# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022335Orig1s000

# OTHER REVIEW(S)

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | September 26, 2023 |
| Requesting Office or Division: | Division of Imaging and Radiation Medicine (DIRM) |
| Application Type and Number: | NDA 022335 |
| Product Name, Dosage Form, and Strength: | Technegas (kit for the preparation of technetium Tc 99m-labeled carbon inhalation aerosol) for inhalation, 1.25 g |
| Applicant/Sponsor Name: | Cyclomedica Australia Pty Ltd (Cyclomedica) |
| TTT ID #: | 2023-4311-1 |
| DMEPA 2 Safety Evaluator: | Devin Kane, PharmD |
| DMEPA 2 Team Leader: | Stephanie DeGraw, PharmD |

## 1 PURPOSE OF MEMORANDUM

Cyclomedica Australia Pty Ltd (Cyclomedica) submitted revised container labels, blister pack carton labeling, Technegas Plus System labels, Patient Administration Set (b) (4) labeling, and Technegas contacts container labels for Technegas (kit for the preparation of technetium Tc 99m-labeled carbon inhalation aerosol) for inhalation received on September 19, 2023 under NDA 022335. We reviewed the revised labels and labeling for Technegas (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 CONCLUSION

Cyclomedica implemented all of our recommendations and we have no additional recommendations at this time. We note during the review of this NDA the established name was revised from "kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol" to "kit for the preparation of technetium Tc 99m-labeled carbon inhalation aerosol" (hyphen added), and this revision is not reflected on the revised Technegas container label and carton labeling. On September 20, 2023, Cyclomedica was notified that this change may be made as part of the first annual report.

[a] Kane, D. Label and Labeling Review for Technegas (NDA 022335). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 AUG 22. TTT ID No.: 2023-4311.



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**Division of Imaging and Radiation Medicine**

# REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 022335

**Name of Drug:** Technegas™; Technetium Tc-99m carbon aerosol

**Applicant:** Cyclomedica Australia Pty Ltd Represented in the US by Certus International, Inc.

## Labeling Reviewed

**Submission Date:** March 29, 2023; September 19, 2023, and September 21, 2023

**Receipt Date:** March 29, 2023; September 19, 2023, and September 21, 2023

**Background and Summary Description:**

The Applicant, Cyclomedica Australia Pty Ltd represented in the US by Certus International, made this resubmission in response to the FDA Complete Response letter issued on June 25, 2021, to their original NDA submission of March 26, 2020.

This is a Class 2 Resubmission with a 6-month review clock and classified as standard review with a PDUFA due date of September 29, 2023.

Sponsor's proposed indication for Technegas is for functional lung ventilation imaging (b) (4)

## Review

The labeling was reviewed by the following:

**CMC:** Ravindra Kasliwal/Danae Christodoulou

- Drug Product: Ravindra Kasliwal/Danae Christodoulou
- Process: Ravindra Kasliwal/Danae Christodoulou
- Facility: Krishna Ghosh/ Vidya Pai
- CDRH Compliance: Xin He/ Daniel Krainak/Berk Oktem

**Clinical:** Gang Niu/Anthony Fotenos-CDTL

**Biostatistics:** Jyoti Zalkikar, Reviewer/Sue-Jane Wang

**Clinical Pharmacology**: Christy John, Reviewer and TL

**Nonclinical:** Ronald Honchel, Reviewer/Jonathan Cohen

**Labeling:** Younsook Kim, Associate Director of Labeling (ADL)

**DPMH -** Pediatric: Ramy Abdelrahman/Mona Khurana;
Maternal: Jane Liedtka/Tamara Johnson

**OPDP:** David Foss, Reviewer/James Dvorsky, TL

**OSE DMEPA:** Devin Kane, Reviewer/ Stephanie DeGraw

All the reviews are archived in DARRTS and in Panorama for CMC reviews. Labeling review activities were overseen by the Associate Director of Labeling, Younsook Kim.

The labeling comments of prescribing information, container, and carton PAS-IFU (Instructions for Use) and were first communicated to the Applicant on August 16, 2023, and the Applicant's email responses with their revisions were received on August 28, 2023.

Additional FDA revisions and comments to the carton and container, Prescription Information, User Manual, and PAS-IFU were sent to the Applicant on September 13, 2023, and all revisions were accepted with minor changes by the Applicant in their submission of September 19, 2023.

Further revisions which are minor editorial updates to Prescription Information, was sent to the Applicant on September 19, 2023, and a prompt email response in which the changes were accepted by the Applicant was received on September 20, 2023, followed by a formal submission on September 21, 2023.

## Recommendations

The submitted draft labeling, identified as NDA 022335 labeling: Prescribing Information, Carton and Container, and User Manual submitted on, March 29, 2023, is recommended for approval after the acceptance of the Agency's and Applicant's revisions as finally submitted by the Applicant on September 21, 2023.

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 (1

The entire Prescribing Information is included showing the revisions. The attached Prescribing Information is the agreed upon labeling between FDA and the Applicant.

Modupe Fagbami

Regulatory Project Manager Date

Younsook Kim. Pharm.D., Ph.D.

Associate Director, Labeling Date

Kyong (Kaye) Kang, Pharm D.

Chief, Project Management Staff Date

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KYONG A KANG
09/25/2023 10:55:28 AM

**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** August 29, 2023

**To:** Modupe O. Fagbami, Regulatory Project Manager, Division of Imaging and Radiation Medicine (DIRM)

Gang Niu, Clinical Reviewer, DIRM

Younsook Kim, Associate Director for Labeling, DIRM

**From:** David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Jim Dvorsky, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for TECHNEGAS® (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol), for oral inhalation use

**NDA**: 022335

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**Background:**

In response to DIRM's consult request dated June 22, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Instructions for Use (IFU), User Manual, and carton and container labeling for the original NDA submission for Technegas.

**PI/IFU/User Manual:**
OPDP's review of the proposed PI/Medication Guide/IFU/User Manual is based on the draft labeling emailed to OPDP on August 28, 2023, and our comments are provided below.

**Carton and Container Labeling**:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the emailed to OPDP on August 28, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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DAVID F FOSS
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

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|---|---|
| Date of This Review: | August 22, 2023 |
| Requesting Office or Division: | Division of Imaging and Radiation Medicine (DIRM) |
| Application Type and Number: | NDA 022335 |
| Product Name, Dosage Form, and Strength: | Technegas (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol) for inhalation, 1.25 g |
| Product Type: | Combination Product (Drug-Device) |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Cyclomedica Australia Pty Ltd (Cyclomedica) |
| FDA Received Date: | March 26, 2020, November 12, 2020, November 13, 2020, March 29, 2023 and June 30, 2023 |
| TTT ID #: | 2023-4311 |
| DMEPA 2 Safety Evaluator: | Devin Kane, PharmD |
| DMEPA 2 Team Leader: | Stephanie DeGraw, PharmD |

# 1 REASON FOR REVIEW

Cyclomedica Australia Pty Ltd (Cyclomedica) submitted a Class II resubmission of NDA 022335 for Technegas (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol) for inhalation on March 29, 2023. The Technegas crucible is proposed for the production of Technetium Tc 99m Carbon Labeled Inhalation Aerosol (Technegas Aerosol), which is a diagnostic imaging agent indicated for functional lung ventilation imaging (b) (4) in adult and pediatric patients. We note Technegas Aerosol is produced in the TechnegasPlus System from a reaction involving Sodium Pertechnetate Tc 99m Injection, argon gas, and the Technegas crucible. We evaluated the proposed Techengas prescribing information (PI), Technegas Plus System User Manual, Patient Administration Set Instructions for Use, container labels, blister pack carton labeling, Technegas Plus System labels, and Patient Administration Set carton labeling for areas of vulnerability that may lead to medication error.

## 1.1 BACKGROUND OR REGULATORY HISTORY

Technegas was originally submitted under NDA 022335 by Cyclomedica Australia Pty Ltd (Cyclomedica) on March 26, 2020. We previously reviewed and provided recommendations for the Technegas PI, Technegas Plus System User Manual, Patient Administration Set Instructions for Use, container labels, blister pack carton labeling and Technegas Plus System labels.[a] However, on June 25, 2021, NDA 022335 received a Complete Response (CR) letter due to product quality, device, and clinical issues.[b] As such, our label and labeling recommendations were not communicated to Cyclomedica.

# 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Human Factors Study | C – N/A |

[a] Kane, D. Label and Labeling Review for Technegas (NDA 022335). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 15. RCM No.: 2020-609.

[b] Fagbami, M. Complete Response Letter (NDA 022335). Silver Spring (MD): FDA, CDER, OND, OSM, DIRM. (US); 2021 JUN 25. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805fcbf6

| Table 1. Materials Considered for this Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| ISMP Newsletters* | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Other – Response to Information Request(s) | F |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

On March 29, 2023, Cyclomedica Australia Pty Ltd. (Cyclomedica) resubmitted the marketing application for NDA 022335 following the Complete Response (CR) letter that was issued on June 25, 2021. In response to the submission date March 29, 2023, the Office of Pharmaceutical Quality (OPQ) issued an information request (IR) on May 31, 2023[c] stating:

> "We note that the product to be sold by the company will be the carbon crucible, which when used in conjunction with the approved Technegas™ system and commercially available sodium pertechnetate Tc 99m injection solution, as described in the labeling, will produce technetium Tc 99m labeled carbon aerosol, for inhalation use. We also acknowledge the technetium Tc 99m labeled carbon aerosol characterization provided under the current second drug substance section and in the current drug product section (currently indicated as specifications). Since it is the carbon crucible that will be sold by the company, we propose that the marketed drug product should be the "Carbon Crucible Kit" labeled as "Technegas™ (Kit for the Preparation of technetium Tc 99m labeled carbon aerosol), for inhalation use". Accordingly, we recommend that carbon crucible section be relabeled as the drug product section for this NDA, and the drug product specifications be considered as the characterization attributes for the technetium Tc 99m labeled carbon aerosol. As such whenever, there is a strength, purity or quality or change in the carbon crucible or changes that have potential to affect the quality and characteristics of the Tc 99m labeled carbon aerosol in the Technegas™ system, the impact of such changes must be assessed with respect to the characterization attributes currently under the drug substance characterization and under the drug product specifications."

[c] Lalmansingh, A. Information Request for NDA 022335. Silver Spring (MD): FDA, CDER, OPQ, OPRO. (US); 2023 MAY 31. Available from: \\CDSESUB1\EVSPROD\nda022335\0048\m1\us\111-info-amend\fda-information-request-cmc-only-31may2023.pdf

On June 15, 2023 Cyclomedica acknowledged the receipt of the above IR and agreed to the proposed recommendations from OPQ. Additionally, on June 30, 2023 Cyclomedica submitted a formal response to the May 31, 2023 IR which included the requested product specifications for the carbon crucible (i.e. weight, color description, etc.). We agree with OPQ's proposed regulatory pathway for Technegas from a medication error perspective, and we defer to OPQ regarding the acceptability of the product quality information submitted by Cyclomedica.

We performed a risk assessment of the proposed Techengas prescribing information (PI)[d], Technegas Plus System User Manual, Patient Administration Set Instructions for Use, container labels, blister pack carton labeling, Technegas Plus System labels, and Patient Administration Set carton labeling to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed labels and labeling for Technegas identified areas of vulnerability that may lead to medication errors. We provide our recommendations below.

We note in order to align with the recommendations from the OPQ and the Division regarding the naming of the product and its components, the proposed labels and labeling are to be revised such that:

- "Technegas" is the name of the product (the entire kit),
- "kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol" is the established name,
- "Technegas Crucible" is the name of the carbon crucible,
- "TechnegasPlus Generator" is now "Technegas Plus System", and
- "Technegas Aerosol (Technetium Tc 99m Labeled Carbon Aerosol)" is the name for the final product produced by the system.

## 4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Technegas prescribing information (PI), Technegas Plus System User Manual, Patient Administration Set Instructions for Use, container labels, blister pack carton labeling, Technegas Plus System labels, and Patient Administration Set carton labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Cyclomedica Australia Pty Ltd so that recommendations are implemented prior to approval of this NDA.

### 4.1 RECOMMENDATIONS FOR DIVISION OF IMAGING AND RADIATION MEDICINE (DIRM)

A. Prescribing Information

[d] We previously provided comments and recommendations for the Technegas prescribing information and User Manual in our March 15, 2021 Label and Labeling Review. These comments were incorporated into DIRM's current working PI and User Manual for Technegas. Thus, we assessed the working PI in DIRM's Sharepoint and our comments and recommendations in this review are new and pertain to the working PI.

1. General Recommendations for Highlights of Prescribing Information and Full Prescribing Information
    a. As currently presented, there are numeric values greater than 1,000 presented throughout the PI without the use of a comma. We recommend including the comma for all numeric values greater than 1,000 to avoid confusion. For example, in the highlights of Dosage and Administration, revise "1500" to read "1,500".

    b. We note there are numeric values presented throughout the PI that are not immediately followed by the appropriate units. We recommend including the appropriate units after all numeric values to avoid confusion. For example, in the highlights of Dosage and Administration, revise "1,500 to 2,500 counts per second" to read "1,500 counts per second to 2,500 counts per second".

    c. We note the Agency has made regarding the naming of the carbon crucible and the final product. Thus, we recommend revising the PI to align with these revisions such that "Technegas Crucible" is used to refer to the carbon crucible, and the final product produced by the Technegas Plus system is referred to as "Technegas Aerosol (Technetium Tc 99m Labeled Carbon Inhalation Aerosol)".

2. Section 2: Dosage and Administration

    a. We note Section 2: Dosage and Administration includes trailing zeros. We recommend removing trailing zeros to avoid misinterpretation of the numeric value. For example, in Table 2 revise "2.0" to read "2".

3. Section 3: Dosage Forms and Strengths

    a. As currently presented, Section 3: Dosage Forms and Strengths lacks a physical description of the Technegas carbon crucible. We note from the Sponsor's submission dated June 30, 2023 that the Technegas carbon crucible is "dark grey to black small oval crucible". We recommend including this description in the first line of Section 3.

B. Technegas Plus System User Manual
    1. We note the proposed User Manual refers to the "TechnegasPlus Technegas Generator". We recommend revising the product name throughout the User Manual to read "Technegas Plus System" to align with regulatory recommendations from the Agency regarding the naming of the product. Additionally, we note the Agency made revisions regarding the naming of the carbon crucible and the final product. Thus, we recommend revising the User Manual to align with these revisions such that "Technegas Crucible" is used to refer to the carbon crucible, and the final product produced by the Technegas Plus system is referred to as "Technegas Aerosol (Technetium Tc 99m Labeled Carbon Inhalation Aerosol)".

2. As currently presented, each page of the proposed User Manual presents a footer which includes the proposed proprietary name "Technegas" (b) (4) . We recommend removing the (b) (4) .

3. We note the proposed User Manual includes numeric values that are not immediately followed by the appropriate units and the symbol "-" is used to represent the word "to" when presenting numeric values in a range. We recommend including the appropriate units after all numeric values with a space included between the value and the units in order to avoid confusion and removing the hyphen symbol and replacing it with its intended meaning of "to". (b) (4)

4. As currently presented, there are numeric values greater than 1,000 presented in the User Manual without the use of a comma. We recommend including the use of a comma for all numeric values greater than 1,000 to avoid misinterpretation of the numeric value. For example, under Section 2.6 Principle of Operation, revise "2750°C" to read "2,750°C". Additionally, we recommend including the Fahrenheit equivalent values in parentheses after the Celsius temperatures.

5. We note the use of the symbol "µ" in Section 8 to represent "micro". We recommend avoiding the use of this symbol and presenting the units as "(b) (4) microL". Additionally, we recommend including a space in between the numeric value and the units for readability.

6. We note that there are abbreviations used throughout the User Manual that are specific to this product. For example, 'TPS' is used to refer to the Technegas Plus System and 'PAS' is used to refer to the patient administration set. We recommend including a glossary of abbreviations and their intended meanings in the beginning of the User Manual for quick reference.

7. The Technegas Plus System User Manual currently refers to the Technegas Prescribing Information as the "Technegas Prescribing Information (b) (4)". We recommend removing the word (b) (4) from the description and referring to the material as the 'Technegas Prescribing Information (PI)'.

8. As currently presented, there are numeric values presented with a trailing zero. We recommend removing trailing zeroes to avoid misinterpretation of the numeric value. For example, under Section 8 Dosimetry, revise "(b) (4) mCi" to read "(b) (4) mCi".

9. We note Section 16.5 Identifying the Date of Manufacture presents the proposed manufacture date format as "TPYYWWID", where YY represents the year of manufacture, WW represents the calendar week of manufacture, and ID represents the unique identifier for the device within the batch. We recommend revising the format for the manufacture date to appear in YYYY-MM-DD format if

only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the label, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month.

C. (b) (4)

4.2 RECOMMENDATIONS FOR CYCLOMEDICA AUSTRALIA PTY LTD

We recommend the following be implemented prior to approval of this NDA:

A. Technegas Crucible Container Label

1. We recommend removing the proposed proprietary name "(b) (4)" and replacing it with the proposed proprietary name "Technegas" to align with the prescribing information (PI) and current recommendations from the Agency regarding the naming of your product.
2. We recommend revising "Graphite crucible for the preparation of Technegas inhalation" to read "Kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol" to align with the PI and current recommendations from the Agency regarding the naming of your product.
3. We note that each Technegas crucible is intended for single use only, and that the remnants are to be considered radioactive waste and discarded appropriately. We recommend including a statement on each Technegas crucible container label that states "Each Crucible is single use only. Fragments are Radioactive waste, discard all fragments appropriately".
4. As currently presented, there are no storage requirements provided on the three Technegas crucible labels. We recommend including storage requirements on the labels presented as a temperature range in degrees Celsius with Fahrenheit

equivalent temperatures provided in parenthesis in alignment with the format used in the PI.

5. We recommend including the statement "For use in the Technegas Plus System Only. See Technegas Prescribing Information for more Information".
6. We note the strength of the product is based on the weight of the Technegas crucible. As currently presented, the proposed crucible container label lacks a product strength. We recommend including the weight of the crucible as the strength on the proposed container label.
7. As currently presented, the proposed Technegas crucible container label lacks the required statement "Rx Only". We recommend including "Rx Only" on the labels for the carbon crucible. Ensure the "Rx Only" statement does not compete in size or prominence with critical information on the label.
8. We note the proposed container label lacks the product NDC. Include the human-readable and machine-readable forms of the NDC (i.e., linear barcode).

B. Technegas Crucible Container Label and Batch Label

1. We note the placeholder for the expiration date is in the format of MM/YYYY. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. Batch Label and Technegas Crucible Blister Pack Carton Labeling

1. As currently presented, the batch label is separate from the carton labeling and includes the batch number and expiration information. We recommend combining the information from the batch label and the Technegas Crucible blister pack carton labeling onto one label to prevent the important information being overlooked.

D. Technegas Crucible Blister Pack Carton Labeling

1. As currently presented, the proposed crucible carton labeling lacks required information for drug product labeling. This required information includes the proprietary name, established name, weight of the crucible as the strength, dosage form, route of administration, and net quantity statement. For the product name, we recommend increasing the prominence of the proprietary name and established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance

for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

2. We note the proposed crucible carton labeling includes information presented in (b) (4)

3. We note the crucible carton labeling states “Crucibles” at the top. We recommend having the top of the labeling state “Technegas (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol)”, to align with the PI and the Technegas Plus System User Manual.

4. As currently presented, the proposed Technegas crucible carton labeling lacks the required statement “Rx Only”. We recommend including “Rx Only” on the proposed carton labeling. Ensure the “Rx Only” statement does not compete in size or prominence with critical information on the label.

5. We note the proposed crucible carton labeling lacks storage information for the Technegas crucibles. We recommend including the statement “Store at room temperature between 20°C to 25°C (68°F to 77°F). Store unused Technegas Crucibles in the original package to prevent contamination of crucibles.”

6. We note the proposed crucible carton labeling lacks a statement referring the end user to the prescribing information. We recommend including the statement “Recommended Dose: See Prescribing Information” on the carton labeling.

7. We request that you include the NDC number or placeholder on the principal display panel of the crucible carton labeling per 21 CFR 201.2.

E. Technegas Plus System Labels

1. We recommend revising the proposed Technegas Plus System labels to align with current Agency recommendations regarding the naming of your product. We note these recommendations include removing the term “generator” and replacing it with “system”, revising the name of the carbon crucible to “Technegas”, and referring to the final product from the Technegas Plus System as “Technegas Aerosol”.

(b) (4)

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Technegas received on March 29, 2023 and based on the Information Request Response received on June 30, 2023 from Cyclomedica Australia Pty Ltd.

| Table 2. Relevant Product Information for Technegas | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol |
| Indication | Indicated for functional lung ventilation imaging (b) (4) in adult and pediatric patients. |
| Route of Administration | Inhalation |
| Dosage Form | for inhalation |
| Strength | 1.25 g |
| Dose and Frequency | The recommended quantity of sodium pertechnetate Tc-99m to be loaded in the crucible is (b) (4). The Technegas Plus System converts sodium pertechnetate Tc-99m to Tc-99m labeled carbon particles dispersed in argon gas. The solid in gas aerosol is conveyed to the patient through an interconnecting patient administration set through which the patient inhales.<br>Delivery of the aerosol is continued until a count rate of approximately 1,500 counts per second to (b) (4) counts per second is achieved. |
| How Supplied | Multiple single-dose kit consisting of 10 single-use Technegas crucibles. Each crucible contains (b) (4) high purity graphite for use in the Technegas Plus System. Each kit consists of five thermoformed blister packs of 10 crucibles in a cardboard box.<br><br>The radionuclide sodium pertechnetate Tc-99m is not part of the kit. |
| Storage | Store the crucibles (b) (4). Store the crucibles in the original package. |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 3, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Technegas. Our search identified 1 previous review[e], and we considered our previous recommendations to see if they are applicable for this current review.

[e] Kane, D. Label and Labeling Review for Technegas (NDA 022335). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 15. RCM No.: 2020-609.

APPENDIX F. CYCLOMEDICA AUSTRALIA PTY LTD. RESPONSE TO INFORMATION REQUEST

F.1 Response to Information Request Received on June 14, 2023, available from:
\\CDSESUB1\EVSPROD\nda022335\0047\m1\us\12-cover-letter\cover-letter-0047.pdf

- Information relevant to our review:
    - Cyclomedica agrees with Dr. Lalmansingh's recommendations and commits to submitting a Complete Response to the May 31, 2023 correspondence, including the new documents needed and a reorganization of existing documents and data to facilitate the ongoing review.

F.2 Response to Information Request Received on June 30, 2023, available from:
\\CDSESUB1\EVSPROD\nda022335\0048\m1\us\111-info-amend\m1-11-1-response.pdf

- Information relevant to our review:
    - Cyclomedica has amended the NDA to relabel the carbon crucible section as the "drug product" section as requested. The drug product section has now been expanded to include the Technegas crucible information as part 1 of the drug product section to include batch release and the description and information for the Technegas Aerosol final drug product produced for patient information as Part 2. Both sections now align with information provided to FDA as part of the reply to the Complete Response Letter.
    - Each crucible is "Black/dark grey carbon graphite small oval crucible from chips and cracks".
    - Each crucible has a target weight of "1.25 g", with a range of "(b) (4)".

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Technegas labels and labeling submitted by Cyclomedica Australia Pty Ltd.

- Technegas Container Label received on March 26, 2020
- Technegas Carton Labeling received on March 26, 2020
- Technegas Plus System Labels received on March 26, 2020
- Patient Administration Set Carton Labeling received on November 12, 2020
- Prescribing Information (Image not shown) received on March 29, 2023, available from \\CDSESUB1\EVSPROD\nda022335\0044\m1\us\114-labeling\114a-draft-label\uspi-tgas-mr03-15-2023-redline.pdf
- Technegas Plus System User Manual received on March 29, 2023, available from \\CDSESUB1\EVSPROD\nda022335\0044\m1\us\114-labeling\114a-draft-label\mnl-0009-technegasplus-user-manual-us-redline.pdf
- Patient Administration Set Instructions for Use (Image not shown) received on November 13, 2020, available from \\CDSESUB1\evsprod\nda022335\0018\m1\us\114-labeling\114a-draft-label\pas-ifu-k200916-7jul2020.pdf

### G.2 Label and Labeling Images

(b) (4)

[redacted]

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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DEVIN R KANE
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STEPHANIE L DEGRAW
08/22/2023 04:33:34 PM

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Division of Pediatrics and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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# Division of Pediatrics and Maternal Health Review

**Date:** 7/19/23 **Date consulted:** 5/16/23

**From:** Jane Liedtka, M.D., Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)
Office of New Drugs (OND), Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)

**Through:** Tamara Johnson, M.D., M.S., Team Leader, Maternal Health, DPMH

**To:** Modupe Fagbami, Regulatory Project Manager (RPM)
Division of Medical Imaging and Radiation Medicine (DIRM)

**Drug:** Technegas (technetium Tc 99m labeled carbon aerosol for inhalation)

**NDA:** 22335

**Applicant:** Cyclomedica Australia Pty Ltd

**Subject:** Pregnancy and Lactation Labeling Rule (PLLR) language for NDA resubmission after complete response (CR) [New 505(b)(2) NDA]

**Indication:** functional lung ventilation imaging (b) (4)

**Materials Reviewed:**

- 3/29/23, applicant's submitted background package after complete response, NDA 22335
- DPMH consult review for Technegas[1] (technetium Tc 99m labeled carbon aerosol for inhalation), NDA 22335. Jane Liedtka, M.D., 11/16/20. DARRTS reference ID 4702466.
- DPMH consult review for Kit for the Preparation of Technetium Tc 99m Exametazime Injection[2], NDA 208870. Carrie Ceresa, Pharm. D., MPH, March 29, 2017. DARRTS reference ID 4076476.
- DPMH consult review for Draximage DTPA (Kit for the Preparation of Technetium Tc 99m) Injection[1], NDA 18511. Carrie Ceresa, Pharm. D., MPH, November 13, 2017. DARRTS reference ID 4180141.

**Consult Question:** DIRM is requesting DPMH's review and feedback regarding the Sponsor's proposed labeling for subsections 8.1 and 8.2.

**INTRODUCTION AND BACKGROUND**

- On 3/26/20, Cyclomedica Australia Pty Ltd, Inc., submitted a New Drug Application (22335) via the 505(b)(2) pathway, for Technegas™ (technetium Tc-99m carbon aerosol) for use in adults.
- The indication is for functional lung ventilation imaging (b) (4) .
- A previous NDA for the same product had been submitted on 12/15/08 but was withdrawn in 2009 (not due to clinical concerns).
- Outside the US, Technegas has been approved since 1987 (Australia) and has been used widely in Europe (approved in France 1996) and in a total of 59 countries worldwide.
- On 4/6/20, DIRM consulted DPMH to review labeling subsections 8.1 Pregnancy and 8.2 Lactation.
- DPMH has conducted reviews for two previous technetium 99 products. See these reviews (noted above under "Materials Reviewed") for "Drug Characteristics", "Radiation Units and Conversions", "Radiation Exposure and Pregnancy", "Guidelines on Radiopharmaceuticals and Pregnant Women, American College of Radiology (ACR)", "Case Reports of Exposures to Technetium during Pregnancy" and literature review up to March of 2017 in PubMed.
- DPMH completed a review for NDA 22335, which was archived in DARRTS on 11/16/20. On 6/25/21, the Agency issued a Complete Response (CR) letter to NDA 22335.
- On 3/29/2023, the applicant submitted a response to the CR. The division reconsulted DPMH on 5/16/23.

**REVIEW**

***PREGNANCY***

See previous DPMH review for Technegas[1] for "Radiation and Pulmonary Embolism", "Nonclinical Experience", "Applicant's Review of the Literature" and "DPMH's Review of the Literature". A review of the literature in PubMed encompassing 1/1/20 through 7/1/23 did not identify any new publications that would alter the risk-benefit profile for Technegas use during pregnancy.

[1]DPMH consult review for Technegas (technetium Tc 99m labeled carbon aerosol for inhalation), NDA 22335. Jane Liedtka M.D., 11/16/20. DARRTS reference ID 4702466.

[2] The Kit for the Preparation of Technetium Tc 99m Exametazime Injection review and the Draximage DTPA review were part of the materials reviewed but were not a source relied upon for the labeling recommendations below.

***LACTATION***

See previous DPMH review for Technegas[1] for "Nonclinical Experience", "Applicant's Review of the Literature" and "DPMH's Review of the Literature". A review of the literature in PubMed encompassing 1/1/20 through 7/1/23 did not identify any new publications that would alter the risk-benefit profile for Technegas use during lactation. For convenience, below I have reproduced the entry from Hale's *Medication and Mothers Milk*[3], in which a specific reference to Technegas requiring only a 4-hour interruption of breastfeeding was noted.

> L3 - Limited Data-Probably Compatible
> The American Academy of Pediatrics (AAP) and the International Commission on Radiological Protection [ICRP], recommend different periods of breastfeeding cessation depending on which formulation of Tc-99m is used (see list below).[4,5,6] These recommendations still permit a minimal amount of radiation transfer to the infant (<1 mSv or 100 mrem)[14]. For the following salts do not breastfeed for 4 hours:
> DMSA, DTPA, DISDA, ECD, Gluconate, Glucoheptonate, HM-PAO, Sulfur Colloids, MAG3, MIBI, PYP, phosphonates (MDP), **Technegas**, tetrofosmin.

*Reviewer comment: After discussions with DIRM on 11/16/20, the decision was made to recommend a time period of 4 hours for pump and discard based on ICRP guidelines. There was no new information found during the 2020-2023 literature review to suggest a need to alter this recommendation.*

***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

See previous DPMH review for Technegas[1] for "Nonclinical Experience", "Applicant's Review of the Literature" and "DPMH's Review of the Literature". A review of the literature in PubMed encompassing 1/1/20 through 7/1/23 did not identify any new publications that would alter the risk-benefit profile for Technegas.

***DISCUSSION AND CONCLUSIONS***

Pregnancy

The findings from the available data found in published literature with Technegas and use in pregnant women are insufficient to evaluate for a drug associated risk for major birth defects and miscarriage or other maternal or fetal adverse outcomes. Limited published literature describes other forms of Technetium 99 crossing the placental barrier and visualization of radioactivity in the fetal liver. No adverse fetal effects or radiation-related risks have been identified for diagnostic procedures involving less than 50mGy, which represents less than 10mGy fetal doses. At this time, DPMH does not recommend a post-marketing pregnancy safety study for this product.

Lactation

There is no information regarding the presence of Technegas in human or animal milk, its effects on the breastfed infant or its effects on milk production. Limited information from several case

[3] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.
[4] Sachs HC, Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics 2013;132(3):e796-809.
[5]International Commission on Radiological Protection. Annex D. Recommendations on breast-feeding interruptions. Annals of the ICRP 2008;38(1-2):163-84.
[6]Stabin MG. Radiating dose concerns for the pregnant or lactating patient. Semin Nucl Med 2014;44:479-88.

reports describes the presence of technetium 99 in human milk. Exposure of a breast fed infant to radiation from Technegas can be minimized by discontinuation of breastfeeding anywhere from 4-24 hours after administration. This recommendation is based on clinical guidelines but there are no clinical pharmacology studies that confirm this recommendation. At this time, DPMH does not recommend a post-marketing lactation study for this product.

Females and Males of Reproductive Potential

There are no human or animal data available on the effects of Technegas on fertility to inform a potential clinical risk. In addition, pregnancy testing and contraception recommendations are not warranted; therefore, this subsection will be omitted from labeling.

**LABELING RECOMMENDATIONS**

DPMH revised the HPI, and subsections 8.1, 8.2, and section 17 of labeling for Technegas to be in compliance with the PLLR (see below). DPMH presented our labeling recommendations to the Division on 7/7/23. DPMH refers to the final NDA action for final labeling.

**DPMH Proposed Pregnancy and Lactation Labeling**

(b) (4)

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U.S. FOOD & DRUG ADMINISTRATION

# Consulting Memorandum

**FOR CONSULTED CENTER'S (CDER) USE ONLY**

**To:**

**RPM:** Fagbami, Modupe CDER/OND/ORO/DROSM

**From**:

**Reviewer:** Xin He, Ph.D.
CDRH/OPEQ/OHT7/DRH/NMRT

**Team Lead**: Daniel Krainak, Ph.D.
CDRH/OPEQ/OHT7/DRH/MREP

**Through**: Michael O'Hara, PhD.
Deputy Director
CDRH/OPEQ/OHT7/DRH

Michael D. O'Hara

**Submission:** 022335 Technegas

**Trade Name:** Technegas

**Sponsor:** Cyclomedica Australia Pty Ltd

**CDRH Review team:** VOC Berk Oktem (CDRH/OSEL/DBCMS)
EMC Amarjeet Bhullar (CDRH/OPEQ/OIDRH/DMQS/PMB)
Toxicology Eric Sussman (CDRH/OSEL/DBCMS)

**Date:** May. 20, 2021

## *Summary*

Our review covered the following device-related subjects to assure safety and effectiveness

- General device review: this covers the device functions, safety features and technological characteristics to assure effectiveness.
- General electrical and mechanical safety, and electromagnetic compatibility review: this is to assure the device safety as a medical electronic device.
- Software review: this is focused on the quality system of the software life cycle.
- Biocompatibility including volatile organic compound (VOC) review: This issue was identified during the review of Technegas administration set as a 510k device, K200916. In one of the reports, we noted the device emits a large variety of VOC. We decided to clear the 510k because the VOC appeared not to be emitted by the administration set but by the generator, and we agreed with the sponsor to deal with the VOC issue as part of the drug/combination product review.

During the first round of the review, we identified a five main concerns:

1) the lack of data to support the yield,
2) the lack of the data/rationale to support the parameters used during production,

3) the lack of the data to support the purging process, which is related to device safety,
4) the lack of data supporting safety of the gas pathway with respect to VOC, and
5) the lack of data to demonstrate EMC.

In the second round of review, sponsor submitted some data to address these concerns. However, some aspects of the above issues remain unresolved for items 1), 3), and 4). Items 2) and 5) have been resolved. At the end of the memo, we make recommendations about how to address these issues.

## 2.2 Intended Use

The nanoparticle size and hydrophobic properties of Technegas™ provide ideal characteristics for gaseous behaviour and alveolar deposition in the lungs. This facilitates gamma-ray imaging of the functional ventilation distribution for diagnosing pathological processes.

Technegas™ is a ventilation agent for ventilation-perfusion imaging studies. In (b) (4) breaths and following gamma camera imaging, SPECT or SPECT/CT, the clinician can produce planar or 3D images providing information on lung function and pulmonary physiology.

*Please refer to the drug label for final Indication and Usage.*

## Device Description

The TP is an electrically powered medical device for creating hydrophobic Technetium-99m labelled carbon nanoparticles dispersed in air as an aerosol with an activity median aerodynamic diameter of (b) (4) nm. Technegas™ is the brand name for the system of medical devices and pharmaceuticals used in the production of the Technetium-99m radiolabelled carbon aerosol also referred to as Technegas™. The Technegas™ system comprises of the TechnegasPlus Technegas™ Generator (TP), (b) (4) (Crucible), the Technegas™ Contacts, the Technegas™ Patient Administration Set (PAS), and other proprietary components. The system requires a general purpose 20 A electrical outlet, user supplied Technetium-99m (99mTc) as sodium pertechnetate solution, pure non-denatured ethanol (≥ 95%), and high purity (≥ 99.997%) argon gas to create Technegas™.

*Figure 1. TechnegasPlus Technegas™ Generator (TP)*

The TP is a bespoke high temperature furnace and is a medical device. It uses a combination of graphite in the form of the (b) (4) (Crucible) and an inert atmosphere (argon) to reduce and then vaporise 99mTc generator eluate (sodium pertechnetate) in a steel chamber.
It does this by first drying the eluate to remove the water from the saline carrier solution over 6 minutes, during which the chamber is purged of oxygen and filled with argon. The TP then raises the graphite (b) (4) (Crucible) to a temperature of 2750°C ±100℃ within 2 seconds and maintains this temperature for a period of 15 ±1 seconds to produce Technegas™ . An optical sensor maintains high temperature phase within the specified temperature limits. This validated process is intended to release (b) (4) % of the supplied 99mTc into Technegas™.

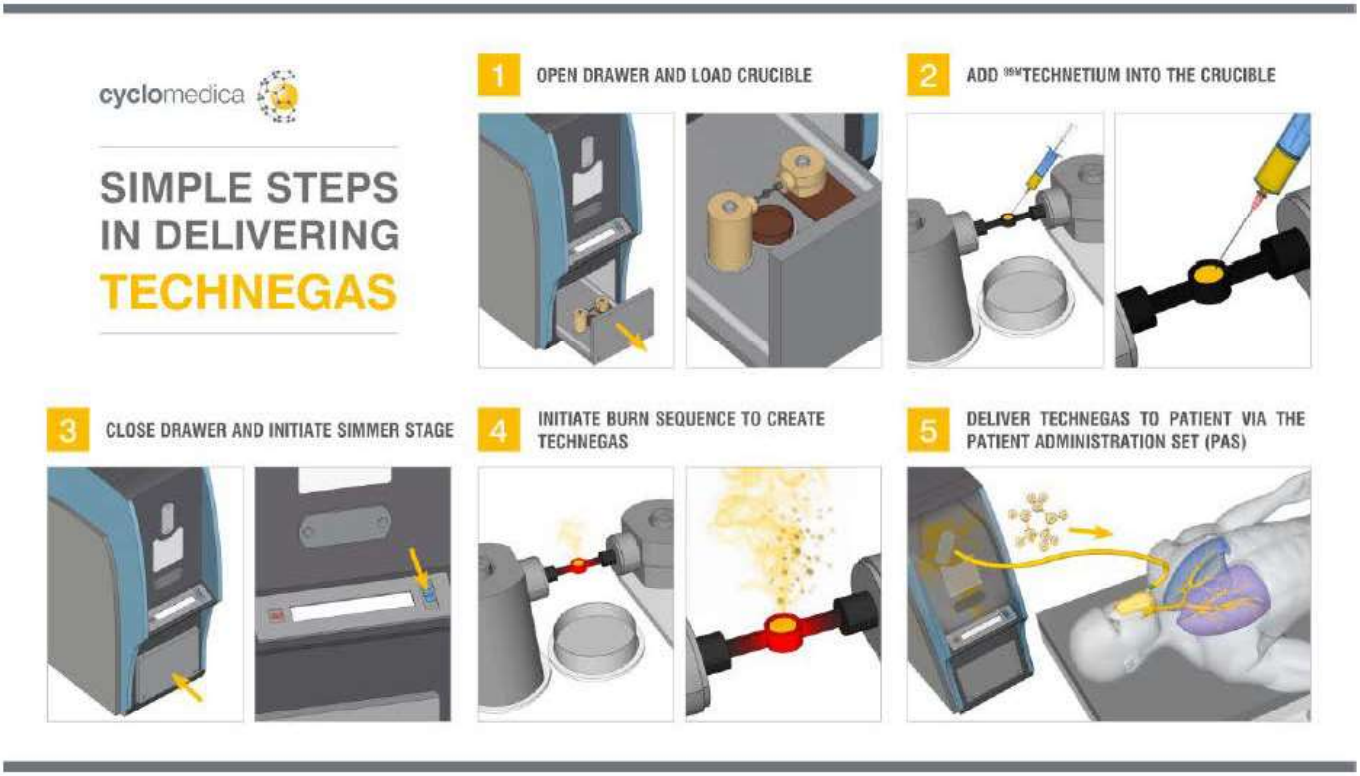


*Figure 2 Technegas™ generation and delivery summary*

Technegas™ (Technetium (Tc-99m) carbon aerosol) is used for functional lung ventilation imaging(b) (4)

Production Process:

- The manufacture of Technegas™ Aerosol takes place within the chamber of a Technegas generator inside of a specially designed reaction vessel fabricated from high purity graphite carbon. The graphite carbon crucible serves a dual role: first as the reaction vessel and second as the source of the carbon needed to form the Tc-99m labeled carbon particle aerosol.
- The crucible is positioned between two electrodes, its reservoir filled with sodium pertechnetate Tc-99m, and is heated in a series of stages with an electrical current.
- The water is first evaporated to dryness, then the crucible is heated to ~2750ºC.
- The pertechnetate anion is reduced to zero valence by high temperature reaction with carbon and Tc-99m and carbon volatilized.
- The hot Tc-99m and carbon ascend from the hot crucible (b) (4) resulting in Tc-99m-labeled carbon particles that are instantaneously dispersed in inert argon gas to form the formulated drug product aerosol, Technegas™.
- When the generation cycle is completed, the operator disconnects the main power supply, the argon gas line, and attaches the patient administration set (PAS).
- The patient is instructed to continue breathing Technegas™ Aerosol through the patient administration

(b) (4)

## Software

I. Sponsor has followed FDA's software guidance entitled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" and provided necessary documentation including software requirement, design requirement, hazard analysis, traceability, life cycle, etc. The documentation contains the information to meet our requirement, although it appears all documents were created before the FDA submission rather than through the software development cycle.

**First round of the review**

During the first round of the review, we identified a few major issues, including

- The sponsor claims the yield of the generator is (b) (4) however, no data were provided to support this yield.
- The device purges after each patient. The purpose of the purge incudes 1) to assure the safety of the operator who opens the drawer to prepare the next batch 2) to assure the residue from this batch of aerosol will not contaminate the next batch for the next patient. The efficiency of the purges is unclear.
- The software design specifications include a series of error messages to assure the user the parameters for operating the devices, e.g., temperature, flow rate, pressure, etc. are appropriate. However, it is not clear how the sponsor developed the thresholds for these error messages.
- We issued deficiencies concerning VOC (see the VOC memo from Dr. Berk Oktem) related to the biocompatibility of the gas pathway.
- We did not find the complete electrical immunity test report, which is part of the expectation needed to meet the EMC requirements for safety.

Deficiencies issued during the first round of the review:

1. In the information provided in section 3.2.P.5.2.2. Radioactivity yield Test (June 10-24, 2005), you note that "Generator Performance testing using the standard Technegas Production settings consistently achieved yields that were above (b) (4)". In the design input requirements document (REQ-003-D) under section 1.7 Principle of Operation, you note that "This validated process releases greater than (b) (4) of the supplied $^{99m}$Tc into Technegas$^{TM}$." However, Section 3.1.24 Yield Test is cross-lined. Please explain why. You stated the production process is validated to produce a (b) (4) yield. Yield is one of the most important characterization of the generator output. Please provide validation data.

2. You described the aerosol generation process (in Design Input Requirements REQ-003-D under section 1.7 and elsewhere), which involves purging. You did not describe the mechanism of purging and the expected outcome. Please explain the mechanism of the purging process. You stated the purging time is 3min, please clarify what is the outcome of the 3-min purge, what is the efficiency of purge. Please provide data to support this outcome. The purpose of purging is to prevent the leftover aerosol in the chamber from one batch to contaminate the next batch.

This information is needed to understand whether the goal of purging is accomplished through each purge. This appears to also be related to the need for system cleaning/maintenance, as described below.

3. (b) (4)

4. You specified a set of potential error messages in your design document. However, you did not provide the rationale/data concerning how these thresholds were set for the computer to generate these errors. Please provide your rationale and supporting data. This information is needed to understand how various factor may affect the quality/quantity of the Technegas output. For example,

    a. You have a flow rate sensor during the simmer and clean burn purge operation. If the flow rate is below 8l/min or above 16liter/min, then there should be an error message. Please explain how you set the threshold of 8 and 16l/min.

    b. (b) (4)

    c.

    d.

    e.

    f.

5. (b) (4)

6. (b) (4)

(b) (4)

7. You stated there is a simmer process before the burn. You did not specify what is maximum time between end of simmer and beginning of burn? Is there an error message if this period is too long. How is this period controlled? Please provide this information. This information is needed to understand the various factors that may affect the quality/quantity of the aerosol.

8. We have following concerns about your VOC analysis:

   a) In the reports you submitted (b) (4) Environment Test report #1000722837-2361429 as well as (b) (4) Environment Test report #1000722837-2361429BA, (Appendix 37a and 39a) the determination of VOCs are not documented sufficiently to determine the exposure estimate originated from the chemical analysis reports. This is important as the Table 1 of report #1000722837-2361429BA indicates some MoS (margin of safety) figures are (b) (4) and these may be an underestimate of the actual release of these VOCs. Please provide additional details including the collection methods, calibration curves, validation data as well as calculations that lead to the determination of the quantities reported."
   b) For TTC limits, you cited "US EPA 40 § CFR Part 50" instead of ISO 18652 standard which is written for gas pathway devices. Although you used the same table from ISO 18652, you ignored the phrases about acceptance criteria which is "The dose-to-patient of any substance for which a TI is calculated shall be below that TI." This is important as the TI (tolerable intake) of some compounds may be much lower than the TTC values in the standard.
   c) In your risk assessment, you divided the total dose by the number of days. That is not acceptable by the Agency standard recognition statement for ISO 10993-17:2002 (FR Publication Date 07/26/2016; FR Recognition Number 2-237 ) as the following part of the standard is not recognized: Annex C, Clause C.2.1. Therefore, please calculate toxicological risk in a per day basis as the release kinetics is unknown and consider the worst case release of the total amount released in a single day.

9. You have provided the emissions tests as per IEC 60601-1-2:2014 in Design Verification document VER-003 Appendix 27-A. Under "Immunity Requirements" in this document, you state that the Generator "complies with EMC emissions requirements." In Design Verification VER-003 Appendix 29-A, you include some immunity test requirements. On page 22/58 (page 18 of the 60601-1-2 report) of VER-003 Appendix 27-A, it notes that several of the immunity tests were not performed at customer's request and refers instead to VER-003 Appendix 11-C.

   *VER-003 Appendix 30-A includes testing related to immunity to* (b) (4).
   *VER-003 Appendix 27-A includes testing related to immunity to* (b) (4)

   In other words, you have not provided the required immunity test for the subject device. Please provide all missing immunity tests to demonstrate that the subject device will operate safely and effectively in the intended use environment. You should follow FDA's guidance entitled "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Device" to address EMC of the subject device. Here is the link to "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices":
   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM470201.pdf
   This guidance document describes the types of information that should be provided to support a claim of EMC in a premarket submission for an electrically powered medical device.

## Second round of the review

Sponsor has addressed our deficiencies. However, the deficiencies concerning yield and purge are not satisfactory. Specifically, the following outstanding concerns remain:

- Yield: Sponsor did provide a document (b) (4) to demonstrate the yield test. It appears that the yield test was done for three test modes, one test each. The question is whether the yield can be consistently achieved. In a separate document (b) (4) sponsor did provide multiple consecutive tests for 3 "new" crucibles (total 18 tests), and 18 tests may not be enough to demonstrate the consistency.
    a. (b) (4) shows that it is possible to have onboard yield test as a QA measure, specifically (b) (4)
    b. (b) (4) shows that the temperature is crucial for the yield. In a separate document, (b) (4) shows that maintaining a steady temperature during pre-burn and main burn is not easy.

  So the question is whether the yield can be consistent in practice, over the life cycle, and how to detect a yield drop. While a yield drop may not affect image quality, which is assured by gamma camera counts. In a discussion with Dr. Ann Marie Russell, we noted that a drop in yield may lead to patients inhaling a larger amount of aerosol to achieve the same counts on the camera, which may be a safety issue.
  Our recommendation is, if inhaling a large amount of aerosol is a safety concern, and depends on the severity of the safety concern,
    c. Since measuring yield appears to be feasible, the sponsor may consider adding a yield test as a regular QA procedure done by medical physicists in user facilities
    d. Another mitigation approach is "time-to-minimum counts," if sponsor can provide data to demonstrate the distribution of time-to-minimum counts, considering patients variations in size, lung volume, breathing frequency, etc.
    e. Or sponsor should consider demonstrate the yield is consistent for the lifecycle or maintenance cycle of the device.
    f. We note that based on the history of use outside the US, some consideration of benefit/risk may be advisable.

- Purge: The purpose of purge is to remove the aerosol, so that 1) it is safe for operator when opening the drawer. 2) reduce deposit on the chamber. In the response, the sponsor described the purging mechanism and stated that goal is to displace (b) (4) in the chamber. It is not clear whether (b) (4) can achieve the goal of safety for operators, and to what extent it reduces deposit. In other words, it is not clear what is the efficiency of the purge.

Other deficiencies from the first round of the review.

- Potential error messages: sponsor explained when the error messages are triggered and the threshold, however, they were not clear on the rationale behind the threshold. From other documents, e.g. (b) (4), it appears that sponsor used trial and error approach to come up with threshold and these parameters are to assure the yield. As long as the yield and purging issues are resolved, we do not further raise issues with these error messages.
- VOC: Please refer to Dr. Berk Oktem's review memo. Dr. Oktem continues to have concerns concerning VOC, and sponsor has not provided sufficient data.

- EMC: sponsor provided immunity test, and it is sufficient.
- Pressure relief: we accept sponsor's responses for pressure relief as a safety measure.
- Other minor clarifications are acceptable.

## Recommendations

To CDER reviewer

- We are concerned the consistency of the yield. If the yield is reduced over time, then PT needs to inhale a larger amount of aerosol to accomplish the same count on the gamma camera, and thus this may be a safety concern. It is generally a good practice to have a QA procedure to check the yield of the device periodically by a medical physicist in the user facility (this is a practice done by most imaging device sponsors). Since the sponsor will develop a test to evaluate yield, CDRH will work with CDER to issue the deficiency that incorporates our concern on consistency of the yield. **Depending on CDER's assessment of the potential safety issues that may occur if the yield is not consistent, this yield issue may be an approvability issue.**
- Dr. Oktem has identified multiple issues related to VOC, which may be safety issues. **If sponsor cannot successfully address them, these may be approvability issues**. Please work with Dr. Berk Oktem Concerning the VOC issues.
- Our deficiency to sponsor below expresses our concerns on purge. **Since there are industrial standards for filters used in collecting radioactive materials, we do not consider this an approvability issue. Sponsor just needs to provide a justification.**

To Sponsor

- The purpose of purge is to remove the aerosol, so that 1) it is safe for operator when opening the drawer. 2) reduce deposit on the chamber. You stated the goal of purging is to (b) (4) in the chamber. Please provide a justification or data demonstrating that (b) (4) can achieve the goal of safety for operators, and to what extent it reduces deposit. You may refer the labeling of the filter you use, to deduce your efficiency based on the data provided by the filter manufacturer.

### Second round of the review (after Feb. 26).

- We reviewed the sponsor's response (Feb. 26, 2021) to our questions concerning purge, and it sufficient.
- Dr. Oktem and Sussman reviewed response from sponsor on VOC and toxicology (Feb 26 and May 3, 2021) Dr. Oktem found sponsor response to #26 is acceptable However, Dr. Sussman still have concerns on the toxicology, provided in the final comments below.

### Final Comments for sponsor

We have reviewed the sponsor's Responses 1 through 5 (May 03, 2021). The response does not clarify the sponsor's methods for calculation of patient exposure dose as it only refers to methodologies found in standards instead of providing the requested information. In their future submission, the sponsor is recommended to explicitly provide details the calculations it 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, adequate details (e.g. 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. This information is requested because the description of the methodology in absence of full details of the approach does not provide adequate information for FDA to complete its review and corroborate the sponsor's review.

**Attachment**

EMC and electrical safety review memo
VOC review memo
Chemical characterization memo

| **Digital Signature Concurrence Table** | |
|---|---|
| Reviewer Sign-Off | Xin He -S Digitally signed by Xin He -S Date: 2021.05.26 13:55:14 -04'00' |
| Team Lead Sign-Off | Daniel Krainak -S 2021.05.28 14:34:29 -04'00' |
| Division Sign-Off | |

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| **Consult Number:** | ` |
| **Document Number:** | ICC2000352 |
| **Applicant:** | |
| **Trade Name:** | |
| **Consult Type:** | Toxicology and Chemical Risk Assessment |
| **Requestor:** | Xin He [XIN.HE] |
| | xin.he@fda.hhs.gov |
| **Requestor Home:** | CDRH\ OIR\ DRH\ NMRT |
| **Requested Consultant:** | |
| **Gatekeeper / Consultant:** | Eric Sussman [ERIC.SUSSMAN] |
| | eric.sussman@fda.hhs.gov ; 301-796-7008 |
| **Consultant Home:** | CDRH\ OSEL\ DBCMS |
| **Date Requested:** | March 5, 2021 |
| **Due Date:** | May 7, 2021 |
| **Instructions:** | |

SPONSOR RESPONSES TO PREVIOUS FEEDBACK

(b) (4)

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(b) (4)

**CURRENT REVIEW**

The response does not clarify the sponsor's methods for calculation of patient exposure dose as it only refers to methodologies found in standards instead of providing the requested information. In their future submission, the sponsor is recommended to explicitly provide details the calculations it 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, adequate details (e.g. 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. This information is requested because the description of the methodology in absence of full details of the approach does not provide adequate information for FDA to complete its review and corroborate the sponsors' claims.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | March 15, 2021 |
| Requesting Office or Division: | Division of Medical Imaging and Radiation Medicine (DMIRM) |
| Application Type and Number: | NDA 022335 |
| Product Name, Dosage Form, and Strength: | Technegas (Technetium Tc-99m labeled Carbon) aerosol for inhalation |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Cyclomedica Australia Pty Ltd (Cyclomedica) |
| FDA Received Date: | March 26, 2020, June 15, 2020, June 29, 2020, July 28, 2020, September 4, 2020, November 12, 2020 and November 13, 2020, and January 15, 2021 |
| OSE RCM #: | 2020-609 |
| DMEPA Safety Evaluator: | Devin Kane, PharmD |
| DMEPA Team Leader: | Hina Mehta, PharmD |

## 1 REASON FOR REVIEW

Cyclomedica Australia Pty Ltd submitted NDA 022335 Technegas (Technetium Tc-99m labeled carbon aerosol) for inhalation on March 26, 2020. Technegas is a radioactive diagnostic agent being proposed for functional lung ventilation imaging (b) (4) in adult and pediatric patients. We note Technegas is produced in the TechnegasPlus Technegas generator from a reaction involving Sodium Pertechnetate, argon gas, and the (b) (4) carbon crucible. We evaluated the proposed (b) (4) crucible container label, (b) (4) crucible blister pack labeling, TechnegasPlus generator labels, TechnegasPlus Technegas Generator User Manual, and Technegas prescribing information (PI) for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B – N/A |
| Human Factors Study | C – N/A |
| ISMP Newsletters* | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Cyclomedica Australia Pty Ltd submitted a 505(b)(2) marketing application for Technegas (Technetium Tc-99m labeled carbon aerosol) for inhalation. Technegas is produced through the use of the TechnegasPlus Technegas Generator. Per Cyclomedica, "the system requires a general purpose 20 A electrical outlet, user supplied Technetium-99m (Tc 99m) as sodium pertechnetate solution, pure non-denatured ethanol (greater than or equal to 95%), and high purity (greater than or equal to 99.997%) argon gas to create Technegas". The TechnegasPlus Technegas Generator is a Class IIb medical device, and it "uses a combination of graphite in the

form of the (b) (4) crucible and an inert argon atmosphere to reduce then vaporize Technetium Tc-99m generator eluate in a steel chamber".

We note the aerosol is administered to the patient using a patient administration set. As such we sent an information request (IR) to Cyclomedica on November 4, 2020 requesting the submission of the labels and labeling for the patient administration set (PAS). On November 12, 2020 Cyclomedica submitted a response to the IR stating "The PAS, K200916, that will be used with the TechnegasPlus Generator to deliver Technegas to a patient received 510(k) clearance from FDA on September 1, 2020". See Appendix G for the approved patient administration set labels and instructions for use.

We performed a risk assessment of the proposed (b) (4) label, (b) (4) blister pack labeling, TechnegasPlus generator labels, TechnegasPlus Technegas Generator User Manual,, and Technegas prescribing information (PI)) to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation identified areas of vulnerability that may lead to medication errors. We note there are areas of the proposed PI and TechnegasPlus Technegas Generator User Manual that can be revised in order to improve the overall readability of important material.

# 4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed (b) (4) crucible label, (b) (4) crucible blister pack labeling, TechnegasPlus generator labels, TechnegasPlus Technegas Generator User Manual, and Technegas prescribing information (PI) identified areas that can be improved to increase readability and prominence of important information and promote safe use of the product. We provide recommendations for the Division in Section 4.1 and for Cyclomedica in Section 4.2 below.

## 4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DMIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We note the use of the symbol "-" in order to represent the recommended range for sodium pertechnetate Tc 99m to be loaded into the crucible. We recommend removing the use of the symbol and replacing it with its intended meaning "to". Additionally, we note that not all values are followed by their units. We recommend including units after each numeric value to prevent misinterpretation. Revise the (b) (4) " to read " (b) (4) ".

b. We recommend dividing the first bullet into two separate bullets in order to improve the readability of this important information. The second

bullet should read "(b) (4) ."

2. Dosage Forms and Strengths
    a. We note that the dosage form for Technegas is "Aerosol for Inhalation". We recommend revising the first line of this section to read "(b) (4)

B. Prescribing Information

1. Section 2: Dosage and Administration Section
    a. As currently presented, Section 2.2 contains important dosing information presented in paragraph format. We recommend revising this section and utilizing bullet points in order to separate out the information and improve the overall readability.
        i. We recommend leaving the first two lines in paragraph format. The second sentence should be revised to read "(b) (4) follow the pulmonary count rate during inhalation of Technegas, using a gamma camera equipped with a standard collimator (low energy, low/medium resolution)".
        ii. The first bullet underneath the paragraph should contain all of the information pertaining to adult patients. We recommend having this bullet read "For adult patients, a lung count rate between 1,500 cps and 2,500 cps should be obtained. This corresponds to approximately 40 MBq (1.08 mCi) of inhaled Technegas".
        iii. The second bullet should include all of the dosing information for pediatric patients. This second bullet should read, "For pediatric patients, a lung count rate between 500 cps and 1,000 cps should be obtained. Inhalation should then be discontinued (b) (4) The radioactivity to be administered to pediatric patients is a fraction of the recommended activity for adults and adjusted by body weight (b) (4) in Table 1".
        iv. We recommend designating the dosing chart as "Table 1: Weight Based Dosing".
        v. As currently presented, the weight-based dosing table in section 2.2 contains values presented with trailing zeros. We recommend removing the use of the trailing zeros in order to avoid misinterpretation of the recommended dose and potential ten-fold overdose.

b. We note the last line of Section 2.2 regarding patient dosing is presented underneath the pediatric dosing table. In order to avoid this information being missed, we recommend moving this statement to be presented before the table under the bullet points.

c. As currently presented, Step 5 of Section 2.4 contains numeric values that are note followed by their units. We recommend including the appropriate units after each numeric value. Additionally, we note that dosing of Sodium Pertechnetate Tc 99m is only presented in 'MBq' and not in 'mCi' equivalent values. We recommend including both sets of units to align with the rest of the PI. Revise the dose in Step 5 to read "(b) (4)".

d. We note Step 9 of Section 2.4 states "Crucible fragments should be (b) (4)". Since each crucible is single patient use only, we recommend revising this statement to read "Crucible fragments should be (b) (4)".

2. Section 3: Dosage Forms and Strengths

a. We note that the dosage form for Technegas is "Aerosol for Inhalation". We recommend revising the first line of this section to read "Aerosol for Inhalation: (b) (4) .

3. Section 16: How Supplied/Storage and Handling Section

a. We note that Section 16.2 instructs the end user to store the high purity graphite crucibles (b) (4) We recommend providing (b) (4) in order to avoid any confusion.

C. TechnegasPlus Technegas Generator User Manual

1. We note the use of potentially confusing symbols throughout the User manual. We recommend removing the use of these symbols and replacing them with their intended meanings. For example, replace '-' with 'to' and replace '≥' with 'greater than or equal to'.

2. We note that not all numeric values are followed by their appropriate units. We recommend including units after each numeric value throughout the User Manual.

3. Consider stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" (e.g. 1,000 MBq instead of 1000 MBq), per Draft Guidance: Container and Carton April 2013 (lines 475-476), and ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.

4. The TechnegasPlus Technegas Generator User Manual currently refers to the Technegas Prescribing Information as the "Technegas Prescribing Information [(b) (4)] We recommend removing the word '[(b) (4)] from the description and referring to the material as the 'Technegas Prescribing Information (PI)'.
5. As currently presented, Section 6.2 provides the ambient temperature range in degrees Celsius. We recommend including the Fahrenheit equivalent values in parentheses.
6. We note the use of a trailing zero in the first bullet of Section 8. We recommend removing the use of this trailing zero in order to avoid confusion and potential for a ten-fold or 100-fold overdose.
7. We note the use of the symbol "µ" in Section 8 to represent "micro". We recommend avoiding the use of this symbol and presenting the units as "[(b) (4)] microL". Additionally, we recommend including a space in between the numeric value and the units for readability.
8. Section 17.3 provides the end user with the storage temperature conditions in degrees Celsius. We recommend including the Fahrenheit equivalent values in parentheses.
9. We note that there are abbreviations used throughout the User Manual that are specific to this product. For example, 'TP' is used to refer to the Techneplus Generator and 'PAS' is used to refer to the patient administration set. We recommend including a list of abbreviations and their intended meanings in the beginning of the User Manual for quick reference.

## 4.2 RECOMMENDATIONS FOR CYCLOMEDICA AUSTRALIA PTY LTD

We recommend the following be implemented prior to approval of this NDA:

A. Graphite Crucible Container Label, Batch Label, and Blister Pack Labeling

1. We note that each high purity graphite crucible is intended for single use only, and that the remnants are to be considered radioactive waste and discarded appropriately. We recommend including a statement on each [(b) (4)] label that states "Each Crucible is Single Patient Use Only. Fragments are Radioactive waste, discard all fragments appropriately".
2. As currently presented, there are no storage requirements provided on the three [(b) (4)] labels. We recommend including storage requirements on the labels presented as a temperature range in degrees Celsius with Fahrenheit equivalent temperatures provided in parenthesis.
3. We recommend including the statement "For use in the TechnegasPlus Technegas Generator Only. See Technegas Prescribing Information for more Information".

4. [redacted] (b) (4)

B. Graphite Crucible Container Label and Batch Label

1. We note the placeholder for the expiration date is in the format of MM/YYYY. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. Graphite Crucible Blister Pack Carton Labeling

1. We note the graphite crucible blister pack carton labeling states [redacted] (b) (4) at the top. We recommend having the top of the labeling state "[redacted] (b) (4) since it is referred to as [redacted] (b) (4) in the PI and Generator User Manual.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Technegas received on September 4, 2020 from Cyclomedica Australia Pty Ltd.

| Table 2. Relevant Product Information for Technegas | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | Technetium Tc-99m labeled Carbon |
| Indication | Indicated for functional lung ventilation imaging (b) (4) in adult patients. |
| Route of Administration | Inhalation |
| Dosage Form | aerosol for inhalation |
| Strength | Determined by quantity of sodium pertechnetate Tc-99m added to crucible, which is in range of (b) (4) |
| Dose and Frequency | Inhale approximately 40 MBq (1.08 mCi) as needed for functional lung ventilation imaging (until a lung count rate of between 1,500 cps and 2,500 cps is obtained). |
| How Supplied | Technegas (kit for the preparation of Technetium Tc 99m labeled carbon aerosol for inhalation) is supplied as a multiple dose kit consisting of 10 single-use (b) (4) *** crucibles. Each crucible contains about (b) (4) g of (b) (4) high purity graphite for use in the TechnegasPlus Technegas Generator. Each kit consists of five thermoformed blister packs of 10 crucibles in a cardboard box. |
| Storage | Store the crucibles (b) (4). Store the crucibles in the original package. |

APPENDIX G. LABELS AND LABELING

## G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Technegas labels and labeling submitted by Cyclomedica Australia Pty Ltd.

- Container label received on March 26, 2020
- Carton labeling received on March 26, 2020
- TechnegasPlus Generator Labels received on March 26, 2020
- Patient Administration Set Labels received on November 12, 2020
- Prescribing Information (Image not shown) received on September 04, 2020, available from \\CDSESUB1\evsprod\nda022335\0010\m1\us\114-labeling\114a-draft-label\uspi-tgas-redline-02sep2020.docx
- Generator User Manual (Image not shown) received on June 15, 2020, available from \\cdsesub1\evsprod\nda022335\0003\m1\us\114-labeling\114a-draft-label\technegasplus-generator-user-manual-redlined.pdf
- Patient Administration Set Instructions for Use (Image not shown) received on November 13, 2020, available from \\CDSESUB1\evsprod\nda022335\0018\m1\us\114-labeling\114a-draft-label\pas-ifu-k200916-7jul2020.pdf

## G.2 Label and Labeling Images

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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