NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	022335
Priority or Standard	Standard
Submit Date	March 29, 2023
Received Date	March 29, 2023
PDUFA Goal Date	September 29, 2023
Division/Office	DIRM/OSM
Review Completion Date	August 29, 2023
Established/Proper Name	Kit for the preparation of technetium Tc 99m-labeled carbon inhalation aerosol
Trade Name	Technegas
Pharmacologic Class	Radioactive Diagnostic Agent
Code name	5081030
Applicant	Cyclomedica Australia Pty Ltd.
Dosage form	Aerosol
Applicant Proposed Dosing Regimen	• (b) (4) • For adults, the target administered dose is achieved at an imaging count rate of 1,500 to 2,500 per second. • For pediatric patients, the target administered dose is achieved at an imaging count rate of 500 to 1,000 per second.
Applicant Proposed Indication/Population	Functional lung ventilation imaging (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	(b) (4)
Recommendation on Regulatory Action	Approval

Recommended Indication/Population	TECHNEGAS, when used with sodium pertechnetate Tc 99m in the Technegas Plus System, provides technetium Tc 99m-labeled carbon inhalation aerosol (Technegas Aerosol), a radioactive diagnostic agent for use in adults and pediatric patients aged 6 years and older for: • Visualization of pulmonary ventilation • Evaluation of pulmonary embolism when paired with perfusion imaging
Recommended SNOMED CT Indication Disease Term for each Indication	764864002 |Radionuclide imaging of lung ventilation using technetium (99m-Tc) Technegas (procedure)
Recommended Dosing Regimen	• For adult patients, the recommended activity of sodium pertechnetate Tc 99m injection to be loaded in the Technegas crucible is 400 MBq to 1,000 MBq (10.8 mCi to 27 mCi) to achieve a lung count rate between 1,500 counts per second (CPS) and 2,500 CPS at the end of the last respiration. Discontinue Technegas inhalation at that point. • For pediatric patients aged 6 years and older, a sufficient amount of technetium Tc 99m labeled carbon aerosol should be inhaled until a lung count rate is obtained between 500 CPS and 1,000 CPS at the end of last respiration.

Abbreviations: COPD, chronic obstructive pulmonary disease; CPS, counts per second; DIRM, Division of Imaging and Radiation Medicine; Ltd, limited; NDA, new drug application; OSM, Office of Specialty Medicine; Pty, proprietary; Tc, technetium; TM, trademark; USP, United States Pharmacopeia

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Abbreviations: DIRM, Division of Imaging and Radiation Medicine

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Abbreviations: ATL, application team lead; CDRH, Center for Devices and Radiological Health; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology

Glossary

CMC	chemistry, manufacturing, and controls
CR	complete response
CRL	complete response letter
DTPA	diethylenetriamine pentaacetate
EANM	European Association of Nuclear Medicine
FDA	Food and Drug Administration
IR	information request
NDA	new drug application
PAS	Patient Administration Set
PE	pulmonary embolism
PI	prescribing information
TP	Technegas Plus System

1. Executive Summary

1.1. Product Introduction

Technegas, when used with sodium pertechnetate Tc 99m in the Technegas Plus System (TP), provides technetium Tc 99m-labeled carbon inhalation aerosol, a radiopharmaceutical imaging agent intended for ventilation imaging of the lungs. When inhaled, Technegas Aerosol distributes to areas of the lungs that are ventilated, where it can be imaged using a gamma camera. Areas of the lungs that are visualized correspond to ventilated segments.

Technegas Aerosol is a structured dispersion of technetium Tc 99m-labeled carbon. Technegas Aerosol formation is achieved by using a Technegas carbon crucible, loaded with sodium pertechnetate Tc 99m injection. Technegas Aerosol is prepared at the point of use by the TP and is delivered to patients using a separate Patient Administration Set (PAS). For ventilation/perfusion imaging, Technegas Aerosol distributes into the bronchoalveolar regions and remains in place sufficiently long to capture multiple views of the lungs enabling comparison of the ventilation to the perfusion images.

Technegas is a ventilation imaging agent marketed in 59 countries worldwide. It was first approved in Australia in 1987, and as of the end of 2019, Technegas is estimated to have been administered a total of 3.9 million times.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The application contains substantial evidence of effectiveness based upon one adequate and well-controlled phase 3 clinical trial (CYC-009) and confirmatory evidence from a published clinical study by Miles et al., 2009. Technegas has been shown to be effective as a radioactive diagnostic imaging agent to visualize pulmonary ventilation and pulmonary embolism (PE) when paired with perfusion imaging. The effectiveness of Technegas was also supported by literature studies of clinical applications of Technegas.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Technegas, when used with sodium pertechnetate Tc 99m in the Technegas Plus System, provides technetium Tc 99m labeled carbon inhalation aerosol (Technegas Aerosol), for use in adults and pediatric patients aged 6 years and older for visualization of pulmonary ventilation and evaluation of pulmonary embolism when paired with perfusion imaging.

The Applicant-conducted prospective phase 3 study CYC-009 provides the primary evidence of efficacy for this application. The study CYC-009 protocol was agreed upon with FDA under a SPA and included an imaging comparator (Xe-133), multiple independent imaging readers, as well as pre-specified success criteria and analyses. Study CYC-009 was adequate and well-controlled and supported the indication of Technegas as a radioactive diagnostic imaging agent for lung ventilation scintigraphy in adult and pediatric patients to evaluate pulmonary ventilation. A second study provided confirmatory evidence of effectiveness and supported the indication of Technegas for evaluation of PE, when paired with perfusion imaging.

Dyspnea and hypoxia may occur during or after the inhalation of Technegas, especially in patients with compromised respiratory function. This potential adverse reaction can be controlled with the mitigation strategies included in the prescribing information. The review team identified no other major safety issues for Technegas based upon data from studies conducted by the Applicant as well as published literature and postmarket reports.

With the resolution of product quality issues that had been identified in the original application, the overall body of evidence supports a favorable benefit-risk assessment for performing ventilation scans with inhaled Technegas aerosol.

Abbreviations: FDA, Food and Drug Administration; PE, pulmonary embolism; SPA, special protocol agreement; Tc, technetium; Xe, xenon

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pulmonary embolism (PE) is a blockage of an artery in the lungs by a substance that has moved from elsewhere in the body through the bloodstream. The clinical presentation of acute PE ranges from shock or sustained hypotension to mild dyspnea. • PE can cause death acutely or through chronic thromboembolism-induced pulmonary hypertension.	• Based on the rapidly changing pattern of perfusion in PE, imaging tests for PE diagnosis should be carried out as soon as possible, preferably within 24 hours after onset of symptoms.
Current Treatment Options	• The diagnosis of PE follows a sequential workup consisting of clinical probability assessment, d-dimer testing, and multidetector computed tomography (CT) or ventilation–perfusion (V/Q) scanning. • In patients with a low or intermediate clinical probability but positive D-dimer, and in patients with a high or likely clinical probability, lung imaging is required. • Computed tomography of the pulmonary arteries (also known as computed tomography pulmonary angiography [CTPA]) using iodine-based contrast, and V/Q imaging are the main imaging modalities for PE diagnosis. • Drugs approved for pulmonary ventilation include the inert gases Kr-81m and Xe-133 as well as the ^{99m}Tc-diethylenetriaminepentaacetate (DTPA) aerosol.	• CTPA is associated with relatively higher radiation exposure to the thorax and potential adverse reactions to the contrast agent. • Kr-81m has been withdrawn from the market for commercial reasons. • The acquisition time for Xe-133 gas is limited, and consequently the available imaging positions are limited. • DTPA aerosol may deposit in central airways in patients with COPD, potentially degrading images.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant-conducted study CYC-009 provides the primary evidence of effectiveness, as the prospective protocol was agreed upon with FDA under an SPA and included multiple independent imaging readers as well as pre-specified success criteria. The data from this study show that Technegas is similar to Xe-133 with respect to pulmonary ventilation distribution imaging of all six lung regions using a three-point ventilation score. • Miles et al., 2009 was a well-controlled, prospective study to compare SPECT V/Q scintigraphy with multi-slice CT pulmonary angiography (CTPA) for diagnosis of PE. The study provides confirmatory evidence of effectiveness and supports the indication of Technegas for evaluation of PE, when paired with perfusion imaging. The results of three blinded independent readers indicate that Technegas SPECT V/Q scintigraphy has comparable diagnostic performance as CTPA for PE diagnosis.	• The efficacy data in the original NDA application supported the use of Technegas as a radioactive diagnostic imaging agent to evaluate pulmonary function and PE when paired with perfusion imaging.
Risk and Risk Management	• Dyspnea and hypoxia may occur during or after the inhalation of Technegas, especially in patients with compromised respiratory function or underlying pulmonary disease. The review team identified no other major safety issue for Technegas based upon data from trials conducted by the Applicant as well as published literature and review of postmarket reports. • The radiation exposure to the lung with one administration of Technegas (40 MBq) is approximately 4.4 mGy, and the effective dose is approximately 0.6 mSv.	• The risk of hypoxia can be mitigated by monitoring oxygen saturation with pulse oximetry, interruption of the procedure, and administration of supplemental oxygen. • The labeling describes safe drug handling and patient preparation procedures to protect patients and health care providers from unintentional radiation exposure.

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; CTPA, computed tomography pulmonary angiography; DTPA, diethylenetriaminepentaacetate; FDA, Food and Drug Administration; Kr, krypton; NDA, new drug application; PE, pulmonary embolism; SPA, special protocol agreement; SPECT, single photon emission tomography ; V/Q, ventilation–perfusion; Xe, xenon

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application and was not needed**			

2. NDA Resubmission Multi-Disciplinary Review

2.1. Clinical Review

2.1.1. Introduction

Since quality and manufacturing facility review issues were foremost in leading to FDA's complete response (CR) action after the first review cycle, for Multi-Disciplinary Review and Evaluation including basis for approval recommendations from the non-quality/facility disciplines during the first review cycle, see Section 6. Summaries provided under Section 2 below cover the Applicant's response to clinical deficiencies identified in the complete response letter (CRL).

2.1.2. Regulatory History

- March 26, 2020: Original 505(b)(2) new drug application (NDA) submission.
- June 25, 2021: A CRL was sent to the Applicant, Cyclomedica.
- October 29, 2021: Cyclomedica requested a teleconference with FDA to discuss the CRL. To the Applicant's question in the meeting package (summary for all three clinical questions), the review team responded as excerpted below:
  - Reference is made to the Post-CRL Meeting Request and Information Package you submitted on October 29, 2021. We acknowledge your responses and efforts to address the clinical review issues identified in the CRL. For both adult and pediatric patients, we have no objection to the inclusion of lung count rates as part of prescribing information for the administration of Technegas. We also agree with your strategy to cover the to-be-marketed range of sodium pertechnetate Tc 99m loadings from minimum to maximum when conducting new chemistry manufacturing control (CMC) investigation under CMC Issue #1. Hypoxia remains a safety concern during Technegas inhalation. Regarding breathing instructions, strategies for mitigation should be included in revised prescribing information (PI), including but not limited to specification of a primary method for Technegas administration (or instructions for how to select a primary method tailored to patient characteristics) and instructions for how to approach the question of pre-oxygenation.
- July 29, 2022: FDA granted the Applicant's request for an extension to respond to the CRL until January 31, 2023.
- January 4, 2023: FDA granted a further extension due to the global shortage of Molybdenum 99 (Mo 99), the precursor to sodium pertechnetate Tc 99m, the isotope used to manufacture Technegas.
- March 29, 2023: Cyclomedica re-submitted the NDA

2.1.3. Clinical Deficiencies in the CRL

12. Risks of Dyspnea and Hypoxia

Raw data submitted from the CYC-009 study indicate that only 21% of subjects inhaled Technegas without operator intervention to provide supplemental oxygen or to interrupt Technegas flow for the subject to breath room air. You have proposed that adult patients should be instructed to (b) (4) A clear upper time limit for Technegas administration and instructions for the operator to provide room air and supplemental oxygen before, during, and/or after Technegas administration are lacking in your NDA. Also lacking is discussion of breathing instructions for optimal or near optimal risk mitigation and instructions for operators to monitor and prepare for this risk. Therefore, you will need to include the following information in your CR:

1. For each patient breathing method:
   - Specify or estimate the proportion of CYC-009 subjects who used this method alone or in specific mixture of methods
   - Clarify the relationship to methods studied in other investigations, including (Lloyd et al. 1994) and (James et al. 1991)
   - Discuss data on relative advantages and disadvantages to the patient for maximizing the likelihood of targeted biodistribution and minimizing the risk of dyspnea and hypoxia
2. Add the information lacking in the current NDA to instructions for prescribers and device operators and add or re-prioritize patient breathing instructions based on analysis specified under Issue #3a.

13. Recommended Loading Range in Adults

Justify the same or a revised range for your recommended loading range of (b) (4) sodium pertechnetate Tc 99m injection, United States Pharmacopeia, accounting for the range, volume, and number of loadings actually administered in study CYC-009. If gaps remain between studied and recommended use, provide a discussion of operator and patient tradeoffs for justification of each gap. Also note our recommendation to cover the to-be-marketed range of sodium pertechnetate Tc 99m loadings from minimum to maximum when conducting new CMC investigation under CMC Issue #1.

14. Recommended Loading Range and Lung Count Rate in Pediatric Patients 6 Years of Age and Older

Justify the same or a revised range for recommended lung count rate of 500 CPS to 1000 CPS and loading range (b) (4) accounting

for data on these parameters in actual use. Provide range estimates with source information for the total number of pediatric patients 6 years of age who have received Technegas in total in both of the following populations:

1. Investigations reported in published literature.
2. Postmarket experience where Technegas is marketed, either based on marketing information available to you or on estimation from a surveyed sample of Technegas administrators focused on pediatric patients.

Please note our recommendation to cover the to-be-marketed range of sodium pertechnetate Tc 99m loadings from minimum to maximum when conducting new CMC investigation under Product Quality Issue #1.

2.1.4. Applicant's Response to the CRL and Clinical Review

The Applicant addressed the clinical deficiencies in the CRL through the Post-CRL Meeting held on January 27, 2022, and a CRL response in the NDA resubmission.

12 Risks of Dyspnea and Hypoxia

12.a. Breathing Method for Technegas Administration

12.a.i. Specify or Estimate the Proportion of CYC-009 Subjects Using Different Breathing Methods

The Applicant's position:

- The following breathing method was specified in the pivotal study CYC-009:
  - "Technegas is administered by inhalation through the PAS within 10 minutes after preparation. This consists of a plastic tube connected to the Technegas Plus Generator, fitted with a mouthpiece, one-way flow values and expiration filter."
  - "The subject will be instructed to breathe through the mouthpiece in one of the methods described below:
    - Slow, deep breathing from the residual functional capacity (end of calm expiration) followed by a 5-second breath-hold (recommended method)
    - Normal breathing with deep inhalations without breath-holding
    - Rapid and deep inspirations from the residual functional capacity followed by a breath-hold of about 5 seconds at the end of the inspiration"
  - "The count rate should be monitored until a rate of 1.5-2.5 kCPS is achieved. This typically requires 1 to 5 breaths, but additional breaths may be necessary to achieve this target."

- The breathing method used for each subject was not recorded during the study. The proportion of CYC-009 subjects who used a given method alone or in specific mixture of methods is not able to be specified or estimated.
- The specific breathing method used was assessed/determined at the time of Technegas administration by the Nuclear Medicine professional administering Technegas and using assessment methods standard at that institution and in medical practice. These included considering ability to follow instructions, respiratory rate, subjective feeling of shortness of breath, and comfort level in applying a certain breathing technique.
- The PI of DRAXIMAGE diethylenetriaminepentaacetate (DTPA) does not specify the breathing technique to be used for the agent to achieve the level of radioactivity (DraxImage 2017).

Reviewer comment: *We acknowledged that the breathing methods used in CYC-009 were not recorded. It is acceptable that the breathing method should be patient-specific based on standard assessment methods in medical practice after considering ability to follow instructions, respiratory rate, subjective feeling of shortness of breath, and comfort level of each patient. However, those standard assessment methods should be listed in the labeling as general instruction.*

DTPA aerosol, which is usually prepared using oxygen, may not induce hypoxia as Technegas did since Technegas is prepared using pure Argon gas. Therefore, we disagree with the Applicant's reference to the precedent case of DTPA. In addition, there is no standard or established clinical practice for Technegas administration in the United States.

Based on the Applicant-provided data in the meeting package dated October 29, 2021 (Table 1), the supplemental oxygen requirement is similar between Technegas inhalation and Xe-133 inhalation.

Table 1. Study CYC-009: Percentages of Subjects With Supplemental Oxygen Usage and Allowance to Breathe Room Air (n=210)

Inhalation Gas	Supplemental Oxygen Required	Allowed to Breathe Room Air	No Intervention
Technegas Inhalation	77 (36.7%)	144 (66.6%)	43 (20.5%)
Xe-133 Inhalation	74 (35.2%)	0 (0%)	136 (64.8%)

Source: Reviewer's data summary based on Table in CRL-response, page 36 of 77.
Abbreviations: CRL, complete response letter; n, number of subjects; Xe, xenon

The following information request (IR) was sent to the Applicant on May 1, 2023:

> *Reference is made to the table "Study CYC-009: Supplemental Oxygen Usage / Allowed to Breathe Room Air" in your CRL response submitted March 29, 2023. Please confirm that during Xe-133 inhalation, the patients were not requested to breathe room air between inhalations.*

The Applicant responded to the above IR on May 11, 2023, and confirmed that the CYC-009 protocol did not request patients to breathe room air between Xe-133 inhalations. During

Xe-133 administration, inhalation and exhalation is continuously maintained within a closed system to ensure radioactive gas containment.

The Applicant re-stated that the upper time limit for Technegas administration and providing room air and supplemental oxygen before, during, and/or after Technegas administration are variable and determined by Nuclear Medicine personnel as the imaging session progresses.

Reviewer comment: *We acknowledged that the supplemental oxygen requirement is similar between Technegas inhalation and Xe-133 inhalation and the usage of supplemental oxygen is not unique to Technegas. However, for Technegas inhalation, up to 67% of the patients were allowed to breathe room air while no patients in Xe-133 group were allowed to breathe room air. Therefore, hypoxia is still a concern during Technegas inhalation, and necessary and proper mitigation should be included in PI.*

12.a.ii. Clarify the relationship to methods studied in other investigations

The Applicant's position**:**

- Protocol CYC-009 used the same three Technegas administration techniques as were used in Protocol CYC-008, VM-001-01, and VM-002-01 clinical trials.
- Those clinical trials used the same Technegas administration techniques as were evaluated and reported in (Lloyd et al. 1994). The Lloyd et al publication (page 397) concluded: "in normal subjects good quality Technegas images are produced irrespective of the inhalation technique used and differences between images acquired with the different breathing patterns were slight."
- (James et al. 1991) titled "Evaluation of ^{99}Tcm Technegas ventilation scintigraphy in the diagnosis of pulmonary embolism" (page 712), reported on the use of one of the recommended breathing techniques, followed by "normal tidal breathing". The technique used was described as "the inhalation technique which involved taking a slow deep inspiration and breath holding for 5 s before expiring and returning to normal tidal breathing".
- (James et al. 1991) concluded that "administration appears feasible even in patients with compromised respiratory function."

Reviewer comment: *There are no data available to assess the correlation between Technegas distribution/imaging quality and different breath pattern used in CYC 009. Based on (James et al. 1991), a slow deep inspiration and breath holding for 5 seconds before expiring and returning to normal tidal breathing is the preferred method, and the administration appears feasible even in patients with compromised respiratory function. The concern is that this breath pattern may induce hypoxia in patients with compromised respiratory function. Therefore, we agree to include other breath patterns in the labeling and that room air should be allowed to the patients if needed.*

12a.iii. Discuss Data on Relative Advantages and Disadvantages to the Patient for Maximizing the Likelihood of Targeted Biodistribution and Minimizing the Risk of Dyspnea and Hypoxia

The Applicant's position:

- The CYC-009 study, other clinical studies included in the Technegas NDA, and pharmacovigilance reports for the worldwide use of Technegas in over 4 million patients over a period of 20+ years has shown an extremely low incidence of dyspnea and hypoxia.
- In the CYC-009 study, oxygen saturation exhibited small but statistically significant mean increases from baseline measurements (prior to Xe-133 imaging) following both Xe-133 and Technegas imaging sessions during Visit 1. Mean changes from baseline were 0.4% at each of the 3 postbaseline time points with individual changes ranging from -9% to 9%. For subjects with 24-hour follow-up measurements, no statistically significant change in oxygen saturation was observed. These data demonstrate that the variability for using supplementary oxygen between sites did not significantly affect oxygen saturation level between patients.

Reviewer comment: *In one published study (James et al. 1992), oxygen saturation was monitored in a series of patients undergoing Technegas ventilation scintigraphy. Twenty-eight patients were referred for lung studies because of suspected PE and another 10 patients known to have respiratory disease but in whom PE was not suspected were studied. Of the 38 patients without pre-oxygenation, oxygen saturation fell < 90% in 26 (68%) patients, < 85% in 15 (39%) patients, and to as low as 60%. The recorded lowest value for each patient was usually observed after the first or second inhalation.*

The definition of hypoxia for Study CYC-009 was blood oxygen saturation levels <90%. Oxygen saturation was measured at 10 ± 5 min prior to Technegas inhalation, within 15 min postimaging, and at the 24 hr follow-up. This measurement strategy might miss the nadir of oxygen saturation.

12.b. Add the Information Lacking in the Current NDA to Instructions for Prescribers and Device Operators and Add or Reprioritize Patient Breathing Instructions

The Applicant's position:

- The upper time limit for Technegas administration and the potential options to provide room air and supplemental oxygen before, during, and/or after Technegas administration are variable and determined by nuclear medicine personnel as the imaging session progresses.
- Decreased oxygen saturation was observed in CYC-009 during Technegas inhalation, but the symptoms were transient and recoverable. None of the subjects had an oxygen saturation measurement below 90% at the 24-hour Follow-up Visit.

Reviewer comment: *See reviewer comment in 12a.iii above. The appropriate revision of labeling is warranted.*

13. Recommended Loading Range in Adults

The Applicant's position:

- From inception of Technegas ventilation imaging and as with other nuclear medicine ventilation imaging agents, the amount of Technegas administered to patients has been titrated by monitoring the count rate of the lungs with a radiation detector during active administration of the Technegas.
- For protocol CYC-009, the recommended activity of Tc 99m sodium pertechnetate to be added to the Technegas crucible ranged between 6.8 and 19 mCi (250-703 MBq).
- The protocol further states that subjects will inhale Technegas Aerosol until radiation monitors positioned over the lungs indicate that an adequate amount of radioactivity has localized in the lungs. The amount required for imaging is 1.5-2.5 kCPS in the posterior projection as measured on a gamma camera.
- A similar titration procedure is described in the recently approved Tc 99m DTPA prescribing information for aerosol administration.
- The CYC-009 study used the 0.14 mL dose crucible with multiple simmers being employed for several patients enrolled in the study. The entire loading dose range used in the study was from 2.9 to 45.0 mCi (107 to 1665 MBq). The radioactive loading range used in the CYC-009 study covers a broader range (b) (4) (Table 2).

Table 2. Distribution of Compliance With Volume and Activity Loaded in CYC-009 Study

Volume of sodium pertechnetate loaded	**≤ 0.14 mL (N=115)**	**> 0.14 mL (N=95)**
Count rate at end of inhalation categories, n (%)		
< 1.5 kcps	22 (19.1%)	18 (19.0%)
1.5 to 2.5 kcps	47 (40.9%)	42[a] (44.2%)
> 2.5 kcps	46 (40.0%)	35[b] (36.8%)
Net sodium pertechnetate activity loaded	**≤ 19 mCi (703 MBq)[c] (N=95)**	**> 19 mCi (703 MBq) (N=115)**
Count rate at end of inhalation categories, n (%)		
< 1.5 kcps	32 (33.7%)	8 (7.0%)
1.5 to 2.5 kcps	46 (48.4%)	43[a] (37.4%)
> 2.5 kcps	17 (17.9%)	64[b] (55.6%)

[a] Includes 1 subject with 2 loadings.
[b] Includes 5 subjects with 2 loadings.
[c] Includes loadings for 2 subjects < 6.8 mCi.

Source: Table Applicant's CRL Response, page 43 of 77. (b) (4)

Abbreviations: CRL, complete response letter; kcps, kilocounts per second; MBq, megabecquerel; mCi, millicurie; mL, milliliter; N, total number of subjects; n, number of subjects in sample; NDA, new drug application; (b) (4)

Reviewer comment:

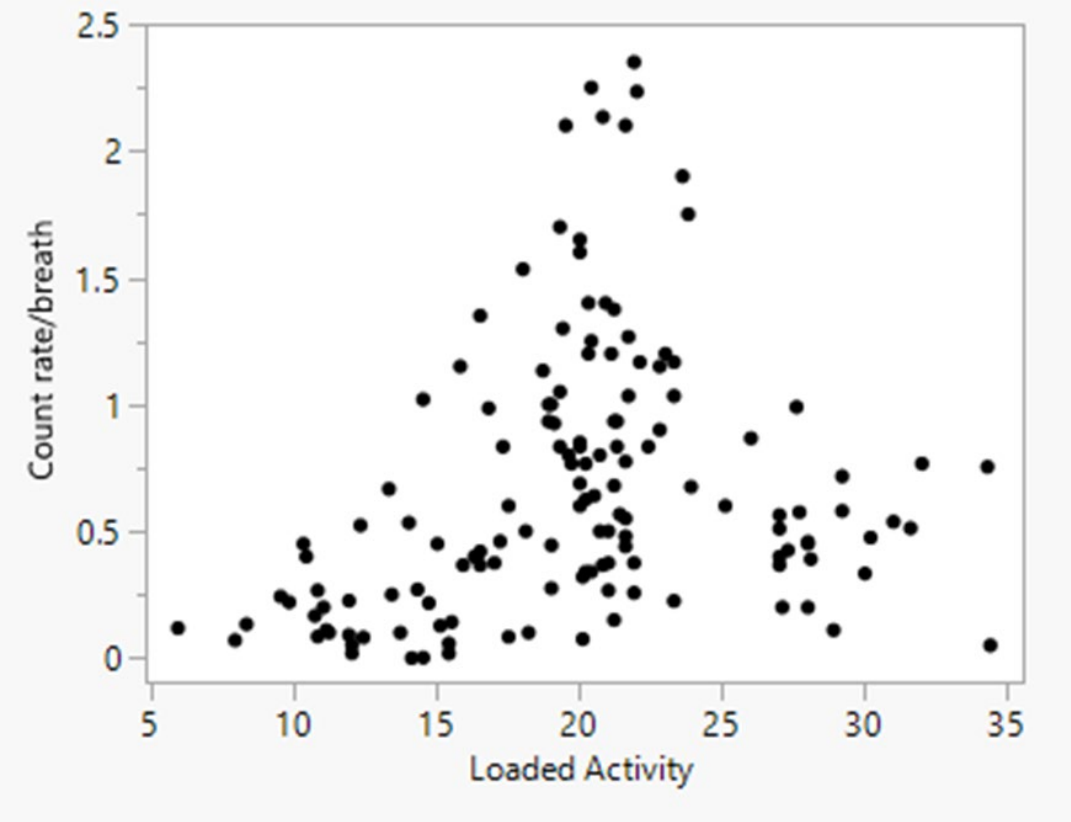
- *In view of the approval of DTPA aerosol, the results of study CYC-009, and postmarket experience with Technegas, we have no objection to using an appropriate count rate range as a source of feedback for Technegas administration. The recommended count rate in the DTPA PI is 833 to 1667 CPS and the proposed count rate of Technegas is 1500 to 2500 CPS.*
- *The Applicant's calculation to justify the lower limit of the loaded activity is inaccurate without properly accounting for the radioactivity delivered to the patient after each breath. In addition, the deposition of Technegas is not 100% since some of particles (up to 80%) will be exhaled at each breath cycle, especially without breath holding.*
- *In CYC-009, with a mean loaded activity of 19.5 mCi, the count rate in 42.4 % of subjects ranged from 1.5 kCPS to 2.5 kCPS (Table 3).*
- *We agree with the Applicant that the radioactive loading range used in the CYC-009 study is broad. The range from 10% to 90% percentile is 11.11 to 27.97 mCi. We also found an apparent correlation between loaded activity and count rate per breath (Figure 1).*

Table 3. Distribution of Count Rate at End of Inhalation in CYC-009 (n=210)

Count Rate at End of Inhalation	n (%)
<1.5 kCPS	40 (19.0%)
1.5 to 2.5 kCPS	89 (42.4%)
>2.5 kCPS	81 (38.6%)

Source: Clinical Reviewer's summary of Table 2.
Abbreviations: kCPS, kilocounts per second; n, number of subjects

Figure 1. Loaded Activity Versus Count Rate/Breath During Technegas Administration in Study CYC-009



Source: **FDA Reviewer Data Analysis**

- *Our aim for the range of recommend loading activity is to avoid overdosing the patients at the upper limit. At the same time, the lower limit should ensure that most patients can inhale sufficient activity with no more than 5-6 breaths.*

The following IR was sent to the Applicant on May 1, 2023:

> *In the CRL response you submitted on March 29, 2023, you stated, "Assuming a target lung deposition of 1 mCi (37MBq) for an average patient, and an average yield of 45%, the minimum loading amount of Tc-99m would calculate to be ~6 mCi (222 MBq)." Please provide data to support this statement, including a literature summary of count rates of gamma cameras (CPS/mCi) under clinical conditions, and the average yield of Technegas from your conducted new CMC investigation under CMC Issue #1.*

The Applicant responded to the IR on May 11, 2023. Using data obtained with validated analytical methods, the yield was measured to average 55.4% with a high degree of run to run and generator to generator reproducibility (see Integrated Quality Review for additional information). Using the new yield value, the minimum loading amount would now calculate to be 4.9 (~5 mCi). For kCPS induced by the inhaled radioactivity, the Applicant cited DraxImage's DTPA PI from 2017 (DraxImage 2017).

Reviewer comment: *In the DPTA labeling, 0.5 to 1.0 mCi corresponds a count rate of 50 kCPM to 100 kCPM, which is 0.83 to 1.67 kCPS. The most recent Technegas proposed PI states,* (b) (4) [redacted]

14. Recommended Loading Range and Lung Count Rate in Pediatric Patients 6 Years of Age and Older

14.a. Investigations Reported in Published Literature.

The Applicant's position:

- Technegas is administered to pediatric patients by monitoring the count rate of the lungs with a radiation detector during active administration of the Technegas to obtain a count rate typically between 500 to 2000 CPS.
- The Pediatric Committee of the European Association of Nuclear Medicine (EANM) specifically addresses the dose titration protocol used for Technegas ventilation imaging (Ciofetta et al. 2007).
- The EANM protocol for pediatric Technegas ventilation imaging is to familiarize the patient with the single-use plastic breathing set with a filter to capture breathed Technegas. A 5-second breath-hold at the end of the inspiration is strongly recommended because it increases tracer retention for each breath from 20% to 80%.
- (Lassmann and Treves 2014) published the EANM pediatric dosage card which included Technegas for pediatric ventilation imaging. Technegas is included in Cluster B of the pediatric dosage card with a baseline activity of 70 MBq for calculating the radioactive dose based on the weight of the pediatric patient as shown in the following table.

The following IR was sent to the Applicant on May 1, 2023:

(b) (4) [redacted] with the average yield of Technegas from your conducted new CMC investigation under CMC Issue #1.

The Applicant responded to the IR on May 11, 2023, (b) (4) Response to CMC Issue #1 clearly shows that the estimated yield was significantly higher than the 45% value estimated from yield measurements made using unvalidated analytical methods. The decrease in baseline activity from 70 to 49 in the 2016 EANM dosage card is justified in large part by the increase in yield (45% estimated from historical unvalidated analytical methods) to the average yield of 55.4% recently determined using newly developed and validated analytical methods. The PI has been updated to reflect the Applicant's revised proposal for pediatric dosing.

Table 4. Applicant's Summary of Literature References for Technegas in Pediatric Patients

Reference	No. of Pediatric Patients	Dosing Information Provided	Imaging Modality
(Van der Wall et al. 1992)	20 patients with age range from 8 weeks to 81 years, with 9 patients under 3 years of age	Chamber loaded with 400-800 MBq of Tc 99m pertechnetate and heated in carbon crucible at 2500° C. Count rate of 2000-3000 counts per second achieved with 4 to 6 inspirations	Planar
(Kropp et al. 1993)	17 infants with a mean age of 9.3 months (range 4-18 months) and 7 children with a mean age of 8.1 years (range 2-11 years	Maximum of 4 10-second inhalation intervals to achieve a count rate of 1000 counts per second.	Planar
(Sanchez-Crespo et al. 2008)	15 infants, ages not specified	Loaded crucible with 2000-3000 MBq. Used count rate to monitor inhaled Technegas	SPECT
(Bjorkman et al. 2011)	12 infants – average age 6 months (range 3-12 months)	5 MBq administered during normal tidal breathing	SPECT
(Kjellberg et al. 2013)	32 newborns at 36 weeks postmenstrual age	5 MBq administered to immobilized and spontaneously breathing infants through facemask.	SPECT

Source: Applicant response to CRL, page 48 of 77
Abbreviations: C, Celsius; MBq, megabecquerel; No., number; SPECT, single photon emission tomography

Reviewer comment: *The lung dose is around 0.5 mCi for DTPA for its indication in lung ventilation for pediatric patients (167 to 833 CPS), while the proposed count rate for Technegas in pediatric patients is 500-1000 CPS.*

14.b. Postmarket Experience With Technegas

The Applicant's position:

- There are just over 1400 active Technegas sites worldwide. The survey was sent to 739 of these nuclear medicine departments (approximately 52.7% of all Technegas sites) to inquire about their use of Technegas in pediatric patients.
- Of the 739 sites contacted, Cyclomedica received a total of 102 responses (13.8% response rate). Out of the 102 responses, a total of six sites confirmed they have performed pulmonary ventilation imaging with Technegas in pediatric patients.
- With respect to loading activity and lung count rate for pediatric patients, the sites were assessed based on the following questions:
  - Is the crucible activity loaded recorded when producing Technegas for a pediatric patient?
  - What is your CPS (Counts | Second) target dose rate used in your department for pediatric patients for Lung Ventilation Imaging?
  - Are your CPS (Counts | Second) target dose rates adjusted for weight or age in your department for pediatric patients for Lung Ventilation Imaging?
  - If yes, are dose rates adjusted for weight or age?
- The Royal Children's, Melbourne, Australia performs between 20-25 pediatric ventilation studies per year using Technegas. They follow the EANM guidelines for conducting Technegas ventilation imaging. Patients inhale Technegas to obtain a count rate of approximately 500 CPS. This count rate is usually achieved with 2-4 inhalations.
- The Lady Cilento Hospital, Queensland, Australia has conducted over 70 pediatric Technegas ventilation studies since 2015. Currently they are conducting between 15-20 pediatric Technegas studies a year with an age range from under 1 to 18. They utilize a weight-based calculation for both the % of activity loaded in the Technegas crucible with a maximum load of 400MBq of Tc 99m pertechnetate. Pediatric patients inhaled the Technegas to achieve a maximum count rate of 400 CPS.

The following IR was sent to the Applicant on May 1, 2023:

> *You mentioned that "a total of six sites confirmed they have performed pulmon*ary ventilation imaging with Technegas in pediatric patients." Please include a tabulated summary of your surveys regarding loading activity and lung count rate for pediatric patients.

The Applicant responded to this IR on May 11, 2023, and the data are presented in Table 5.

Table 5. Summary of Survey of Usage of Technegas in Pediatric Patients

Responder Title and Affiliation	Is Crucible Activity Loaded Recorded?	Target CPS Rate (kCPS) Used in Pediatric Patients for Lung Ventilation Imaging?	Are Target CPS Rates Adjusted for Weight or Age?	If yes, are Dose Rates Adjusted for Weight or Age?
Nuclear Medicine Technologist, Queensland Children's Hospital, Brisbane, Australia	Yes 3.6 to 10.8 mCi *		Yes	Weight
Sr. Nuclear Medicine Technologist, Health Sciences Centre, Winnipeg, Canada	Yes 13.5-16.2 mCi (± 10%)*	1-1.6 0.5-1.8 *	Yes	Weight
Nuclear Medicine Technologist, Alberta Health Services	Yes	< 1 with a range between 0.7-1.0	Yes	Weight
Nuclear Medicine Technologist, British Columbia Children's Hospital	Yes - Dose measured in Dose Calibrator 8.1 mCi*	0.4 - 0.5 0.8-0.1*	Yes	Age
Alberta Children's Hospital	0		No	
Medical Director, Nuclear Medicine, Brantford General Hospital	Not sure 5-6.8 mCi*	not sure 0.5-0.7*	No	

Source: Data provided by the Applicant's IR response, date 05/11/2023, page 3 of 4, plus reviewer's data analysis.
*Confirmed data from the second survey. Four out of six sites responded.
Abbreviations: CPS, counts per second; IR, information request; kCPS, kilocounts per second; mCi, millicurie; Sr., senior

Reviewer comment: *The proposed lung count rate for pediatric patients is 500 CPS to 1000 CPS. The rate seems appropriate based on the literature and postmarket survey performed by the Applicant.*

3. NDA Resubmission Product Quality Review and Evaluation

Reference is made to the Integrated Quality Assessment for a complete review of product quality and facility inspectional deficiencies. The final overall recommendation of the Integrated Quality Assessment is an approval action. A summary of the main topics is presented below.

Expiration dating is 24 months for the Technegas Kit when stored between 15 and 30^0 C.
At the time of the original NDA submission, an initial designation of the drug chemical type as a new molecular entity was made. However, a thorough analysis of the resubmission has led to the conclusion that the final product does not meet new molecular entity criteria for the following reasons. No chemical bond exists between the carbon derived from the crucible and the technetium Tc 99m in the aerosol particles. Instead, technetium Tc 99m is intercalated between graphene layers of graphite. Moreover, while the technetium Tc 99m is in the zero-oxidation state, this isotope of technetium is present in approved products. The Tc 99m oxidation state is considered to be a formulation change. It was noted that the Technegas aerosol is also a dosage form that differs from the injectable dosage forms of currently approved Tc 99m products. As a result, the final determination of the product chemical type is Type 3, namely new dosage form.

Subsequent to further review of the resubmission, FDA determined that the product to be marketed by the Applicant is the carbon crucible, which when used with the TP and commercially available sodium pertechnetate Tc 99m injection solution, as described in the labeling, produces the final drug product. Therefore, FDA recommended to the Applicant that the carbon crucible section of the NDA be relabeled as the drug product section, and the drug product specifications be considered the attributes for the technetium Tc 99m labeled carbon aerosol. The Applicant agreed with FDA's recommendations.

The product and its components were renamed as follows. The established name is kit for the preparation of technetium Tc 99m-labeled carbon inhalation aerosol. The name of the product (the entire kit) is Technegas. The name of the carbon crucible is Technegas Crucible. Given that the system does not produce a radionuclide, the name Technegas Plus System replaces the name Technegas Plus Generator. The final product produced by the system is named Technegas Aerosol (Technetium Tc 99m-Labeled Carbon Aerosol).

The Applicant has provided updated specifications for the crucible and has developed criteria and analytical methods to characterize the identity, radiochemical purity, radioactive concentration, mass concentration, and particle size distribution of the Technegas aerosol. These methods provide for aerosol composition and information on the availability of the particles over the 10 minutes when Technegas aerosol is available for administration. The methods have been qualified with all commercial sources of sodium pertechnetate Tc 99m marketed in the United States.

The manufacturing assessment concludes that the Applicant has satisfactorily addressed all the deficiencies listed in the CR letter and provided supporting studies, new controls and specifications, and addressed major good manufacturing practice deficiencies issued in the FDA 483 form during the initial pre-approval inspection. A follow up pre-approval inspection was conducted during this resubmission which resulted in a voluntary action classification with easily correctable FDA 483 form deficiencies. Based on the review of all the corrective actions and the follow up inspection, the Applicant's facility is acceptable for manufacturing the Technegas Plus System, the crucible, and the ancillary PAS used to administer the Technegas aerosol. Therefore, the resubmitted application is recommended for approval.

4. Other Discipline Reviews

The Technegas prescribing information, TP user manual, PAS instructions for use, and container and carton labels were reviewed and revised by the Division of Imaging and Radiation Medicine's associate director for labeling as well as reviewers from the Division of Medication Error Prevention and Analysis, Center for Devices and Radiological Health, Division of Pediatrics and Maternal Health, and Office of Prescription Drug Promotion, and final labeling agreements were reached with the Applicant.

No new information or data were required for the resubmission by the Nonclinical, Clinical Pharmacology, or Statistical disciplines, and no re-reviews were needed.

5. Labeling

Modifiers of Proprietary Name

The proposed proprietary name for the marketed drug product is Technegas and its recommended established name is "kit for the preparation for technetium Tc 99m-labeled carbon inhalation aerosol". However, to prepare the final drug product for administration, multiple components are involved including a device. In the labeling text, the multiple components involved in the preparation and administration of the finished drug product are distinguished with a modifier after the proprietary name as shown below:

- Technegas Crucible: The marketed kit for the preparation of technetium Tc 99m carbon inhalation aerosol
- Technegas Aerosol: Final dosage form to be administered
- Technegas Plus System (TP): A device for drying, burning, and simmering to prepare the final product
- Technegas PAS: An administration tube and mouthpiece
- Technegas Contacts: Replacement electrodes

Table 6. Prescribing Information

Full Prescribing Information Sections	Considerations
1 INDICATIONS AND USAGE	The indication statement was revised to convey: • The final dosage form, Technegas Aerosol, to be prepared from the supplied product with sodium pertechnetate Tc 99m using Technegas Plus System • Similar wording for the indicated disease and condition to an approved product, DraxImage DTPA

Full Prescribing Information Sections	Considerations
	(kit for the preparation of technetium Tc 99m pentetate injection) • Pediatric patient population as 6 years and older
2 DOSAGE AND ADMINISTRATION	• In general, the dosing unit for radioactive drugs is in terms of MBq or mCi. However, the recommended dose of Technegas Aerosol is in terms of pulmonary count rate (e.g., 1,500 to 2,500 CPS for adult patients) measured by a gamma camera during oral inhalation of Technegas Aerosol that is prepared from one Technegas Crucible and 400 MBq to 1,000 MBq sodium pertechnetate Tc 99m. • For pediatric patients, the recommended loading activity of sodium pertechnetate Tc 99m is a fraction of the recommended activity for adults adjusted by body weight, and the recommended pulmonary count rate is 500 to 1,000 CPS. • The applicant proposed (b) (4) breathing methods for inhalation of the aerosol, but the clinical team decided to recommend the same method used in the clinical study conducted by the Applicant: slow deep breathing from the residual functional capacity followed by a 5-second breath-hold and normal breathing with deep inhalation without breath-holding as an alternative method for patients who are unable to hold their breath as well as pediatric patients aged 6 years and older. • The dosimetry table was reformatted (b) (4) 5 years was retained with a statement, "Technegas is not approved for pediatric patients younger than 6 years old *[see Indications and Usage (1)],*" because 5 years is close to 6 years.
5 WARNINGS AND PRECAUTIONS	• A warning for decreased oxygen saturation was added based on the adverse reactions reported during the clinical trial for efficacy. Continuous oxygen saturation monitoring and breathing room air during the imaging procedure were added as

Full Prescribing Information Sections	Considerations
	mitigations. Supplemental oxygen was also added for consideration. • Radiation risk for radioactive diagnostic drugs and bronchospasm for inhaled aerosol medications were added as class labeling.
6 ADVERSE REACTIONS	Hypoxia was listed as the most common adverse reaction reported in 1% of patients receiving Technegas Aerosol.
14 CLINICAL STUDIES	Two clinical studies were added to support the labeled indications: One study conducted by the applicant comparing the effectiveness of Technegas Aerosol to that of an approved drug for lung ventilation imaging, Xe-133, and the second study from literature showing the effectiveness of Technegas Aerosol in PE assessment when paired with lung perfusion imaging.

Abbreviations: CPS, counts per second; DTPA, diethylenetriamine pentaacetate; MBq, megabecquerel; mCi, millicurie; PE, pulmonary embolism; Tc, technetium; Xe, xenon

User Manual for TP and Instructions for Use for PAS

The device labeling was revised to be consistent with the prescribing information including the nomenclature for the Technegas components. The labeling for the PAS is not part of the NDA package, but the labeling recommendations were communicated to the Applicant for consideration.

6. Original NDA Multi-Disciplinary Review and Evaluation

The NDA signatory authorities at the Division and Office levels concurred with the Quality and Clinical reviewers' findings of important deficiencies in the original NDA application and with their recommendations for addressing these deficiencies.

The most important deficiencies were related to product quality issues and involved the following: characterization and control of the finished Technegas drug product; validation of the product preparation process and of various critical analytical methods; specifications for the crucible; and data on volatile compounds during the product preparation procedures. In addition, FDA inspection of the Cyclomedica manufacturing facility identified deficiencies with the manufacturing and testing of the final drug product, the patient delivery device, and the crucible. Concerns also arose by review of information on specifications, performance data, and process controls for the TP.

The clinical deficiencies concerned the need for more information on risk minimization steps to address the potential for inducing hypoxia during the inhalation of the anoxic gas mixture and the need to justify the proposed technetium Tc 99m loading ranges to be used for adult and pediatric patients.

In view of these important deficiencies, the Quality and Clinical reviewers recommended a CR action for the NDA application. The review team and management agreed. No deficiencies were identified by the Nonclinical, Clinical Pharmacology, and Statistical review disciplines.

7. Division Director Summary Review

I concur with the clinical reviewers that the clinical deficiencies in the original application have been resolved in the resubmission and that, given the resolution of the product quality issues, the benefit-risk profile of the product is favorable.

- The risk of dyspnea and anoxia associated with different Technegas aerosol breathing methods, the upper time limit for aerosol administration, and provision of room air and supplemental oxygen before, during, or after aerosol inhalation were evaluated in literature reports and the Applicant's marketing experience. As a result, the PI recommends aerosol breathing methods for adults who can or cannot hold their breath and for pediatric patients. A warning advises to monitor oxygen saturation with continuous pulse oximetry. If clinically indicated, patients should breathe room air throughout the procedure and receive supplemental oxygen before and at any time during the procedure as needed.
- The recommended range of activity of sodium pertechnetate Tc 99m to be added to the Technegas crucible to produce the Technegas aerosol and the range of radioactivity amounts accumulated in the lung during inhalation of the aerosol that is considered adequate for imaging in adult and pediatric patients have been defined and justified and are described in the PI.

I concur with the assessment by the product quality reviewers that the drug quality and inspectional deficiencies have been addressed, and the biocompatibility data are adequate. I concur with their recommendation for an approval action.

- The most important deficiencies were related to product quality issues and involved the following: characterization and control of the finished Technegas drug product, validation of the product preparation process and of various critical analytical methods, and specifications for the crucible.
- Moreover, the Applicant has addressed major good manufacturing practice deficiencies identified in the FDA 483 form during the initial pre-approval inspection. A follow up inspection was conducted during this second review cycle and resulted in a voluntary action classification.

With regard to the TP, the device component used for the preparation of the finished drug product, deficiencies concerned the need to evaluate risks posed by all detected chemicals

including [redacted] (b) (4), and an unlabeled unidentified peak in a chromatogram. I concur with the device reviewer assessment that in this second review cycle, the information provided by the Applicant and a literature search have addressed the biocompatibility concerns.

8. Reference List

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9. Signatures: Participants in the Original NDA and the NDA Resubmission

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ronald Honchel, Ph.D.	OND/ORDPURM/DPTRDPURM	Sections: 5 (original), 4, 6	**Select one:** X Authored ___ Approved
	Signature: Ronald Honchel -S Digitally signed by Ronald Honchel -S Date: 2023.09.27 10:36:54 -04'00'			
Nonclinical Supervisory Pharmacologist	Jonathan Cohen, Ph.D.	OND/ORDPURM/DPTRDPURM	Sections: 5 (original), 4, 6	**Select one:** ___ Authored X Approved
	Signature: Jonathan E. Cohen -S Digitally signed by Jonathan E. Cohen -S Date: 2023.09.27 10:44:26 -04'00'			
Nonclinical Division Director	Mukesh Summan, Ph.D.	OND/ORDPURM/DPTRDPURM	Sections: 5 (original),4, 6	**Select one:** ___ Authored X Approved
	Signature: Mukesh Summan -S Digitally signed by Mukesh Summan -S Date: 2023.09.27 11:27:32 -04'00'			
Clinical Pharmacology Reviewer and Team Leader	Christy John, Ph.D.	OCP/DCPI	Sections 6 (Original), 4. 6	**Select one:** X Authored ___ Approved
	Signature: Christy S. John -S Digitally signed by Christy S. John -S Date: 2023.09.27 11:49:48 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Deputy Division Director	Olanrewaju Okusanya, Ph.D.	OCP/DCPI	Sections: 6 (original), 4, 6	**Select one:** ___ Authored X Approved
	Signature: Olanrewaju Okusanya -S Digitally signed by Olanrewaju Okusanya -S Date: 2023.09.27 13:14:50 -04'00'			
Statistical Primary Reviewer	Jyoti Zalkikar, Ph.D.	OB/DBI	Sections: 8 (original), 1.2, 1.3, 6	**Select one:** X Authored ___ Approved
	Signature: Jyoti Zalkikar -S Digitally signed by Jyoti Zalkikar -S Date: 2023.09.27 09:22:36 -04'00'			
Statistical Deputy Division Director	Sue Jane Wang, Ph.D.	OB/DBI	Sections: 8 (original), 1.2, 1.3, 6	**Select one:** Authored X Approved
	Signature: Suejane Wang -S Digitally signed by Suejane Wang -S Date: 2023.09.27 10:08:51 -04'00'			
Clinical Reviewer	Gang Niu, M.D.	OSM/DIRM	Sections:1, 2.1, 6	**Select one:** X Authored ___ Approved
	Signature: Gang Niu -S Digitally signed by Gang Niu -S Date: 2023.09.27 13:23:25 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader and CDTL	Anthony Fotenos, M.D., Ph.D.	OSM/DIRM	Sections:1, 2.1, 6	**Select one:** ___ Authored X Approved
	Signature: Anthony F. Fotenos -S Digitally signed by Anthony F. Fotenos -S Date: 2023.09.27 13:35:11 -04'00'			
Deputy Division Director	A. Alex Hofling, M.D., Ph.D.	OSM/DIRM	Sections: All	**Select one:** ___ Authored X Approved
	Signature: August Hofling -S Digitally signed by August Hofling -S Date: 2023.09.27 15:10:44 -04'00'			
Division Director	Libero Marzella, M.D., Ph.D.	OSM/DIRM	Sections: All	**Select one:** ___ Authored X Approved
	Signature: Libero L. Marzella -S Digitally signed by Libero L. Marzella -S Date: 2023.09.28 11:12:29 -04'00'			

Abbreviations: CDTL, cross-disciplinary team lead; DIRM, Division of Imaging and Radiation Medicine; DBI, Division of Bioequivalence I; DCPI, Division of Cancer Pharmacology I; DCPII, Division of Cancer Pharmacology II; DPTRDPURM, Division of Pharmacology Toxicology for Rare Disease, Pediatrics, Urology, and Reproductive Medicine; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OND, Office of New Drugs; ORDPURM, Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine; OSM, Office of Specialty Medicine

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MODUPE O FAGBAMI
09/28/2023 11:32:35 AM