflufolastat 18F is approved, similar to other pcPE radiotracers such as fluciclovine F 18[13], Warnings and Precautions in the labeling, will be used to communicate the safety issues and management of toxicities associated with piflufolastat 18F, as well as information to be included in Patient Counseling Information.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of piflufolastat 18F. The management of the risks associated with piflufolastat 18F treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

10 References

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[17] Masters S. Clinical Review Presentation. Mid-Cycle Meeting, dated February 23, 2020.

[18] Nuclear Regulatory Commission (NRC) Regulations. *Code of Federal Regulations* (CFR). Title 10, parts 19, 20, and 35, last updated February 16, 2018.

[19] Food Drug Administration Center for Drugs Evaluations Research. Guidance for Industry: Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities. FDA Maryland, 2016.

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