CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022335Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

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:

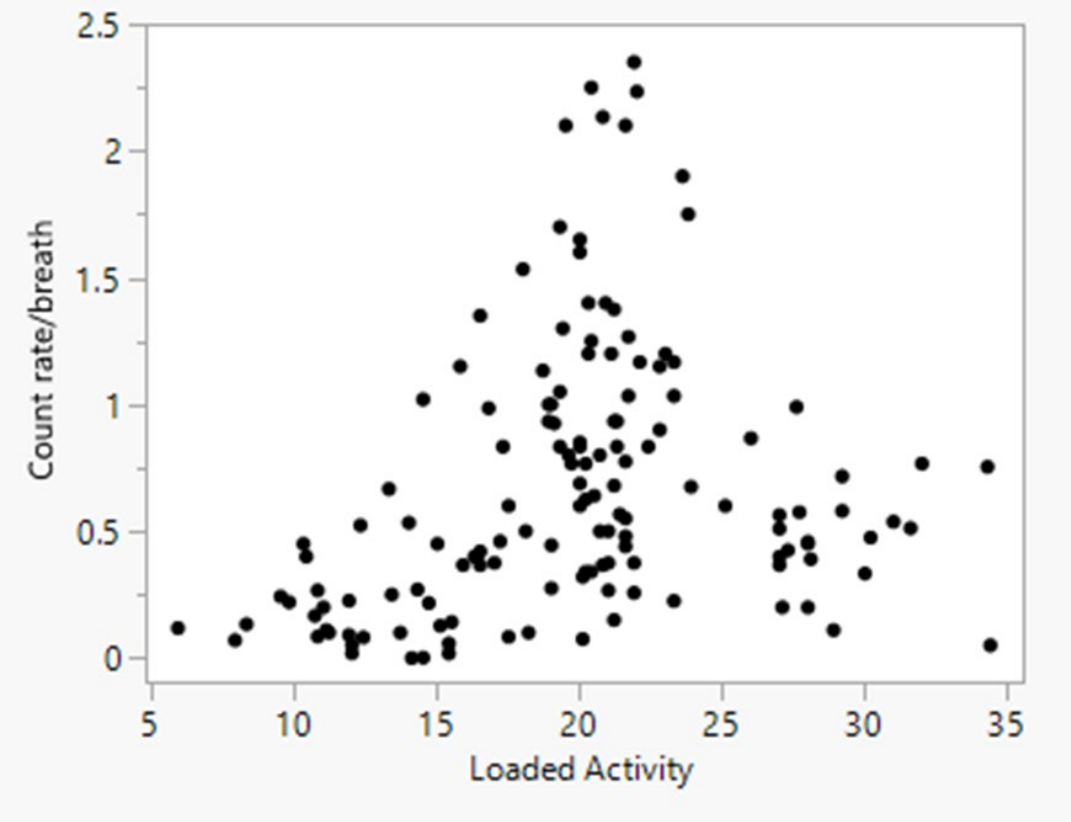
- *In view of the approval of DTPA aerosol, the results of study CYC-009, and postmarket experience with Technegas, we have no objection to using an appropriate count rate range as a source of feedback for Technegas administration. The recommended count rate in the DTPA PI is 833 to 1667 CPS and the 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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NDA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number	022335
Priority or Standard	Standard
Submit Date	March 26, 2020
Received Date	March 26, 2020
PDUFA Goal Date	June 26, 2021
Division/Office	DIRM/OSM
Review Completion Date	June 10, 2021
Established/Proper Name	Tc 99m carbon inhalation aerosol
(Proposed) 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	Complete Response
Recommended Indication/Population	TECHNEGAS is indicated for lung ventilation imaging in adults and pediatric patients 6 years of age and older for visualization of pulmonary ventilation and evaluation of pulmonary embolism when paired with perfusion imaging.

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Reviewers of Multidisciplinary Review and Evaluation

Regulatory Project Manager	Modupe Fagbami
Nonclinical Reviewer	Ronald Honchel, Ph.D.
Nonclinical Team Leader	Adebayo Laniyonu, Ph.D.
Nonclinical Division Director	Mukesh Summan, Ph.D.
Office of Clinical Pharmacology Reviewer/Team Leader	Christy John, Ph.D.
Office of Clinical Pharmacology Team Leader	Nam Atiqur Rahman, Ph.D
Clinical Reviewer	Gang Niu, M.D.
Clinical Team Leader	Anthony Fotenos, M.D., Ph.D.
Statistical Reviewer	Jyoti Zalkikar, Ph.D.
Deputy Division Director DBI	Sue-Jane Wang, Ph.D.
Cross-Disciplinary Team Leader	Anthony Fotenos, M.D., Ph.D.
Division Director (DIRM)	Libero Marzella, M.D., Ph.D.
Deputy Office Director (OSM)	Alex Gorovets, M.D.
Office Director (OSM)	Charles Ganley, M.D.

Additional Reviewers of Application

OPQ Branch Chief	Danae Christodoulou, Ph.D.
OPQ Quality and Substance	Anne Marie Russell, Ph.D.
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DPMH (Maternal) Reviewer	Jane Liedtka, M.D.
DPMH (Maternal) Team Leader	Miriam Dinatale, M.D.

Abbreviations: CDRH, Center for Devices and Radiological Health; CMC, chemistry, manufacturing, and controls; DMEPA, Division of Medication Error Prevention and Analysis; DIRM, Division of Imaging and Radiological Medicine; DPMH, Division of Pediatric and Maternal Health; DRISK, Division of Risk Management; OB, Office of Biostatistics; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
Cps	counts per second
CT	computed tomography
CTPA	computed tomography pulmonary angiography
DIRM	Division of Imaging and Radiological Medicine
DPMH	Division of Pediatric and Maternal Health
DPVII	Division of Pharmacovigilance II
DTPA	diethylenetriaminepentaacetate
EANM	European Association of Nuclear Medicine
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
ESC	European Society of Cardiology
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GEE	generalized estimating equation
IND	investigational new drug
iPSP	initial pediatric study plan
MBq	megabecquerel
mCi	millicurie
MDCT	multidetector computed tomography
mSv	millisievert
NDA	new drug application
NME	new molecular entity
NPA	negative percent agreement
OCP	Office of Combination Products
OSHA	Occupational Safety and Health Administration
OSM	Office of Specialty Medicine
PA	percent agreement
PAS	Patient Administration Set
PE	pulmonary embolism
PEL	permissible exposure limits
PK	pharmacokinetics
PPA	positive percent agreement
PPV	positive predictive value

ROI	regions of interest
SAE	serious adverse event
SAP	statistical analysis plan
SPECT	single photon emission tomography
TP	TechnegasPlus
V/Q	ventilation/perfusion

1. Executive Summary

1.1. Product Introduction

Technegas is a radiopharmaceutical imaging agent intended for ventilation imaging of the lungs. When inhaled, Technegas distributes to areas of the lungs that are ventilated, where it can be imaged and visualized using a gamma camera. Areas of the lungs that are visualized correspond to ventilated segments.

Technegas is a structured dispersion of Technetium-99m-labeled carbon. Technegas formation is achieved by using a (b) (4) carbon crucible, loaded with sodium pertechnetate (Tc-99m) injection. Technegas is produced at the point of use by the TechnegasPlus (TP) device and is delivered to patients using a separate Patient Administration Set (PAS). For ventilation/perfusion (V/Q) imaging, Technegas distributes into the bronchoalveolar regions and remains in place sufficiently long to collect multiple views of the lungs enabling comparison to the perfusion images.

1.2. Complete Response

Please refer to your New Drug Application (NDA) dated March 23, 2020, received March 26, 2020, and your amendments, including major amendment received February 26, 2021, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for technetium Tc 99m carbon inhalation aerosol for oral inhalation use (Technegas).

We have completed our review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CHEMISTRY MANUFACTURING AND CONTROLS

1. You propose to market Technegas for lung ventilation scintigraphy after preparation at the point of use in the TechnegasPlus (TP) device based on instructions to load (b) (4) pertechnetate Tc 99m injection, USP. For the following reasons, your NDA lacks data to establish that Technegas is standardized at the point of delivery to patients across the range of recommended prescribing information.

    a. *Characterization and control of the aerosol drug*. In the current review cycle, the NDA has not provided adequate characterization of the aerosol, including aerosol composition, batch formula, batch data, stability data, identity, strength, purity, delivered dose, TP device yield, TP device duty cycle and TP device recertification period. You have not established aerosol critical quality attributes and specifications to ensure the identity, strength, quality, purity, or potency of

the drug product under 21 CFR 314.50(d)(ii)(a). This includes attributes, methods and acceptance criteria. To address this issue, you must develop a quality program to characterize and control your Technegas aerosol drug product. Validate your aerosol production method at the highest and lowest end of the radioactivity range that you load to the crucible and measure particle size distribution, radioactivity of the aerosol and yield of the aerosol in this range. Propose and describe analytical methods suitable for their intended purpose, with appropriate validation. Establish specifications and justify acceptance criteria for the critical product quality attributes based on data. Submit results from at least three production runs at the minimum and maximum radioactivity load of your range.

b. *Validation of the aerosol drug production preparation process and documentation*. To address this issue, as described in Issue #1a, provide aerosol batch data from validated analytical methods for at least three registration batches to support your commercial aerosol drug production and in-process controls at the minimum and maximum crucible load of sodium pertechnetate radioactivity. The batches must meet specifications and be prepared according to the proposed regulatory commercial process under the in-process controls using sodium pertechnetate injection solution supplied by the three manufacturers approved in the United States (Technelite, Ultra-TechneKow and Radiogenix). Revise your regulatory production process description as advised in the Discipline Review Letter sent December 7, 2020. As advised, implement the following revisions: remove (b) (4); include the volume and strength of the sodium pertechnetate injection solution loaded in the crucible; include the production percent yield based on batch data prepared at minimum and maximum range of radioactivity loaded in the crucible; and remove the statement, "(b) (4) ."

c. *Analytical methods to characterize the aerosol particle size distribution, radioactivity and the aerosol yield.* To address this issue, as outlined in Approvability Issue #1a, develop validated analytical methods suitable to characterize the aerosol drug particle size distribution, radioactivity and the aerosol yield. Due to the short expiry (10 minutes) and radioactivity of the aerosol, standard analytical methods for pharmaceutical aerosols may not be suitable for this product. Consequently, analytical methods may need to be developed for drug product quality. We refer you to published methods, such as those described by Pourchez et al in their article titled: "Generation and characterization of radiolabeled nanosized carbonaceous aerosols for human inhalation studies", J Aerosol Sci, 2013, 55, 1-11. For each method, submit the analytical method description and the method validation. We recommend that you partner with radiopharmaceutical drug development experts to develop and

validate your new methods and to submit the necessary documentation to the NDA to meet requirements of drug regulations.

d. *Control of a critical component of the radioactive drug substance (crucible).* In the current review cycle, the NDA has not provided adequate specifications for the crucible, on release or stability. Batch data, stability data and a postapproval stability protocol for the crucibles have been agreed upon but not provided. To address this issue, develop a quality program to characterize and control your crucible. Revise your crucible specifications as advised, submit crucible release and stability data that meet specifications, and submit a stability protocol for the crucible.

e. *Information regarding volatile organic compounds and* (b) (4) *in the TP device.* Provide details on the calculations performed in determining exposure doses and threshold values that were used in calculating margin of safety values for all detected chemicals. This information can be provided in tabulated form for instances where the same calculation was repeated; however, explanatory notes should be provided to describe and justify the selection of specific values including but not limited to measured analytical concentrations, exposure metrics (e.g., assumed maximum breathing volumes), conversion factors, toxicity threshold values, and uncertainty factors.

2. A NDA may not be approved if the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. During a recent inspection of the Cyclomedica Australia Pty Ltd (FE1#3009638066) manufacturing facility for this NDA, our field investigator observed objectionable conditions that were conveyed to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility. The following is a description of outstanding issues:

a. *Crucible manufacturing process and PAI*:

(b) (4)

b. Manufacturing of TP device (from application assessment):

i. Lack of acceptable final approved specifications and validated analytical release testing procedures to assure reliable and consistent Technegas production meeting approved specification for patient use
ii. Lack of supporting data to establish performance reliability of the TP device and the "contacts" as claimed in the operator's manual
iii. Inadequate process controls defined in annual certification program to ensure final drug product specifications are consistently met in absence of drug product functional testing

c. *Manufacturing and testing of final drug product (from PAI inspection)*

i. Control manufacturing and testing procedures have not been established to ensure reliable process control strategy for Technetium (Tc-99m) to ensure the final DP can be prepared consistently
ii. Exhibit batch records and approved production process and testing procedures for final drug product not available
iii. The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established or documented
iv. Specifications, reference standards, sampling plans of products manufactured by the firm not approved by Quality Control Unit. The specifications for the final drug product aerosol has not been approved for US market in the Quality system.
v. Master Batch record or exhibit batch records for final DP has not been generated or available for review during inspection. Especially, the yield of final drug product (actual and theoretical) has not been established under GMP controls
vi. Training deficiencies and analytical testing expertise identified during inspections

d. *Manufacturing of patient delivery device (from PAI inspection)*

i. Inadequate controls identified in testing procedure for PAS device QC testing
ii. Use of unvalidated manufacturing equipment for PAS manufacturing

CLINICAL

3. *Risk 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 complete response:

a. For each patient breathing method:
    i. Specify or estimate the proportion of CYC-009 subjects who used this method alone or in specific mixture of methods
    ii. Clarify the relationship to methods studied in other investigations, including NDA022335\0001\m5\54-lit-ref\lloyd-1994-2.pdf and NDA022335\0001\m5\54-lit-ref\james-1991c.pdf
    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

b. 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.

4. *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, USP, 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.

5. *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:
    a. Investigations reported in published literature.
    b. Post-market 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 CMC Issue #1.

2. Therapeutic Context

2.1. Analysis of Condition

The principal use of pulmonary ventilation imaging is as a component of lung scintigraphy for the evaluation of patients suspected of acute pulmonary embolism. For this use, ventilation imaging is combined with pulmonary perfusion imaging in the so-called ventilation/perfusion (V/Q) scan.

A 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. Clinically, PE commonly results from venous thromboembolism, especially from the veins of the lower extremities. The clinical presentation of acute PE ranges from shock or sustained hypotension to mild dyspnea. PE may even be asymptomatic and diagnosed by imaging procedures performed for other purposes (Agnelli and Becattini 2010). PE can cause death acutely or through chronic thromboembolism-induced pulmonary hypertension. Anticoagulation is the foundation of therapy for PE. Based on the rapidly changing pattern of perfusion in PE, imaging for PE diagnosis should be carried out as soon as possible, preferably within 24 hours after onset of symptoms (Bajc et al. 2019).

2.2. Analysis of Current Treatment Options

PE is suspected in all patients who present with new or worsening dyspnea, chest pain, or sustained hypotension without an alternative cause. In general, the diagnosis of PE follows a sequential workup consisting of clinical probability assessment, d-dimer testing, and multidetector computed tomography (MDCT) or V/Q scanning. Clinical probability for PE can be assessed by clinical prediction rules, foremost Wells' and the revised Geneva scores (Wells et al. 2000; Penaloza et al. 2011), which have been validated and recommended by the European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the European Society of Cardiology (ESC). Usually, patients are clinically stratified into two or three risk categories: unlikely/likely and low/intermediate/high likelihood of PE.

Plasma D-dimer is a breakdown product of fibrin clot. Although the specificity of D-dimer test is low, the test can be used to exclude PE in patients with either low to intermediate or unlikely clinical probability (Konstantinides et al. 2014). 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 recommended.

Computed tomography pulmonary angiography (CTPA) and V/Q imaging are the principal imaging modalities for PE diagnosis. CTPA requires intravenously injected iodinated contrast. Pulmonary emboli are visualized as filling defects within otherwise homogenously contrast filled pulmonary arterial branches. A PE located centrally in the pulmonary circulation can be detected by CTPA with a high positive predictive value (PPV). The PPV decreases at segmental

and subsegmental levels (Stein et al. 2006; Bajc et al. 2019). CTPA associated risks include radiation exposure and adverse reactions caused by the concomitant use of iodinated contrast.

As shown in Table 1, drugs approved for pulmonary ventilation studies include the inert gases Kr-81m, Xenon-133 and the aerosol ^{99m}Tc-diethylenetriaminepentaacetate (DTPA). Kr-81m has been withdrawn from the market for commercial reasons. Using Xe-133 ventilation, single-breath, wash-in or equilibrium, and washout images can be obtained, thus providing a full characterization of ventilation (Parker et al. 2012). The acquisition time for Xe-133 is limited and therefore the imaging views are limited. The imaging room for Xe-133 should be negatively pressured with appropriate exhaust for radioactive gas.

For DTPA aerosol, images can be obtained in multiple projections or with single photon emission tomography (SPECT) to match perfusion images. Delivery of DTPA aerosol requires a closed nebulizer. DTPA aerosol has the propensity to deposit in central airways that experience turbulent airflow (Bajc et al. 2009) especially in patients with chronic obstructive pulmonary disease (COPD) (Jogi et al. 2010).

Table 1. Reviewer's Tabulation of Radiopharmaceuticals Approved for Ventilation Scans

Product Name	Approval Date	Indication	Status
Xenon Xe 133 gas	10/10/1974	for the evaluation of pulmonary function and for imaging the lungs	On the market
Krypton Kr-81m Gas	06/12/1980	pulmonary ventilation studies to assess and evaluate regional pulmonary function in lung diseases	Withdrawn on 04/26/2001 (not for safety reasons)
DRAXIMAGE DTPA Tc99m pentetate	12/26/2017	lung ventilation imaging and evaluation of pulmonary embolism when paired with perfusion imaging in adult and pediatric patients.	On the market

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Technegas is a new molecular entity (NME).

3.2. Summary of Presubmission/Submission Regulatory Activity

The following is a summary of the regulatory history of Technegas relevant to this application:

- October 28, 1991: A 510(k) submission (K913416) for a patient administration set (PAS) classified as a radionuclide rebreathing system was cleared.
- July 24, 2001: investigational new drug (IND) 062660 was submitted for the development of Technegas.
- January 04, 2004: OCP issued a determination that Technegas is comprised of drug (Technegas) and device components (TechnegasPlus and PAS). January 04, 2004: OCP issued a determination that Technegas is comprised of drug (Technegas) and device components (the TP and PAS). CDER was assigned as the lead center for review.
- May 23, 2018: OCP notified the Applicant that the Technegas combination product was categorized as Type 7, separate products requiring cross labeling.
- December 15, 2008: The Applicant submitted a 505(b)(2) new drug applications (NDA) and was assigned NDA Number 22335.
- February 17, 2009: The Applicant withdrew the NDA prior to its filing date.
- November 15, 2016: Protocol Number CYC-009 under IND 062660 obtained Special Protocol Assessment-Agreement.
- October 22, 2019: Cyclomedica obtained an “Agreed Initial Pediatric Study Plan – Agreement” (Agreed iPSP), including a Planned Request for Partial Waiver and Planned Request for Deferral of Pediatric Study.
- March 26, 2020: NDA 022335 was resubmitted in the electronic Common Technical Document (eCTD) format.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Product Quality

See also 131-page Integrated Quality Assessment (IQA) archived May 28, 2021 and approvability issues (Issues #1a to #1d) in Section 1 of this review. The review team recommends a Complete Response. A summary rationale was provided in the IQA Executive Summary (excerpt):

> There are a multitude of issues remaining from the Discipline Review letter and several TCON's with the Applicant that remain unresolved. In essence, all of this distills down to lack of characterization of the aerosol (containing 99mTc-Carbon Particles) that precludes an understanding of what a patient is getting for strength during its inhalation in terms of both radioactivity and particle size distribution. Only from sufficient characterization can there be derived meaningful and robust quality controls of the aerosol.
>
> Because of this lack of characterization of the aerosol, the alternative has been to rely on in-process controls constituting both device components and what can be gleaned from the starting amount of Sodium Pertechnetate Tc 99m Injection and the (b) (4) reports for particle size distribution. What has confounded this are the unrealistic nature of the measurements from validation studies. Needed are measurements at the mouthpiece which basically is analogous to strength for a drug dose. Response to this issue (in subsequent TCON's with the Applicant) have led to further problems involving how the measurements of particle size distribution and radioactivity were done…
> The issues that compose the overall lack of characterization of the aerosol can be divided into four major categories that make up the basis for the non-approvability of the NDA . The first has already been described in the foregoing summary (inadequate characterization of the aerosol) and includes e.g., composition, particle size distribution, radioactivity per particle or other appropriate measure, delivered dose uniformity, and other documentation (batch formula, batch data, etc.). The second is an insufficient validation of the aerosol manufacturing process and documentation (absence of batch data from validated analytical methods – critical for quality controls since reliance is on in-process controls). Thirdly is insufficient analytical methods to characterize the aerosol particle size distribution and radioactivity, along with the aerosol yield. The fourth approvability issue is an insufficient control of critical components (namely the carbon crucible) that produce the radioactive drug substance (99mTc-Carbon Particles).

The IQA includes a Manufacturing and Facility Assessment summarizing multiple inspectional issues outstanding as of May 28. See also approvability issues (Issues #2a to #2d) in Section 1 of this review.

4.2. Devices and Companion Diagnostic Issues

A multi-disciplinary CDRH review team was consulted throughout the review cycle and primarily collaborated with the OPQ review team, reflecting the tight nexus between drug and device components of this combination drug product. See also the Consulting Memorandum archived June 8, 2021 and approvability issues (Issue #1e) in Section 1 of this review regarding missing information on volatile organic compounds and (b) (4) in the TP device.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Technegas is Tc-99m sodium pertechnetate enclosed in a carbon nanoparticle sphere. Pending CMC corroboration, the medium particle size for Technegas is less than (b) (4) nm. The nonclinical study report that evaluated Technegas particles was a rat biodistribution study. Technegas is considered a microdose product because the clinical mass dose is less than 100 µg. Nonclinical studies to evaluate absorption, distribution, metabolism, excretion (ADME), pharmacokinetics (PK), genetic toxicology, carcinogenicity, and reproductive and developmental toxicology are not typically required for microdose radiopharmaceutical applications as described in the Guidance "Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations" (https:www.fda.gov/media/107641). However, this microdose radiopharmaceutical application is notable because the drug product is a nonpharmacologically active, technetium 99m labelled carbon nanoparticle in argon gas, the route of administration is inhalation, and the mechanism of action is mediated by the physiologic distribution and localization of the product determined by the aerodynamic function of the bronchoalveolar tree. Taking these factors into consideration the pharmacology/toxicology reviewer concurs that nonclinical studies evaluating absorption, metabolism, excretion, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology are not needed. A single-dose general toxicology study in a rodent species is typically recommended before initiation of clinical studies for a microdose radiopharmaceutical intended to be administered once or infrequently. The Applicant provided a justification for not conducting a general toxicology study of Technegas. The evaluation of the Applicant's justification is discussed below.

Technegas particles are administered via inhalation with the distribution determined by particle size and the patency of the bronchoalveolar tree. Larger particles are localized in the upper airway whereas particles less than 500 nm in diameter are distributed into the bronchoalveolar regions similarly to inhaled gases. The mechanism of action of Technegas is essentially based on its distribution in the lungs as a function of the aerodynamics of the bronchoalveolar tree. In a rat biodistribution study, inhaled Technegas remained in the lungs with no apparent redistribution for 24 hours following administration.

Toxicology studies have not been performed using Technegas. The technetium 99m radionuclide is enclosed in the graphite shell. While there is radiation exposure as a result of the technetium radionuclide, there is no clinically relevant chemical exposure to technetium. The radiation absorbed dosage of Technegas has been addressed in clinical dosimetry studies. The graphite shell component of Technegas are cleared from the lung via macrophage phagocytosis and removal via the "mucociliary escalator" (a term used to describe the process whereby particles within the lungs are trapped within mucus; cilia then moves the particle-containing mucus up and out of the lungs). However, even relatively nontoxic particles can elicit chronic pulmonary inflammatory responses if the mucociliary escalator becomes overloaded or the patient has underlying lung disease that does not allow for the mucocilliary cells to function properly. For the evaluation of the risks posed by the graphite shell of

Technegas, nonclinical studies of graphite dust are informative. Graphite dust is an occupational health concern and nonclinical studies evaluating the safety of inhaled graphite dust have been reported in the literature. These studies are not adequately designed for evaluating drug safety but did allow the U.S. Occupational Safety and Health Administration (OSHA) to establish permissible exposure limits (PEL). The U.S. OSHA maximum total work average (TWA) PEL for synthetic graphite is 15 mg/m^3 for total dust exposure and 5 mg/m^3 for the respirable fraction of total dust exposure. The mass dose of synthetic particles in a liter of Technegas is estimated to be 15 to 17.6 µg which converts to 15 to 17.6 mg/m^3 concentration of synthetic particles in a 1 L bag of Technegas. Even making a conservative assumption that a patient is exposed to Technegas synthetic particles for 1 minute at a concentration of 17.6 mg/m^3, the average exposure over a 480 minute work day is 0.037 mg/m^3 (17.6 mg/m^3 x 1 min/480 min), approximately 130-fold lower than the OSHA maximum TWA PEL. The Applicant's justification for not performing general toxicology studies is that the mass dose of the Technegas particles is much lower than the daily PEL recommended by the U.S. OSHA for the respirable fraction of graphite particles in total dust exposure. The nonclinical team considers the justification provided by the Applicant for the safety of the proposed clinical mass dose adequate and concurs that additional nonclinical toxicology studies of Technegas are not needed.

The nonclinical review discipline recommends approval of the application.

5.2. ADME/PK

Type of Study	Major Findings
Absorption	N/A
Distribution	N/A
Metabolism	
Biodistribution Studies of Technegas (Tc-99m Labeled Carbon Particles) Given by Three Different Routes of Administration (Study # CYC081213-1)	In a rat biodistribution study, inhaled Technegas remained in the lungs with no apparent redistribution for 24 hours following administration.
Excretion	N/A
TK data from general toxicology studies	N/A
TK data from reproductive toxicology studies	N/A
TK data from Carcinogenicity studies	N/A

Abbreviations: N/A, not applicable; TK, toxicokinetic

6. Clinical Pharmacology

6.1. Executive Summary

Technegas is a dispersion of Tc-99m labeled carbon particles prepared in the TP device. The system converts sodium pertechnetate Tc-99m to Tc-99m labeled carbon particles dispersed in argon gas. Pending CMC corroboration, technetium labeled carbon particles have a median equilibrium particle size of less than (b) (4) nanometers.

The carbon crucible is loaded with (b) (4) megabecquerels (MBq) ((b) (4) mCi) sodium pertechnetate. Technegas aerosol is inhaled 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 1500 to 2500 counts per second in the posterior projection as measured with a gamma camera.

The distribution of the inhaled particles is determined by the aerodynamic function of the lungs. After inhalation, part of the carbon particles may be localized in the upper and central airways. Particles localized in the upper airways are cleared from the lungs by the bronchociliary elevator toward the mouth. A clinical study report estimated that the lung radioactivity ranged from 9.25 to 63.5 MBq and the radioactivity in the mouth plus upper airway ranged from 0.14 to 2.30 MBq.[1] Technegas particles that reach the pulmonary alveoli adhere to the walls of the alveoli and remain in the lungs without clearance across the alveolar capillary membrane. Other particles, after swallowing, are eliminated through the gastrointestinal tract without absorption. Elimination of radioactivity is by the physical decay of technetium-99m.

A dosimetry study was conducted to calculate the radiation absorbed doses to various organs using OLINDA software. The dose limiting organ is the lungs at 0.085 millisieverts (mSv)/MBq. If 50 MBq is administered, that equates to a radiation exposure of 4 mSv. The effective dose was estimated to be 1.34E-02+1.22E-03 mSv/MBq (4.96E-02+4.53E-03 rem/mCi).

The review issues with specific recommendations and comments are summarized below:

[1] NDA022335\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\ (b) (4) report\ 5332- (b) (4) -report.pdf

6.1.1. Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The Applicant conducted a clinical study (CYC-09) to compare Technegas® and Xenon 133 planar lung imaging in subjects referred for ventilation scintigraphy. Study CYC-009 met its the primary efficacy endpoint of percent agreement between Xe-133 and Technegas three blinded readers' ventilation assessments of matching image views from 200 adult patients. Further evidence for support of effectiveness was based on a literature report (Miles et al. 2009) which reported a high degree of agreement (PPA=95%, NPA=94%) between Technegas SPECT V/Q with CT pulmonary angiography for PE diagnosis (n=100).
General dosing instructions	A radioactivity of (b) (4) MBq ((b) (4) mCi) sodium pertechnetate is loaded in the crucibles. Technegas aerosol is inhaled 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 with a gamma camera. Pending CMC corroboration, this equates to approximately 1.1 mCi (40 MBq). For pediatric patients 6 years of age and older, Technegas is inhaled until a lung count rate between 500 and 1000 composite performance score (cps) is obtained.

Abbreviations: CT, computed tomography; MBq, megabecquerel; mCi, millicurie; NPA, negative percent agreement; PPA, positive percent agreement; SPECT, single photon emission tomography; V/Q, ventilation/perfusion

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Technegas is a dispersion of Tc-99m-labeled carbon particles prepared in the TP device. Technegas formation is achieved by using a carbon crucible loaded with sodium pertechnetate ($Na^{99m}TcO_4$). The Tc-99m sodium pertechnetate is first evaporated to dryness using heating in the presence of argon. Technegas particles are formed by rapidly heating the crucible to approximately 2750°C in an atmosphere of 99.99% argon. The particles reach an equilibrium size distribution with a median size less than 500 nanometers.

Following inhalation, Technegas distributes to normally ventilated regions of the lungs. Initial deposition into the lungs is monitored by placing a gamma camera over the lungs and having the patient inspire Technegas until a desired count rate for pulmonary imaging is achieved.

Dosimetry: Clinical study VM-002-01 was a Phase 1, open-label, multicenter study to evaluate the biodistribution and radiation dosimetry of Technegas for lung ventilation imaging in subjects referred for Technegas as part of their standard care or with a known lung condition. Biodistribution was determined using serial whole-body imaging in eight of the 12 enrolled subjects starting just after inhalation and repeated over the next 24 hours. Whole body scans were collected from anterior and posterior views simultaneously. A marker calibration source was included in the camera field of view for all scans.

As an internal control against counting non-administered activity, a background scan was done without the subject in the room after all the scans were completed on Day 0. The calibration marker was not included in the background scan. A second background scan was done prior to

subject arrival for the 24-hour scan on Day 1. After the 24-hour scan, each subject was injected with Tc-99m macroaggregated albumin and underwent a whole-body scan to serve as a counting efficiency standard in the event that extrapulmonary activity was observed on the serial Technegas whole body scans.

The percent of injected activity was determined by constructing regions of interest (ROI) on the images and integrating the radioactivity in each ROI for each of the whole-body images. Activity was quantified using geometric mean calculations, and distributions of activity in different body regions over time were calculated.

Data were analyzed using a compartment model, followed by a calculation of organ dose. The data analysis and dosimetry calculations were performed by OLINDA method. The data were entered into the OLINDA/EXM software, using the adult male model, and standard dose estimates for this model were reported.

Radioactivity in whole body and lungs was usually well fit with a single exponential term that represented only physical decay of Tc-99m. All subjects had visible amounts of radioactivity in the gastrointestinal tract (1.2% to 6% of administered activity); a few subjects had visible activity in the oral cavity and esophagus. In a few cases, lung activity was better fit with two exponential terms. In three subjects, minor amounts of activity were seen in thyroid, salivary glands, and urinary bladder, possibly indicating the presence of free Tc-99m pertechnetate. These values were a fraction of a percent of the administered activity and did not greatly influence the dose calculations. The biodistribution showed no translocation of particulates into the systemic circulation during the 24-hour study period.

Table 2. Dosimetry Estimates for Inhaled Technegas Calculated From Human Biodistribution Data

	Average	
	mSv/MBq	rem/mCi
Adrenals	6.58E-03	2.43E-02
Brain	9.09E-04	3.36E-03
Breasts	6.10E-03	2.26E-02
Gallbladder Wall	3.27E-03	1.21E-02
Lower Large Intestine Wall	3.82E-03	1.41E-02
Small Intestine	3.31E-03	1.23E-02
Stomach Wall	4.84E-03	1.79E-02
Upper Large Intestine Wall	5.29E-03	1.96E-02
Heart Wall	1.14E-02	4.20E-02
Kidneys	2.67E-03	9.89E-03
Liver	5.68E-03	2.11E-02
Lungs	8.49E-02	3.14E-01
Muscle	3.10E-03	1.15E-02
Ovaries	2.04E-03	7.54E-03
Pancreas	5.41E-03	2.00E-02
Red Marrow	3.57E-03	1.32E-02
Osteogenic Cells	6.36E-03	2.35E-02
Skin	1.53E-03	5.64E-03
Spleen	4.93E-03	1.83E-02
Testes	8.37E-04	3.09E-03
Thymus	7.57E-03	2.80E-02
Thyroid	7.43E-03	2.75E-02
Urinary Bladder Wall	1.86E-03	6.87E-03
Uterus	1.75E-03	6.46E-03
Total Body	4.38E-03	1.62E-02
Effective Dose Equivalent	1.47E-02	5.44E-02
Effective Dose	1.34E-02	4.96E-02

Source: NDA022335\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diagnosis-pe\5351-stud-rep-contr\vm-002-01\csr\vm-002-01-csr.pdf
Abbreviations: MBq, megabecquerel; mCi, millicurie; mSv, millisievert

Absorbed radiation doses assuming an administered dose of 40 to 50 MBq Technegas are acceptable. The dose limiting organ is the lungs at 0.085 mSv/MBq. For a 50 MBq dose, that equates to a radiation exposure of 4 mSv. The effective dose was estimated to be 1.34E-02+1.22E-03 mSv/MBq (4.96E-02+4.53E-03 rem/mCi).

General Dosing and Therapeutic Individualization

General Dosing

The amount required for imaging is 1.5 to 2.5 kcps in the posterior projection as measured with a gamma camera.

Table 3 estimates the number of breaths required to deliver the recommended dose of Technegas based on an estimated yield of 30% with an average volume breath per adult patient at 500 ml per inspiration.

Table 3. Estimated Number of Breaths Required to Deliver Recommended Dose of Technegas

(b) (4)

(b) (4)

Source: NDA022335\0014\m1\us\111-info-amend\1-11-1-cmc-response.pdf
Abbreviations: MBq, megabecquerel; mCi, millicurie

For pediatric patients 6 years and older, Technegas is inhaled until a lung count rate between 500 and 1000 counts per second is obtained.

The inhaled radioactivity is subject to large variations depending on patient's compliance and inhalation capabilities.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The distribution of the aerosol is determined by the aerodynamic function of the lungs.
Active Moieties	Tc-99m labeled carbon particles are the active moieties.
QT Prolongation	Evaluation is not needed. This is a single dose administration via inhalation route. There is no systemic absorption of Tc-99m labeled carbon particles.

General Information	
Bioanalysis	There are no bioanalytical methods. In literature articles, the amount of free pertechnetate was determined by ITLC and was used to distinguished free Tc-99m from Tc-99 labeled carbon particles.
Drug exposure after first dose	There is no systemic absorption of Tc-99m labeled carbon particles.
Drug total exposure at steady state	Not applicable
Minimal effective dose or exposure	The effective dose is 1500-2500 cps in the lungs for adults and 1000-1500 cps in the lungs for pediatric patients
Accumulation	Not applicable as Technegas is a product for single administration.
Distribution	**N/A**

Elimination	
Clearance	
Mean terminal elimination half-life	The biodistribution of inhaled Technegas showed no translocation of particulates into the systemic circulation during the 24-hour study period. Radioactivity is eliminated by the physical decay of Tc-99m ($t_{1/2}$=6 hrs).
Metabolism	
Primary metabolic pathway(s)	N/A
Inhibitor/Inducer	No human drug interaction studies are needed.
Excretion	
Primary excretion pathways (% dose)	Elimination of radioactivity is by the physical decay of technetium-99m. The carbon particles are removed by phagocytosis.

Abbreviations: ITLC, instant thin layer chromatography; N/A, not applicable; $t_{1/2}$, half-life

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant conducted a clinical study to compare Technegas and Xenon 133 planar lung imaging in subjects referred for ventilation scintigraphy. Further support of effectiveness was based on a literature report which reported a high degree of agreement between Technegas SPECT V/Q with CT pulmonary angiography for PE diagnosis (Miles et al. 2009).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Pending CMC corroboration, the proposed dosing regimen may be appropriate for the general patient population for which the indication is sought.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 4. Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ Schedule/Route	Key Objectives	Sample Size	Study Population	No. of Centers and Countries
Controlled studies to support efficacy and safety						
CYC-009	Applicant-conducted within-subject noninferiority trial of Technegas ventilation imaging compared to Xe-133 ventilation imaging.	Inhalation of Technegas to reach 1500-2500 cps Inhalation of Xe-133 gas in accordance with the standard of care	Demonstrate noninferiority of Technegas compared with Xe-133 V/Q planar imaging studies	200	Subjects who have been referred for ventilation scintigraphy for any medical reason	10 (U.S.)
(Miles et al. 2009)	A prospective, observational study to compare SPECT ventilation/perfusion scintigraphy with multislice CT pulmonary angiography (CTPA)	Technegas cps target not reported; 185 MBq (5 mCi) ^{99m}Tc-macro-aggregated albumin (MAA)	Evaluate the agreement between CTPA and SPECT V/Q scintigraphy for the diagnosis of pulmonary embolism (PE)	100	Patients with suspected acute PE	1 (Australia)

Trial Identity	Trial Design	Regimen/ Schedule/Route	Key Objectives	Sample Size	Study Population	No. of Centers and Countries
Additional studies to support efficacy						
(Jogi et al. 2010)	A head-to-head study to investigate differences in ventilation studies performed with 99mTc-DTPA and Technegas in patients referred for V/Q SPECT mainly for diagnosis of PE and in a second group of patients with known COPD	Inhalation of Technegas to reach 30 MBq in the lungs as measured by a collimated Geiger-Muller tube monitor over the chest; IV injection of 100-120 MBq of ^{99m}Tc-MAA	Investigate differences in ventilation studies performed with 99mTc-diethylenetriaminepenta acetate (DTPA) and Technegas	63	35 patients referred for a V/Q SPECT to evaluate clinically suspected PE (n=29), to evaluate alveolitis (n=3) or to evaluate lung function before surgery or after transplantation (n=3); 30 patients with known COPD	1 (Sweden)
(Weinmann et al. 2008)	A study to determine the usefulness of SPECT in patients with suspected acute PE and a nondiagnostic V/Q lung scan, using combination of CT and lower-limb ultrasound as the standard of reference	"Inhalation of 445 to 555 MBq ^{99m}Tc- Technegas" (likely referring to loaded pertechnetate dose) over 3-5 respiratory cycles; 300 MBq ^{99m}Tc- MAA	Assess the usefulness of tomography in patients in whom planar lung scan performed as a first imaging test was not contributive	95	Patients with suspected acute PE and nondiagnostic planar lung scintigraphy	1 (France)

Trial Identity	Trial Design	Regimen/ Schedule/Route	Key Objectives	Sample Size	Study Population	No. of Centers and Countries
Controlled studies to support safety						
VM-002-01	Applicant-conducted, open-label, multicenter study in adults referred for a ventilation study as part of standard care or for a known lung condition	Technegas: 1500-2000 counts/sec	Evaluate biodistribution, calculate radiation dosimetry, valuate safety	12	Adults referred for a ventilation study	2 (Australia)
VM-001-01	Applicant-conducted, multicenter, randomized, crossover study in adults who required ventilation scintigraphy as part of standard care, including those with suspected PE, COPD, and lung cancer undergoing pre-surgical evaluation for lung reduction or lung resection	Technegas: 1500-2000 counts/sec Tc-99m DTPA: 1500 2000 counts/sec (27-4300 MBq)	Compare Technegas with Tc-99m DTPA aerosol ventilation images And evaluate the safety of Technegas	124	Adults who required ventilation scintigraphy	9 (Australia, Canada)
CYC-008	Applicant-conducted, multicenter, nonrandomized, single-blind, crossover, within-subject study in adults with suspected PE	Technegas: 1500-2500 counts/sec	Compare Technegas V/Q SPECT imaging with Xe-133 V/Q planar imaging for the diagnosis of PE and evaluate the safety of Technegas	12	Adults with suspected PE	4 (U.S.)

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; IV, intravenous; MBq, megabecquerel; mCi, millicurie; SPECT, single photon emission tomography; V/Q, ventilation/perfusion

7.2. Review Strategy

The review team mainly relied on the interim analysis of the Applicant-conducted phase 3 study (CYC-009) and the re-analysis of data published in Miles et al. (2009) for efficacy assessment. The data published by Jogi et al. and Weinmann et al. were reviewed for additional supportive efficacy assessment (Weinmann et al. 2008; Jogi et al. 2010). Safety assessment for this submission is based on pooled analysis of four clinical studies performed by the Applicant.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

This is a 505(b)(2) New Drug Application. The Applicant conducted two studies (CYC-008 and CYC-009) with design details summarized in Table 5. The Applicant submitted the interim analysis efficacy report of study CYC-009 during the NDA review period.

Table 5. Summary of Prospective Trials

Trial ID	Design	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
CYC-008	MC, NR, OL, WS, BR, ST- Clinical follow-up, AC-Noninferiority with Xe-133	750 planned,18 enrolled, 12 completed	Primary: Sensitivity, Specificity; noninferiority margin of 10%	Early Termination due to challenges with enrollment and study-design changes. Efficacy assessments were not performed.
CYC-009	MC, NR, OL, WS, BR, agreement (concordance) with Xe-133	240 planned, 200 enrolled, 200 completed*	Primary: agreement with Xe-133 for pulmonary ventilatory distribution	Ongoing at time of NDA submission

Source: NDA 022335 Clinical overview, Table 2.5.5-1 and primary statistical reviewer.
* The interim analysis report was submitted during the NDA review period.
Abbreviations: AC, active-controlled; BR, blinded review of images; MC, multicenter; NR, nonrandomized; OL, open-label; WS, within subject; ST, Standard of Truth

8.1.1. Study 1 CYC-009

Study Population

Subjects are males and females at least 18 years of age who have been referred for ventilation scintigraphy for any medical reason.

Enrollment:

Inclusion Criteria:

- Male or female subject at least 18 years of age.
- Subject is a candidate for ventilation imaging.
- Subject must be willing and able to provide informed consent.
- Subject must be stable and able to undergo Xe-133 planar imaging and Technegas planar imaging.
- Subject must be willing and agree to complete all study procedures, including 24-hour follow-up safety assessments, physical examination and clinical laboratory evaluations.
- Subject is using adequate birth control, if female and fertile. Adequate birth control is defined as surgical sterilization, hormone contraceptive use or intrauterine device.
- Female subject has a negative urine or serum pregnancy test.

- Subject has had or is scheduled to have a chest X-ray within 24 hours prior to the investigational imaging study.

Exclusion criteria:

- Subject has been administered any other radiopharmaceutical within a timeframe that might cause interference with study imaging.
- Subject is a pregnant or lactating female.
- Subject has received Technegas in the past.
- Subject has received an investigational drug within 30 days prior to dosing.
- Subject is hemodynamically unstable.

Trial Design

- Xe-133 planar imaging followed by Technegas planar imaging within 24 hrs.
- Xe-133: posterior/posterior oblique imaging views or anterior/posterior imaging views during wash-in and wash-out
- Technegas: 6 view image set: anterior, posterior, left posterior oblique, right posterior oblique, left anterior oblique, and right anterior oblique.
- 3 blinded readers for efficacy assessment
- 240 subjects planned, 200 subjects had been completed as of June 15, 2020.
- The readers underwent training and independently performed the blinded read of images according to protocol specifications. In each reading session, a reader was blind to all clinical information except the chest X-ray required for the study. At the start of each case read, with the aid of the subject's chest X-ray, a reader visually divided each lung into three regions of approximately equal size arranged craniocaudally and designated as the right apical, left apical, right mid, left mid, right basal, and left basal regions. The reader then assessed each lung region for ventilation, assigning the region a ventilation score on a three point scale:

0 = absent ventilation

1 = decreased ventilation

2 = normal ventilation.

If a lung region was completely obscured (as a result of pleural effusion, for example), or if a lung region was completely absent as a result of lung resection, the region was to be given a score of 99 to indicate that ventilation cannot be assessed.

Study Endpoints

The primary efficacy endpoint is the percent agreement between Technegas and Xe-133 obtained from blinded readers' ventilation assessments of matching image views.

Secondary efficacy endpoints:

1. Percent agreement between Technegas and Xe-133 obtained from blinded readers' ventilation assessments of all image views acquired with Technegas (i.e., not limited to the matched image views).
2. Percent agreement between Technegas and Xe-133 for the subgroups of subjects with and without pleural effusion as noted in subjects' chest X-rays, from blinded readers ventilation assessments.
3. Percent agreement measuring interobserver agreement between pairs of blinded readers for their Technegas ventilation scores and for their Xe-133 ventilation scores.
4. By lung-region kappa statistics measuring interobserver agreement between pairs of blinded readers for their Technegas ventilation scores and for their Xe-133 ventilation scores.

Statistical Analysis Plan

At the time of development of the study protocol for CYC-009, Xenon 133 (Xe-133) was the only approved pulmonary ventilation imaging agent commercially available in the United States. Technegas clinical development focused on a structure delineation indication for use in ventilatory scintigraphy. The primary efficacy objective of Study CYC-009 was to demonstrate the efficacy of Technegas compared to Xenon 133 (Xe-133) using planar scintigraphic imaging with respect to pulmonary ventilatory distribution in subjects that are candidates for ventilation imaging. Efficacy hypotheses for Study CYC-009 were developed through Study CYC-010.

In Study CYC-010, six blinded readers read 75 Xe-133 planar ventilation images in two read sessions separated by a minimum of 4 weeks. The readers scored the six regions of the lung using the same ventilation scoring metric to be used in CYC-009 study protocol, which was as follows: at the start of each case read, with the aid of the subject's chest X-ray, a reader visually divided each lung into three regions of approximately equal size arranged craniocaudally and designated as the right apical, left apical, right mid, left mid, right basal, and left basal regions. The reader then assessed each lung region for ventilation, assigning the region a ventilation score on a three-point scale. The two sets of assessments from the read and reread of the Xe-133 images were used to derive a measure of agreement between successive reads of Xe-133 lung scans for each of the readers as follows: For each subject's six lung regions, if the read and reread of Xe-133 image ventilation scores are the same, the region is assigned an agreement score of 1, otherwise it is assigned a score of 0 for no agreement. These binary agreement scores are used to provide an estimate of overall percent agreement between read and reread of XE-133 images. The compilation of the six readers' estimates were then used to establish a 95% tolerance interval for the population of readers. The lower bound of the tolerance interval was 62%. Since Xe-133 is an approved agent, it by default was considered noninferior to itself, and hence the read/reread results provided a suitable limit for establishing the (noninferiority) threshold of measure of agreement between Technegas and Xe-133. When comparing Xe-133 and Technegas (matched views) images, a small percentage of subjects were expected to show discrepancies. To account for this, a small adjustment was made to the threshold of overall

percent agreement obtained from CYC-010 study from 62% to 60%. Thus, the following efficacy hypotheses were generated for Study CYC-009:

- H_o: percent agreement (PA) ≤ 60% versus H_a: PA > 60%

In the case of a missing ventilation score (score = 99), the binary agreement score was determined as follows: If both Technegas and Xe-133 scores were missing for the region, the binary agreement score was missing for the region. If the score was missing for one of the imaging modalities and not the other, then the region was assigned a score of 0 for no agreement.

The blind-read methodology was as follows: The read of the patients was performed in five (5) batches of 40 patients. For each batch:

1. First, the Xe-133 planar ventilation images were presented in a random order, and the image set for each case was uniquely identified by a five-digit random code number, which the reader entered into an electronic case report form (eCRF).
2. Viewing all the Xe-133 image views together with the chest X-ray for a case, the reader visually divided the right and left lungs into three regions of approximately equal size as described above and then assessed (and entered into the eCRF) a single ventilation score for each of the six lung regions.
3. Following the completion of the Xe-133 assessments and in a separate reading session, the same reader assessed the Technegas planar ventilation images. The image sets for the 40 cases were again presented in a random order but an order distinct from the order of presentation of the Xe-133 scans.
4. Two sequential reads of Technegas ventilation images were conducted for each case. First, together with the chest X-ray for the case, a reader was presented with the subset of ventilation image views that matched the views acquired with Xe-133 for the case (Technegas matched view set). The matched view set was uniquely identified by a five-digit random code number, which the reader entered into an eCRF. In the same manner as the Xe-133 assessment, the reader visually divided each lung into three regions of approximately equal size; then assessed (and entered into eCRF) a single ventilation score for each of the six lung regions.
5. Following submission of the matched view scores for a case, the reader was immediately presented with the complete Technegas image set (Technegas all view set) for the case, also uniquely identified by a five-digit random code number, which the reader entered into the eCRF. Visually dividing the lungs into the same six regions, the reader entered a second ventilation score for each region into the eCRF. If the second ventilation score for a region differed from the matched view score, the reader was asked to document the basis for the changed score.

In this blind-read methodology, the sequence of Xe-133 image-reads and Technegas image-reads was fixed (Xe-133 first and then Technegas) and not randomized.

Subjects who completed Xe-133 and Technegas ventilation imaging, and the images are of interpretable quality, formed the Full Analysis Set (FAS) for efficacy analysis. For FAS

population, each blinded reader's agreement scores for the subjects' lung regions were to be analyzed to determine an overall estimate of PA for each of the 3 blinded readers.

The "win" criterion of CYC-009 was that if at least for two of three readers, the lower boundary of the 95% confidence interval for PA is greater than 60%, Technegas would be considered efficacious for the measurement of pulmonary ventilatory distribution. The planned sample size for the study was 240 subjects. This sample size provided 90% power to establish that percent agreement between the blinded read assessments of Xe-133 and Technegas is better than 60%, assuming an expected true level of PA of 70%.

The Full Analysis Set would be the primary efficacy analysis data set. The Per Protocol Set would be a secondary data set for analysis of efficacy data.

Protocol Amendments

Study CYC-009 was ongoing at the time of the NDA submission. At this time, at odds with the SPA, the Applicant intended for the review team to rely only on published literature for efficacy. The review team thus introduced the concept of interim analysis with alpha-spending function including futility analysis, sent the details of the review team's recommendations to the Applicant and held a teleconference on July 23, 2020. The Applicant agreed to all the recommendations made by FDA and submitted the statistical analysis plan (SAP) addendum on September 17, 2020. According to that SAP addendum, the proposed interim analysis to assess efficacy objectives, based on completed blinded reads of 200 subjects who completed the study, was planned prior to data unblinding. The O'Brien-Fleming alpha-spending function was proposed: the interim analysis would use a one-sided 0.0141 alpha (or 0.0282 alpha two-sided) based on 200 subjects and the final analysis would use a one-sided 0.0210 (or 0.0420 alpha two-sided) based on 240 subjects if no statistical conclusion on PA at the interim analysis could be rendered.

8.1.2. Study Results

Compliance With Good Clinical Practices

The study complied with good clinical practice.

Financial Disclosure

The Applicant certified that none of the listed 57 clinical investigators held a reportable financial interest.

Patient Disposition

Table 6. Applicant's Summary of Disposition of Patients Enrolled in CYC-009

Status	Count
Total Enrolled	225
Full Analysis Set – Interim Read	200 (88.89%)
Patients in Next Blinded Read Batch	5
Xenon Images uninterpretable	1
Other	1
Physician Decision	6
Technical Problems	10
Withdrawal by Subject	2

Source: Interim Blinded Read Report; Protocol CYC-009, Table 6.1.1

Protocol Violations/Deviations

One deviation is reported for not adhering to inclusion and exclusion criteria.

Table of Demographic Characteristics

Table 7. Applicant's Summary of Demographic Characteristics of the Primary Efficacy Analysis Populations of CYC-009

Characteristic	Parameter	FAS Population	PPS Population
Gender	Female	95 (47.50)	90 (48.13)
	Male	105 (52.50)	97 (51.87)
Race	White	178 (89.00)	166 (88.77)
	Asian	1 (0.50)	1 (0.53)
	Native Hawaiian of Other Pacific Islander	1 (0.50)	1 (0.53)
	Black or African American	20 (10.00)	19 (10.16)
Age (years)	N	200	187
	Mean	60.1	60.4
	Std	14.18	13.79
	(Min, Max)	(20, 88)	(20, 88)
Weight (kg)	N	199	186
	Mean	84.0	83.9
	Std	22.87	22.55
	(Min, Max)	(41, 164)	(41, 164)
Height (cm)	N	198	185
	Mean	169.8	169.6
	Std	10.30	10.29
	(Min, Max)	(145, 203)	(145, 203)
BMI	N	198	185
	Mean	29.1	29.2
	Std	7.50	7.44
	(Min, Max)	(14, 59)	(16, 59)

Source: Interim Blinded Read Report; Protocol CYC-009, Table 6.1.2
Abbreviations: BMI, body mass index; FAS, Full Analysis Set; Std, standard deviation; PPS, per protocol set

In addition to demographic characteristics, the Applicant also collected data on the reason for referral to ventilation imaging. Of the subjects for whom a reason was provided, the majority (>65%) was for ventilation imaging without perfusion imaging and the most common reason was “Lung Pre-Surgical Evaluation for Lung Transplant or Reduction” (41%). Consistent with the CYC-009 study design aimed at quantifying agreement between Technegas and approved Xenon imaging within subjects, enrollment in Study CYC-009 more directly reflected the patient population indicated for “visualization of pulmonary ventilation” (for patient population more

directly reflective of those indicated for "evaluation of pulmonary embolism when paired with perfusion imaging", see description of Study 2, below).

Efficacy Results – Primary Endpoint

According to the SAP addendum, in the primary analysis, each blinded reader's binary agreement scores were analyzed using a generalized linear model with SAS® PROC GENMOD. The logit function (log odds ratio) was specified as the link function, and subject was specified as a repeated measure to account for correlation between lung regions within a subject. The estimate of the intercept of the model using generalized estimating equation (GEE) methodology provided an overall estimate of the agreement and its 97.18% confidence interval (CI) in terms of the log odds ratio; simple algebra was used to obtain the corresponding estimates and confidence intervals in terms of PA. These computations are presented in the following table. The review team was able to perform independent review using Applicant-submitted datasets (on November 4, 2020) and verify the Applicant's computations regarding the primary matched Technegas image views.

Table 8. GEE Estimates of Percent Agreement Between Xe-133 Scores and Technegas Scores - FAS Population

Reader ID Paired Image Sets	Estimated % Agreement	Lower CI*	Upper CI*
03			
Xenon images with matched Technegas image views	76.15	72.27	79.64
Xenon images with all Technegas image views	75.66	71.73	79.20
04			
Xenon images with matched Technegas image views	70.74	66.41	74.72
Xenon images with all Technegas image views	69.10	64.48	73.20
05			
Xenon images with matched Technegas image views	80.09	76.40	83.33
Xenon images with all Technegas image views	79.56	75.65	82.99

Source: Interim Blinded Read Report; Protocol CYC-009, Table 6.3.1
* 97.18% CI
Abbreviations: CI, confidence interval; FAS, Full Analysis Set; GEE, generalized estimating equation

One further summary of the data for Percent Agreement based on the individual percent agreements is presented in the following Table. In this table, the Applicant calculated the individual or per patient percent agreement by averaging the agreement scores across the six lung regions. The mean of all individual percent agreements was then calculated across all 200 patients by the Applicant. These computations, along with their respective 97.18% confidence intervals, are presented. The results regarding matched Technegas image views have been verified by the statistical reviewer.

Table 9. Within Patient Estimates of Percent Agreement Between Xe-133 Scores and Technegas Scores – FAS Population

Reader ID Paired Image Sets	Estimated Mean % Agreement	Lower CI*	Upper CI*
03			
Xenon images with matched Technegas image views	76.40	72.57	80.23
Xenon images with all Technegas image views	75.70	71.81	79.59
04			
Xenon images with matched Technegas image views	71.08	66.86	75.31
Xenon images with all Technegas image views	69.25	64.89	73.61
05			
Xenon images with matched Technegas image views	80.25	76.72	83.78
Xenon images with all Technegas image views	79.45	75.70	83.20

Source:CYC-009 interim blinded read report, Table 6.3.3
*97.18% CI
Abbreviations: CI, confidence interval; FAS, Full Analysis Set

The results from the interim analysis clearly indicate the primary efficacy endpoint is satisfied for all three readers for the primary imaging set of Matched Technegas Images as well as the secondary endpoint of All Technegas Images. For two of the three readers, the lower confidence limit is greater than 71%. These results, as specified in the protocol for both the primary and secondary endpoints, indicate that Technegas is noninferior to Xenon with respect to pulmonary ventilator distribution imaging of all six lung regions using the three-point ventilation score.

Data Quality and Integrity

No data quality or integrity issues were found in the submission.

Efficacy Results – Secondary and Other Relevant Endpoints

One secondary endpoint is the Percent Agreement measuring interobserver agreement between pairs of blinded readers for their Technegas ventilation scores and for their Xe-133 ventilation scores. This percent agreement was calculated as the estimates from a GEE model and is presented in Table 10 for all three image sets, the Xenon Images, the Technegas Matched Images, and the all Technegas images for the FAS Population. For all pairs of readers for all image sets, the estimated Percent Agreement is numerically greater than 70%, which demonstrates a strong agreement between the readers when reading the three image sets.

Table 10. Applicant's Summary of Interobserver Estimates of Percent Agreement Between Xe-133 Scores and Technegas Scores, 97.18% CI – GEE Modeling and FAS Population

Image Set	Paired Readers	Estimated Percent Agreement	Lower Confidence Interval	Upper Confidence Interval
Xenon Images	Reader 03 and Reader 04	82.84	79.53	85.71
	Reader 03 and Reader 05	80.40	76.48	83.80
	Reader 04 and Reader 05	79.58	75.65	83.01
Matched Technegas Images	Reader 03 and Reader 04	72.71	68.51	76.54
	Reader 03 and Reader 05	81.23	77.74	84.29
	Reader 04 and Reader 05	73.86	69.49	77.80
All Technegas Images	Reader 03 and Reader 04	71.62	67.35	75.54
	Reader 03 and Reader 05	80.84	77.20	84.02
	Reader 04 and Reader 05	73.43	68.94	77.48

Source: CYC-009 interim blinded read report, Table 6.4.1
Abbreviations: CI, confidence interval; FAS, Full Analysis Set; GEE, generalized estimating equation

Additional Analyses Conducted on the Individual Trial

One additional summary of the data for Percent Agreement based on the individual percent agreements is presented in the following Table. In this table, the review team used the Applicant's calculations for per patient percent agreements to define patient-success given in the table and computed patient-success estimates and their 97.18% confidence intervals for all 3 readers.

Table 11. Patient Success Estimates and 97.18% CIs – FAS Population

Patient Success	Estimate	97.18% CI
Per patient percent agreement >0.6		
Reader 3	80%	(73%, 86%)
Reader 4	73%	(65%, 79%)
Reader 5	83%	(76%, 88%)
Per patient percent agreement >4/6		
Reader 3	59%	(51%, 66%)
Reader 4	52%	(44%, 59%)
Reader 5	69%	(61%, 75%)

Source: CYC-009 interim blinded read report, Table 6.3.3 and computations of the primary statistical reviewer
Abbreviations: CI, confidence interval; FAS, Full Analysis Set

All these finding show that Technegas imaging is efficacious with respect to pulmonary function in subjects who are candidates for ventilation imaging.

Study 2. Miles et al., 2009 Chest; 136: 1546-1553 (Miles et al. 2009)

The prospective study described in this paper enrolled 100 patients with suspected acute PE (median age 67, male 56%). The additional inclusion criterion that patient's age must be greater than or equal to 50 years, may limit the generalizability of the study. All patients underwent

both diagnostic 16-detector CTPA, Technegas planar scintigraphy and Technegas SPECT V/Q scintigraphy. The reference standard was the diagnosis made by a panel of pulmonary physicians who were provided with the planar scintigraphy using Technegas reports, CTPA reports, extensive clinical information and patient status at the 3-month follow-up. Readers of SPECT scintigraphy using Technegas were two nuclear medicine physicians who were blinded to all clinical data and reporting of other scans. Note that both reference standard and reads of SPECT scintigraphy used Technegas. Therefore, positive percent agreement (PPA) and negative percent agreement (NPA) computations given in this paper cannot be used to assess the performance of Technegas. However, in this study, deidentified scans were read separately by two radiologists (CTPA reads) who were blinded to all clinical data and reporting of other scans. Discordant reports were reviewed by a consensus panel comprising three radiologists or three nuclear medicine physicians. The CTPA scan data can be used as "reference scan" data to compute agreement measures (PPA and NPA) of the Technegas scan. When the statistical reviewer collected that information from this paper, the following table emerged.

Table 12. Comparison of Technegas-SPECT Scan With CTPA Scan

	CTPA			
Technegas-SPECT	**Positive for PE**	**Negative for PE**	**Missing**	**Nondiagnostic**
Positive for PE	19	1	0	0
Negative for PE	3	56	4	4
Missing	1	6	1	5

Source: (Miles et al. 2009)
Abbreviations: CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; SPECT, single photon emission tomography

The review team imputed the highlighted entries in the Table 12 using following the imputation-scheme shown in Table 13.

Table 13. Numerical Imputation-Scheme in Comparison of Technegas-SPECT Scan With CTPA Scan

	CTPA			
Technegas-SPECT	**Positive for PE**	**Negative for PE**	**Missing**	**Nondiagnostic**
Positive for PE	19	1	0	0
Negative for PE	3	56	4 as true -	4 as true -
Missing	1 as true +	6 as true -	1 as false +	5 as false – or false+ alternatively

Source: Miles et al. (Miles et al. 2009) and primary statistical reviewer
Abbreviations: CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; SPECT, single photon emission tomography

Exploratory analyses of PPA and NPA based on these data including the imputed data were performed. V/Q results based on Technegas showed a PPA with CTPA of 77% (95 % CI: 56%, 91%) and a NPA of 95% (95% CI: 87%, 99%) for diagnosis of PE.

From the exploratory analyses and those reported in the paper, it appears that this study can provide supportive evidence for the indication of Technegas to evaluate PE when paired with perfusion imaging.

8.1.3. Integrated Assessment of Effectiveness

Study CYC-009 provides the primary evidence of efficacy and Miles et al. supports the primary evidence of efficacy for this application (Miles et al. 2009). Of these, the Applicant-conducted study CYC-009 provides the stronger level of evidence, as the prospective protocol was agreed upon with FDA under a Special Protocol Assessment and incorporated multiple independent imaging readers as well as prespecified success criteria. The data from this study support that the percent agreement of Technegas and Xenon with respect to pulmonary ventilation distribution imaging of all six lung regions using the three-point ventilation score is more than 60%. Study CYC-009 was a well-controlled study and, pending resolution of CMC approvability issues, may be adequate to support the indication of Technegas as a radioactive diagnostic imaging agent for lung ventilation scintigraphy in adult and pediatric patients to evaluate pulmonary function and pulmonary embolism. Data from another controlled study performed by Miles et al. can further support the indication of Technegas to evaluate PE when paired with perfusion imaging (Miles et al. 2009).

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety assessment for this submission is based on pooled-analysis of data (N=291) from four clinical studies performed by the Applicant, the safety information derived from 138 publications (approximately 17,800 patients) in Technegas clinical investigations, as well as the review of postmarket reports.

8.2.2. Review of the Safety Database

Overall Exposure

The overall extent of exposure to Technegas across the clinical trials submitted by the Applicant is summarized in Table 4. In CYC-009, the activity of sodium pertechnetate Tc99m loaded into the crucible ranged from 250 MBq to 1300 MBq (6 mCi to 35 mCi), with over half of loadings exceeding (b) (4) 700 MBq (18.9 mCi; see also approvability issues [Issue #4] in Section 1 of this review).

Adequacy of the Safety Database

The safety database is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity and submission quality were identified.

Routine Clinical Tests

For Study VM-001-01, vital signs were measured at baseline (pre-inhalation) and at 5 minutes, 10 minutes, 30 minutes, 1 hour, 2 hours and 3 hours after each ventilation study. For Study VM-002-01, vital signs were measured at baseline (pre-inhalation) and on Day 1 at approximately 24 hours after Technegas administration. Study CYC-008 assessed adverse events (AEs) from inhalation through 24 hours post inhalation. For Study CYC-009, in the original Protocol, safety was monitored up to approximately 24 hours (20 to 36 hours) post-Technegas administration, while following Protocol Amendment 1, there was no 24-hour Follow-up Visit, and safety was monitored only on the day of Technegas administration.

8.2.4. Safety Results

Deaths

No deaths were reported in the four clinical studies. The Applicant submits that no deaths have been reported in the literature related to Technegas administration.

Serious Adverse Events

In Study VM-001-01, two subjects (0.7%) experienced four serious adverse events (SAEs) following the administration of Technegas. None of the SAEs were considered related to Technegas. No serious AEs have been reported in the literature related to Technegas administration.

Dropouts and/or Discontinuations Due to Adverse Effects

One subject (Study VM-001-01) withdrew due to cardiac tamponade that was considered unrelated to Technegas.

Significant Adverse Events

Dyspnea and Hypoxia After Administration of Technegas

The first breath of Technegas contains no oxygen as the carrier aerosol is argon gas. The inhalation of Technegas reduces oxygen intake, may measurably decrease oxygen saturation, and may cause symptoms of dyspnea or signs of hypoxia. Subsequent inhalations contain proportionately more oxygen as air progressively flows into the chamber to replace the Technegas that is removed.

Hypoxia, defined as oxygen saturation <90%, was reported for three patients in the cross-over study VM-001-01 and another three patients in Study CYC-009. In addition, 14 patients (11.2%) received supplemental oxygen before, 7 patients (5.6%) received supplemental oxygen during, and 14 patients (11.2%) received supplemental oxygen after Technegas administration in Study VM-001-01. One patient (8.3%) in Study CYC-008 and 55 patients (38.5%) in Study CYC-009 received supplemental oxygen during Technegas administration. No patients in Study VM-002-

01 received supplemental oxygen. Overall, approximately 22% of treated patients in the four clinical studies required supplemental oxygen during Technegas administration.

In CYC-009 study, among 143 subjects[2] receiving Technegas, 96 (67%) of them were allowed to breathe room air during drug inhalation. Only 31 of 143 (21.7%) patients finished Technegas inhalation without room air breath and/or supplemental oxygen (Table 14)

Table 14. Reviewer's Summary of Requirement of Room Air Breath or Supplemental Oxygen During Technegas Inhalation in CYC-009 Study

	Supplemental Oxygen, n (%)	
Room Air Breath	**No**	**Yes**
No	31 (21.7)	16 (11.2)
Yes	57 (39.9)	39 (27.3)

Source: NDA022335\0001\m5\datasets\cyc009\tabulations\sdtm and primary clinical reviewer

In one study published by James et al. (1992), oxygen saturation was monitored continuously by means of a finger probe connected to a pulse oximeter, in patients during Technegas inhalation without (n=38, age from 18 to 82 years) or with preoxygenation (n=25, age from 17 to 89 years). The recommended Technegas inhalation procedure in the study is a deep inspiration from functional residual capacity, followed by a 5 s breath-hold before returning to tidal breathing of room air. The procedure may need to be repeated several times to achieve the desired level of lung deposition. Lowering of oxygen saturation was recorded in 87% of patients receiving Technegas without preoxygenation; in 58%, the decrease was more than 5% and in 37%, the decrease was more than 10%. In 15 of 38 (39%) patients, oxygen saturation fell below 85% (50 mm Hg) and in 26 of 38 (68.4%) patients, oxygen saturation fell below 90%. In no patients with pre-oxygenation did oxygen situation fall below 85%. The authors concluded that, "the ability to add oxygen to the newly generated Technegas could usefully be incorporated into the [TP] should the manufacturers consider any revision" and that, "it is probably wise to allow patients who are to undergo Technegas ventilation studies to inhale 40% to 67% oxygen via a face mask for 2 min prior to administration."

The Division of Anesthesiology, Addition Medicine, and Pain Medicine (DAAP) was consulted regarding the risk of dyspnea and hypoxia induced by Technegas inhalation. The review team concurs with DAAP's assessment that labeling revision in future review cycles is indicated to mitigate this risk. See also full review archived October 9, 2020 and approvability issues (Issues #3 and #4) in Section 1 of this review.

[2] The difference in number between the 143 subjects from CYC-009 analyzed here and the 200 analyzed above in Section 8.1 (efficacy) largely reflects completion of the review team's safety analysis based on the the Applicant's original NDA submission, not based on the enlarged dataset submitted late in the review cycle on December 17, 2020. Analysis of updated data by the Applicant and review team (not shown) found no new signals or meaningful differences from those reported here and throughout Section 8.2 (safety).

Treatment-Emergent Adverse Events and Adverse Reactions

The Applicant summarized the common adverse events by body system and preferred term in the four clinical trials as shown in Table 15. Seventy-three of the 291 subjects (25%) who received Technegas reported a total of 144 AEs. Ten of the 291 subjects (3.4%) experienced a total of 12 adverse reactions that were considered related to Technegas (Table 15). No Technegas related adverse reaction was experienced by more than one subject with the exception of hypoxia, which was experienced by three subjects (1%). Other drug-related AEs were blood bicarbonate increase, blood chloride increase, blood urea increase, oxygen saturation decrease, dizziness, dysgeusia, cough, dyspnea, throat irritation, and upper respiratory tract congestion.

All SAEs occurred during the conduct of Study VM-001-01. Two subjects (0.7%) experienced four SAEs following the administration of Technegas. None of the SAEs were considered related to Technegas. Subject (b) (6) was a 74-year-old Caucasian male who experienced cardiac tamponade the day following the Technegas ventilation scan. The event was considered life-threatening and resolved in 5 days. The subject did not undergo the second (Tc-99m DTPA aerosol) ventilation study. Subject (b) (6) was a 42-year-old Caucasian male who experienced three SAEs with onset 2 days after the second ventilation scan. The subject had a vascular pseudoaneurysm that was considered life-threatening and resolved in 17 days. He also experienced severe hypotension and severe tachycardia, both of which resolved within one day.

Four adverse events/complications were reported in 138 publications included approximately 17,800 patients who underwent Technegas clinical investigation. There was only one AE reported, mild tingling, that was possibly related to Technegas. The other reports included an AE of worsening of mild renal impairment after CTPA that was not attributable to Technegas, a death from myocardial infarction approximately 50 days post the Technegas V/Q scan that was not attributable to Technegas, and migration of an endobronchial valve detected prior to a scheduled Technegas V/Q scan on day 30 of the study that caused a post obstructive pneumonia and necessitated removal of the valve and was not attributable to Technegas.

Table 15. Applicant's Summary of Adverse Events by Body System and Preferred Term

System Organ Class / Preferred Term, N (%) [NE]	Study VM-001-01 (N=124)	Study VM-002-01 (N=12)	Study CYC-008 (N=12)	Study CYC-009 (N=143)	Combined (N=291)
Any event	61 (49.2) [129]	1 (8.3) [1]	1 (8.3) [1]	10 (7.0) [13]	73 (25.0) [144]
Gastrointestinal disorders	18 (14.5) [20]	—	—	—	18 (6.2) [20]
Constipation	4 (3.2) [4]	—	—	—	4 (1.4) [4]
Diarrhea NOS	4 (3.2) [4]	—	—	—	4 (1.4) [4]
Nausea	3 (2.4) [3]	—	—	—	3 (1.0) [3]
General disorders and administration site conditions	14 (11.3) [14]	—	—	1 (0.7) [1]	15 (5.2) [15]
Chest pain	3 (2.4) [3]	—	—	—	3 (1.0) [3]
Injury, poisoning and procedural complications	5 (4.0) [6]	—	—	—	5 (1.7) [6]
Laceration	3 (2.4) [3]	—	—	—	3 (1.0) [3]
Musculoskeletal and connective tissue disorders	10 (8.1) [16]	—	—	1 (0.7) [2]	11 (3.8) [18]
Arthralgia	4 (3.2) [5]	—	—	—	4 (1.4) [5]
Back pain	3 (2.4) [3]	—	—	1 (0.7) [1]	4 (1.4) [4]
Pain in limb	3 (2.4) [3]	—	—	—	3 (1.0) [3]
Nervous system disorders	9 (7.3) [12]	—	—	4 (2.8) [4]	13 (4.5) [16]
Dizziness	4 (3.2) [4]	—	—	2 (1.4) [2]	6 (2.1) [6]
Headache NOS	6 (4.8) [6]	—	—	—	6 (2.1) [6]
Psychiatric disorders	3 (2.4) [3]	—	—	—	3 (1.0) [3]
Insomnia	3 (2.4) [3]	—	—	—	3 (1.0) [3]
Respiratory, thoracic and mediastinal disorders	10 (8.1) [12]	1 (8.3) [1]	—	1 (0.7) [2]	12 (4.1) [15]
Dyspnea NOS	3 (2.4) [3]	—	—	—	3 (1.0) [3]
Hypoxia	3 (2.4) [3]			3 (2.1) [3]	6 (2.1) [6]
Skin and subcutaneous tissue disorders	14 (11.3) [16]	—	—	1 (0.7) [1]	15 (5.2) [17]
Ecchymosis	5 (4.0) [7]	—	—	—	5 (1.7) [7]
Vascular disorders	7 (5.6) [8]	—	—	—	7 (2.4) [8]
Hypotension NOS	3 (2.4) [3]	—	—	—	3 (1.0) [3]

Source: Table 14 in Amendment to Integrated Summary of Safety, NDA 022335
Common AEs are defined as those occurring in ≥1% of the combined studies.
If a subject has more than 1 AE in the same category, the subject was counted once under that category and each AE was counted.
Abbreviations: AE, adverse event; N, number of subjects; NE, number of AEs in category; NOS, not otherwise specified

Table 16. Summary of Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Event	N (%) [NE]
Any event	10 (3.4) [12]
Investigations	2 (0.7) [4]
Blood bicarbonate increased	1 (0.3) [1]
Blood chloride increased	1 (0.3) [1]
Blood urea increased	1 (0.3) [1]
Nervous system disorders	2 (0.7) [2]
Dizziness	1 (0.3) [1]
Dysgeusia	1 (0.3) [1]
Respiratory, thoracic and mediastinal disorders	6 (2.1) [6]
Cough	1 (0.3) [1]
Dyspnea NOS	1 (0.3) [1]
Hypoxia	3 (1.0) [3]
Throat irritation	1 (0.3) [1]
Upper respiratory tract congestion	1 (0.3) [1]

Source: Modified from Table 16 in Amendment to Integrated Summary of Safety, NDA 022335
Abbreviations: N, number of subjects; NE, number of AEs; NOS, not otherwise specified

Laboratory Findings

No clinically significant changes in hematology, clinical chemistry, or urinalysis parameters were noted following the administration of Technegas.

Vital Signs

There were no clinically significant shifts in diastolic blood pressure, systolic blood pressure, or pulse rate across all studies.

Electrocardiograms

For Study VM-00-01, relative to pre-inhalation electrocardiograms (ECGs), 27 subjects (22%) had a clinically significant change post-Technegas inhalation and 21 subjects (17%) had a clinically significant change post-DTPA inhalation as noted in the comments on the ECGs. Among them, five subjects were deemed to show a true worsening of ECG status poststudy drug (either Technegas or DTPA). The Applicant states that ECG changes do not represent a drug effect that causes a cardiac safety concern for Technegas. The review team concurs, given the heterogenous timing and lack of possible mechanism, as detailed in the case summaries below.

- Subject (b) (6) had a listing of an inferior infarct at Day 2 approximately 47 hours following Technegas inhalation and just prior to DTPA dosing, and also during the follow-up visit on Days 6 to 11.
- Subject (b) (6) had a new onset incomplete right bundle branch block at Day 2 approximately 44 hours after Technegas dosing and just prior to DTPA dosing.
- Subject (b) (6) had an increase in heart rate at Day 2 approximately 43 hours after DTPA inhalation and just prior to Technegas dosing that was possibly clinically significant.
- A possible myocardial infarction was seen in Subject (b) (6) approximately 5 minutes following DTPA dosing. The subject received DTPA first, then Technegas.

- Subject (b) (6) had a new onset of atrial fibrillation at visit 3 approximately 24 hours after DTPA dosing. The subject received Technegas first, then DTPA.

QT

No formal QT clinical study was performed for this single administration microdose drug and none was needed.

Immunogenicity

Immunogenicity evaluation was not needed and was not performed for this single administration drug.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Radiation exposure

The biodistribution study was performed in eight patients who received Technegas. Lungs received 0.085 ± 0.013 mGy/MBq. Other organs received between about 0.001 to 0.01 mGy/MBq. Based on these estimates, if one administration of Technegas delivers 40 MBq of radioactivity to the patient, then lungs will receive 3.4 mGy of absorbed radiation dose and effective radiation dose will be around 0.54 mSv.

8.2.6. Safety Analyses by Demographic Subgroups

A pooled subgroup analysis of adverse event data by age, sex, race and smoking history was performed for the four Applicant conducted clinical studies: VM-001-01, VM-002-01, CYC-008 and CYC-009 (Table 17). A slightly higher percentage of subjects 65 years or older experienced an AE compared with younger subjects. The differences of AE incidence in male and female were small and not considered to represent a sex-related trend. Of the 291 safety-evaluable subjects in the 4 studies, most (268 subjects) were white, and 69 of these subjects (25.7%) reported 1 or more AEs. Twenty-three subjects were another race, of which only one subject (Asian) (4.3%) reported an AE. No smoking history related trend was identified.

Table 17. Reviewer's Summary of AEs by Demographic Subgroups

Subgroups	AE N (%) [NE]
Age	
18-64 years	33 (20.9) [64]
65+ years	37 (27.8) [77]
Sex	
Male	44 (27.2) [88]
Female	26 (20.2) [53]
Race	
White	69 (25.7) [140]
Other	1 (4.3) [1]
Smoking history	
Never	30 (25.0) [65]
Prior	33 (21.3) [62]
Current	7 (43.8) [14]

Source: Summarized based on Table 24, 25, 26 and 27 in submitted ISS
Abbreviations: AE, adverse event; N, number of subjects; NE, number of AEs; ISS, integrated summary of safety

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There were no human tumors reported during drug development.

Human Reproduction and Pregnancy

The risk for PE is increased about five-fold during pregnancy and the puerperal period due to both changes in the coagulation system and mechanical factors such as vein compression, and more than 50% of events occur in the first 20 weeks of pregnancy. As clinical symptoms are nonspecific, it is important to consider the possibility of PE when a pregnant woman experiences symptoms. Therefore, clinical suspicion of PE always should generally be confirmed by an imaging test.

The radioactive exposure following Technegas ventilation imaging has been evaluated in pregnant women who had suspected PE and had undergone V/Q SPECT (Bajc et al. 2015). Estimated breast absorbed doses were 0.2 mGy after inhalation of 30 MBq of Technegas. The combined breast absorbed dose for the V/Q imaging was 0.8 mGy. The radiation dose to the fetus for Technegas ventilation SPECT imaging was calculated according to the stage of gestation ranging from 0.007 mGy at the early stage through 3-months of gestation up to 0.011 to 0.14 mGy at 6-months and 9-months of gestation, respectively. The maternal absorbed radiation dose is low in comparison to calculated breast absorbed doses of 20 to 50 mGy reported for MDCT. Fetal absorbed doses, on the other hand, are similar for MDCT and V/Q SPECT.

For additional information, see full maternal health review archived November 17, 2020.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Technegas is administered under the supervision of nuclear medicine practitioners and the amount localized in the patient's lungs is monitored by gamma counting to assure sufficient activity for the diagnostic procedure. Overdose issue, potential drug abuse, drug withdrawal and rebound is not applicable to Technegas.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant submitted to the NDA two postmarket safety reports from 2011 and 2013 and a 120-day safety report. The Division of Pharmacovigilance II (DPVII) was consulted. The review team did not identify any clear deficiency or safety signal in the Applicant's submitted postmarket information, though the team's ability to assess the adequacy of the Applicant's pharmacovigilance database remains limited by incomplete understanding of regulations applicable to this combination product across the multiple countries and many years it has been marketed outside of the United States. The DPVII review team concluded that postmarket AE reporting for Technegas is limited and recommends expedited reporting if Technegas is approved in future review cycles.

For additional information, see the full DPVII review archived August 24, 2020.

8.2.9. Integrated Assessment of Safety

Expectations on Safety in the Postmarket Setting

Dyspnea and hypoxia induced by Technegas administration is the major safety concern, especially in patients with respiratory diseases. This adverse reaction can be mitigated by monitoring oxygen saturation and administering supplemental oxygenation before and during imaging studies. From a radiation exposure prospective, the estimated effective dose from Technegas is similar to that of other commonly used diagnostic radiopharmaceuticals.

8.3. Statistical Issues

The review team performed review of key papers in the medical literature.

Table 18. Summary of Key Articles for General Lung Ventilation and Assessment of Pulmonary Embolism

Author/Year	No. of Patients	Truth Standard	Imaging Methodology	Blinded Read
(Jogi et al. 2010)	63	Tc-99m DTPA	SPECT	Yes (2 readers)
(Weinmann et al. 2008)	95	Multidetector CT, Ultrasound; Clinical Follow-up	SPECT	Yes (2 readers)

Source: NDA 022335 Clinical Review, Tables 2.5.4-2 and 2.5.4-3
Abbreviations: CT, computed tomography; DTPA, diethylenetriaminepentaacetate; SPECT, single photon emission tomography

1. Article by Jogi et al. (2010)

The goal of this study was to investigate differences in ventilation studies performed with 99mTc-DTPA and Technegas in patients referred for V/Q SPECT. The sample-size of 63 patients was not based on statistical considerations.

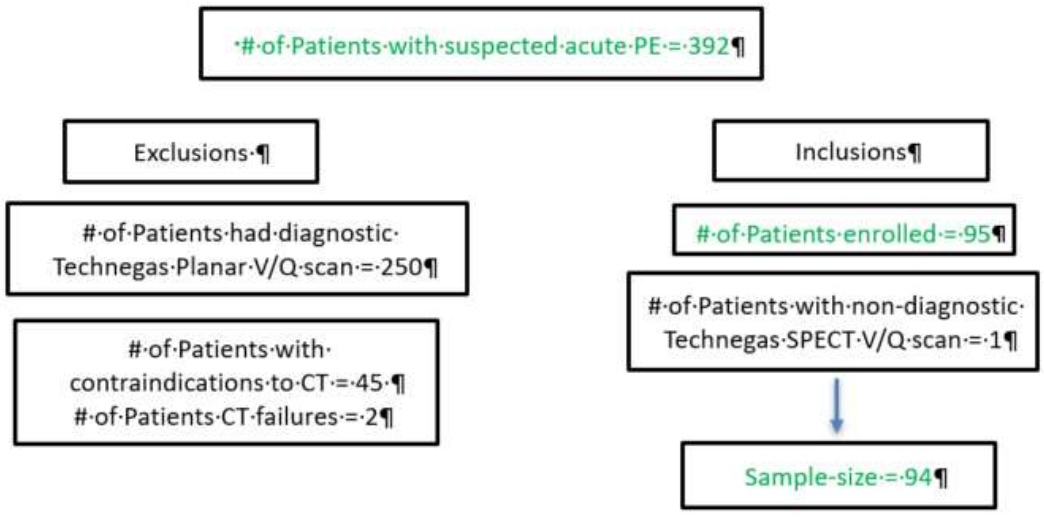
All V/Q SPECT images were reviewed by two experienced physician readers. The readers were blinded to clinical information and to the type of radioaerosol that had been used. It appears that the two readers developed a "consensus read" which was used in this study as the primary read methodology. The readers graded the ventilation images using three parameters: unevenness of radioaerosol distribution; central deposition, i.e., deposition of radioaerosol in major and intermediate conducting airways; and focal peripheral deposition in more distal airways. Each of these parameters was scored from 0 (none or normal) to 10 (very high). Paired comparisons between 99mTc-DTPA and Technegas with respect to the three parameters (variables) were performed using the Wilcoxon signed-rank test.

This study report suggests that, compared with 99mTc-DTPA, Technegas was more homogenously distributed in the lungs, had less central or focal deposition in the airways. This study provides supportive evidence for efficacy of Technegas for SPECT scintigraphy in terms of general pulmonary function (lung ventilation).

2. Article by Weinmann et al. (2008)

This was a prospective, single-center, single-arm study in patients with clinically suspected acute PE. The aim of this study was to evaluate the usefulness of SPECT V/Q imaging (with Technegas) in patients with nondiagnostic planar V/Q studies.

Figure 1. Study Design for Single-Center, Single-Arm Study in Patients With Clinically Suspected Acute PE



Source: Weinmann et. Al. (2008) and primary statistical reviewer
Abbreviations: CT, computed tomography; PE, pulmonary embolism; SPECT, single photon emission tomography; V/Q, ventilation/perfusion

In this study, reference scans for diagnosis of PE were Combined multidetector-row CT and Ultrasound. Reads of SPECT V/Q imaging with Technegas were done by two readers blinded to CT and ultrasound results, but not blinded to patients' clinical information. In the case of discordant results, the same two readers performed a simultaneous interpretation to reach a consensus. The data emerging from this study were as follows:

Table 19. Comparison of Technegas-SPECT Scan With Reference Scans

SPECT V/Q Scintigraphy With Technegas	Reference Scans: CT and Ultrasound	
	PE	No PE
PE	15	13
No PE	4	62

Source: Weinmann et al. (2008)
Abbreviations: CT, computed tomography; PE, pulmonary embolism; SPECT, single photon emission tomography; V/Q, ventilation/perfusion

From the above table, PPA=15/19=79% (95% CI: 61%, 97%) and NPA=62/75=83% (95% CI: 75%, 92%). From these results, this study seems to offer supportive evidence for efficacy of Technegas for assessment of PE by SPECT V/Q scintigraphy.

8.4. Conclusions and Recommendations

Pending resolution of approvability issues, the review team finds that study CYC-009 provides evidence of efficacy of Technegas and at least one paper in the medical literature provides confirmatory evidence of efficacy of Technegas in planar as well as SPECT V/Q scintigraphy imaging with respect to pulmonary function in subjects that are candidates for ventilation imaging. It appears that at least two studies in the medical literature may provide supportive evidence of efficacy of Technegas for assessment of PE by SPECT V/Q scintigraphy when paired with perfusion imaging. Taken together, relying primarily on CYC-009 and Miles 2009 where listed in matching and complimentary supporting positions below in italics, the following indication may thus be approvable upon resolution of outstanding approvability issues:

> Technegas is a radioactive diagnostic agent indicated for lung ventilation scintigraphy in adults and pediatric patients 6 years of age and older for:
>
> - visualization of pulmonary ventilation (*CYC-009*).
> - evaluation of pulmonary embolism when paired with perfusion imaging (*Miles 2009*).

9. Pediatrics

Under the Pediatric Research Equity Act (21 U. S. C. 335), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Applicant submitted a pediatric assessment to support the proposed indication for Technegas, as a radioactive diagnostic imaging agent for lung ventilation scintigraphy in adults and pediatric patients 6 years of age and older to evaluate pulmonary function and pulmonary embolism when paired with perfusion imaging.

Agreed Initial Pediatric Study Plan

On August 16, 2019, Cyclomedica submitted a proposed agreed initial pediatric study plan (iPSP) to IND 062660 including plans to request a partial waiver in pediatric patients from birth to less than 6 years of age based on the conclusion that studies are impractical because administration of Technegas requires active patient participation in a non-sedated state to cooperate with the breathing instructions, ensure proper inhalation of the aerosol, and to comply with instructions on how to breathe while under the gamma camera. The iPSP also includes plans for deferral of pediatric study in patients 6 years and older given the information available in published literature and the limited pediatric population that potentially could benefit from Technegas as a ventilation imaging radiopharmaceutical. The Division of Medical Imaging Products requested time to internally discuss whether pediatric studies need to be completed in pediatric patients 6 years and older or if a pediatric assessment for Technegas would be adequate in a NDA submission to support the proposal to expand the indication to include pediatric patients 6 years and older.

On October 22, 2019, the Division of Medical Imaging Products [recently renamed the Division of Imaging and Radiological Medicine (DIRM)] granted Cyclomedica an Agreed iPSP. There are no agreements in place with other regulatory authorities regarding the conduct of pediatrics studies with Technegas.

Pediatric Assessment

The Applicant submitted a pediatric assessment to support the proposal to expand the indication for use of Technegas for lung ventilation scintigraphy to evaluate pulmonary function and pulmonary embolism to include pediatric patients 6 years and older. As cited above, the threshold of pediatric patients 6 years and older is based on need for patient use of the PAS and cooperation with the breathing instructions for administration of Technegas.

A total of 11 publications were identified and reviewed among which four publications are considered key studies demonstrating safe and effective use of Technegas® for ventilation scintigraphy in pediatric patients. The four articles report outcomes in 75 pediatric patients from 8 weeks to 11 years of age, the majority of whom are infants to less than 3 years of age.

The Applicant submitted additional published literature on Technegas SPECT ventilation imaging in 26 pediatric patients 10 years of age with history of bronchopulmonary dysplasia in infancy that supports use of comparable ventilation imaging. V/Q scan modalities reported include both planar and SPECT imaging. Technegas was administered to achieve a count rate of 1,000 to 3,000 counts per second in the lungs or until approximately 5 MBq was deposited in the lungs via inhalation. The four key published studies, in addition to the submitted supportive publications including case reports, practice guidelines, and two additional publications on the use of Technegas SPECT imaging in older pediatric patients, 10 years of age, supports the use of Technegas in pediatric patients 6 years and older.

See also PeRC Meeting Minutes archived May 26, 2021 and approvability issues (Issue #5) in Section 1 of this review.

10. Division Director (Clinical) Comments

I concur with the CMC and clinical reviewers' findings of important deficiencies in the application and with their recommendations for addressing these deficiencies.

The most important product quality deficiencies regard 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; data on volatile compounds. 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 Technegas Plus system.

The clinical deficiencies concern the need for more information on risk minimization steps to address the potential for hypoxia due to the inhalation of the anoxic gas mixture, and the need to justify the proposed Tc99m loading ranges to be used for adult and pediatric patients.
In view of these important deficiencies I concur with the CMC and clinical reviewers' recommendation for a CR action for the application.

11. Office Director (or designated signatory authority) Comments

I concur with the recommendation of the review staff and Division leadership regarding the application. A complete response action is justified.

12. Appendices

12.1. References

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12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CYC-009

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 57		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

12.3. Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ronald Honchel, Ph.D.	OSM/DIRM	Sections:	**Select one:** X Authored ___ Approved
	Signature: Ronald Honchel -S Digitally signed by Ronald Honchel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald Honchel -S, 0.9.2342.19200300.100.1.1=1300124657 Date: 2021.06.24 10:56:31 -04'00'			
Nonclinical Supervisory Pharmacologist	Adebayo Laniyonu, Ph.D.	OSM/DIRM Dr. Summan Signing for Dr. Laniyonu	Sections:	**Select one:** ___ Authored X Approved
	Signature: Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2021.06.24 11:07:07 -04'00'			
DIRM Nonclinical Nonclinical Acting Division Director	Mukesh Summan, Ph.D.	OND/ORDPURM/DPTRDPURM	Sections:	**Select one:** ___ Authored _X__ Approved
	Signature: Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2021.06.24 21:19:56 -04'00'			
Clinical Pharmacology Reviewer	Christy John, Ph.D.	OCP/DCPII	Sections	**Select one:** __X_ Authored ___ Approved
	Signature: Christy S. John -S Digitally signed by Christy S. John -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150005, cn=Christy S. John -S Date: 2021.06.24 13:54:49 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader and Division Director	Nam Atiqur Rahman, Ph.D	OCP/DCPII	Section:	**Select one:** ___ Authored _X__ Approved
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Statistical Primary Reviewer	Jyoti Zalkikar, Ph.D.	OB/DBI	Section:	**Select one:** _X__ Authored ___ Approved
	Signature: Jyoti Zalkikar -S Digitally signed by Jyoti Zalkikar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jyoti Zalkikar -S, 0.9.2342.19200300.100.1.1=1300162261 Date: 2021.06.24 10:51:14 -04'00'			
Deputy Division Director	Sue-Jane Wang, Ph.D.	OB/DBI	Section:	**Select one:** ___ Authored __X_ Approved
	Signature: Suejane Wang -S Digitally signed by Suejane Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suejane Wang -S, 0.9.2342.19200300.100.1.1=1300088741 Date: 2021.06.24 10:53:25 -04'00'			
Clinical Reviewer	Gang Niu, M.D.	OSM/DIRM	Sections:	**Select one:** __X_ Authored ___ Approved
	Signature: Gang Niu -S Digitally signed by Gang Niu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Gang Niu -S, 0.9.2342.19200300.100.1.1=0014351562 Date: 2021.06.24 11:43:19 -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:	**Select one:** _X__ Authored _X__ Approved
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Division Director	Libero Marzella, M.D., Ph.D.	OS/DIRM	Sections:	**Select one:** ___ Authored __X_ Approved
	Signature: Libero L. Marzella -S Digitally signed by Libero L. Marzella -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300088188, cn=Libero L. Marzella -S Date: 2021.06.24 21:43:03 -04'00'			
Office Deputy Director	Alex Gorovets, M.D.	OSM	Sections:	**Select one:** ___ Authored _X__ Approved
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Office Director	Charles Ganley, M.D.	OSM	Sections:	**Select one:** ___ Authored __X_ Approved
	Signature: Charles J. Ganley -S Digitally signed by Charles J. Ganley -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052350, cn=Charles J. Ganley -S Date: 2021.06.24 16:46:50 -04'00'			

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