CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022335Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 022335 Resubmission, Technegas
OPQ Integrated Quality Assessment (IQA)

Table of Contents

NDA Executive Summary

1. Application/Product Information

NDA Number.	22335
Applicant Name	Cyclomedica Australia, Ltd
Drug Product Name	Technegas™(Kit for the preparation of technetium Tc 99m labeled carbon for inhalation aerosol); 1.25 g carbon crucible
Dosage Form.	Aerosol
Strength	1.25 g carbon
Route of Administration	(Oral inhalation) Oral
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	TECHNEGAS, when used with sodium pertechnetate Tc 99m in the Technegas Plus System, provides technetium Tc 99m labeled carbon inhalation aerosol 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
Drug Product Description	TECHNEGAS (Kit for the preparation of technetium Tc 99m labeled carbon inhalation Aerosol). TECHNEGAS is produced in the Technegas Plus System, a device component of the overall Technegas kit, on-site and inhaled by the patient (directly from the system through a mouthpiece). Inhalation must be within 10 minutes of End of Synthesis.
Co-packaged product information	N/A
Device information:	TechnegasPlus System Patient Administration Set (PAS)

Storage Temperature/ Conditions	N/A		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	N/A	N/A
	Drug Product/ Labeling	Ravindra Kasliwal	Danae Christodoulou
	Manufacturing (process/facilities)	Krishnakali Ghosh	Vidya Pai
	Biopharmaceutics	N/A	N/A
	Microbiology	N/A	N/A
	CDRH	Berk Oktem	Xin He
	RBPM	Anika Lalmansingh	
	ATL	Eldon E. Leutzinger	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months for Technegas™(Kit for the preparation of technetium Tc 99m labeled carbon for inhalation aerosol) stored at 15-30^{0}C (59 – 86^{0}F) may be granted

b. Additional Comments for Action: None

4. Basis for Recommendation:

INTRODUCTION:

An action letter (Complete Response, CR) was issued to Cyclomedica Australia on 6/25/2021 informing the firm of multiple deficiencies that make up the non-approvability

of the NDA. And on 3/29/2023 a response to the CR letter was received and categorized as a "resubmission" Class 2 with a user fee date of September 29, 2023.

From the CR letter of 6/25/2021 there were multiple categories of deficiencies that made up the non-approvability of the NDA and that involved three major areas (Drug Product Quality, Process and Device). **The central theme of it all rests with Characterization and Controls of the Aerosol Drug Product** which is also that shared specifically within the category of **Product Quality**, its inadequacy, including insufficient validation of the aerosol drug production and documentation, insufficient analytical methods to characterize the aerosol particle size distribution and radioactivity, aerosol yield, and a most fundamental piece of it all, the carbon crucible.

Its hard not to recognize the fundamental place occupied by the carbon (graphite) crucible, because **all the carbon in the ^{99m}Tc/C particle of the drug product aerosol originates from this crucible. The carbon is the vehicle that carries the ^{99m}Tc^{0}, together becoming the active ingredient of the aerosol drug product.**

The crucible is being consumed during the burn cycle and converted into graphene vapor (by sublimation). Hence, crucible quality is a function not only of its dimensions, but also in terms of its constitution, including a theoretical insertion of impurities during manufacture. As such it becomes one of the factors connecting crucible quality with ^{99m}Tc/C aerosol product quality. See Notes "On Product Complexity" at end of this ATL Review and Executive Summary. There were additional categories contributing to the approvability enumerated in the Action Letter that included Process and Device.

For **Process**, it was environmental controls, manufacturing control strategy for (b) (4) Crucible, shipping (relating to crucible shipping studies) to production (relating to failure to demonstrate consistent and reliable production of Tcm-99 carbon aerosol under good manufacturing conditions), reliability assessment and yield. And exposure dose for **Device**.

a. Summary of Rationale for Recommendation:

Overall Rationale:

Summarizing over all components (drug substance, drug product, manufacturing and facilities, device, and labeling), all deficiencies identified are resolved and there is nothing left pending. All facilities have been determined to be adequate.

Summary of Assessments (Product Quality):

- **Assessment of Chemical Type and Drug Classification Code**

During review of the original submission, a designation of chemical type (NME) had temporarily been made but awaiting a more thorough analysis during review of the NDA and an updated determination.

Firstly, it is established that there is no chemical bond between ^{99m}Tc and C in the Technescan particle of the aerosol and that the ^{99m}Tc in the particle is in the zero-

oxidation state ($^{99m}Tc^{0}$) (see the ATL/Executive Summary for NDA 22335, Resubmission). ^{99m}Tc, an excited state (energy state) of this isotope of Technetium, does not qualify as a new isotope of Tc because of its appearance among the already FDA-approved products with the same isotope. Hence, Technescan is excluded from NME based on these criteria in MAPP 5018.2.

As for the oxidation state ($^{99m}Tc^{0}$) this can be considered within the scope of a **formulation change**. However, Technegas, an aerosol drug product is also a **different dosage form** than injectable dosage forms previously approved for ^{99m}Tc products. The one administered by a nebulizer is a solution and not as labeled particles in a gas. Based on these considerations, due to the uniqueness of this product, the appropriate chemical type is **Type 3** (New Dosage Form).

- **Meeting with NRC regarding Licensing of TechnegasPlus System**

There was a communication from Cyclomedica Australia Pty Ltd (July 20, 2023) confirming that they have informed the NRC of their application currently under review with the FDA. And, on September 5, 2023 there was a meeting between NRC and FDA to discuss the Technegas application under the NRC-FDA Memorandum of Understanding.

The purpose of this meeting was to discuss the question whether NRC had any licensing concerns for the TechnegasPlus System and associated issues. From this meeting, it is learned that NRC is not issuing any special license for the TechnegasPlus System. So, users who are licensed to use technetium generators and technetium radiopharmaceutical kits may use the TechnegasPlus System under existing NRC regulations.

- **Summary of Assessments (Drug Product)**

Characterization and control of the aerosol drug product.

A central issue (CR Letter of 6/25/2021) regards Technegas product quality was the inadequate characterization and control of the aerosol drug product. This is an issue that, e.g., results in inability to directly measure the dose that will be inhaled by the patient, presenting stumbling blocks to defining its strength. In response to the characterization issue, Cyclomedica partnered with radiopharmaceutical drug and inhalation drug development groups to develop specifications including analytical methods to characterize Technegas aerosol, assuring the identity, radiochemical purity, radioactivity and mass concentration and particle size of the Technegas aerosol. In turn, these analytical methods allow for establishment of the aerosol composition including particle information for the 10 min aerosol administration. These results are described in the Drug Product review (Dr. Ravi Kasliwal).

Along with this, Cyclomedica had Technegas Aerosol produced and tested using Sodium Pertechnate Tc 99m from Curium US, Lantheus and NorthStar Mo-99/Tc-99m generators, at both low end of the recommended activity loading range, and at or near the high end of the recommended activity loading range (at (b) (4)). They showed that Technegas Aerosol can reliably be produced meeting the specifications listed for Sodium Pertechnetate Tc99m Injection from any of the three USA-FDA approved Tc-99m generator manufacturers.

Sodium Pertechnetate Tc99m ($^{99m}TcO_4^-$) is transformed in the TechnegasPlus System to $^{99m}Tc^0$ by ignition while filled in a reservoir in a carbon crucible. This transformation is a chemical reduction by carbon of the carbon crucible, as described in the following equations:

$$2NaTcO_4 + 3C \rightarrow CO_2\uparrow + 2CO\uparrow + 2NaTcO_2 \rightarrow 2NaO_2\uparrow + 2Tc^0$$

Thus, two conclusions can be drawn from these considerations.

♦ The volume of the crucible reservoir determines the upper limit of the amount of Sodium Pertechnetate Tc99m Injection that can be ignited in the crucible of the TechnegasPlus System. This effectively puts a limit on the amount of ^{99m}Tc activity that can be in the Technescan dose inhaled by patients, given that pertechnate is taken from the most efficient point in the transient activity-decay curve and point in the shelf-life of a technetium generator. So, the ^{99m}Tc activity in the dose can vary from a minimum to maximum amount. $^{99m}Tc^0$ represents one of the two components of the Technescan formulation.

♦ The other component of the formulation is carbon, for afterall carbon is one of only two "elements" of the Technescan particle (reminiscent of a mineral, but whose stoichiometry in terms of a range is less well-defined). Although some of the carbon is converted to CO_2 and CO, the amount of carbon is in relation to the amount of pertechnetate in the crucible reservoir and essentially negligible by comparison to the mass of carbon of the crucible. Hence, **for practical purposes, the entire 1.25 g of carbon of the crucible can be considered to be nested within the Technegas particles ($^{99m}Tc^0$/C) of the Technegas aerosol** (refer to Assessment of Chemical Type and Drug Classification Code under Additional Lifecycle Comments). Hence, the active ingredient of the drug product (Technegas aerosol) can be considered the guest-host assembly (^{99m}Tc/C).

The Drug Product Name/Strength has been chosen as **Technegas™(Kit for the preparation of technetium Tc 99m labeled carbon for inhalation aerosol); 1.25 g carbon crucible** (from the Drug Product review of Dr. Ravindra Kasliwal). The "strength" piece makes sense (ATL) when put into the context of the carbon crucible, because it is the crucible from which all of the carbon component in the guest-host assembly of Technegas (the active ingredient) originates. The carbon crucible is the fundamental piece in the TechnegasPlus System.

(ATL). We can do a thought experiment as follows, based on the definition of strength. Strength is the amount of drug in a dosage form or a unit of the dosage form.

The dosage form here is an aerosol. In the most elementary sense, the unit of dosage form would be the ^{99m}Tc/C particle if all such particles were of uniform size (e.g., particle mass). But that's not the case. Rather, it is a distribution of particle sizes. But, if this distribution is uniform throughout the aerosol (not a bad assumption), so that each of our imaginary capsules contains the mass of aerosol, each capsule would represent a unit dosage form and would fit the definition of strength. Since the dosage form is an aerosol, if we blew this imaginary capsule up to the volume of aerosol inhaled the size would be 1.25 g, the strength ("mass strength"), all the mass in the 1.25 g carbon crucible. Since it is a fixed value, whereas the amount of ^{99m}Tc activity is variable, 1.25 g is a suitable strength-characterization of Technegas.

From this, you could define two contributions to a strength specification (mass strength, activity strength) and this is what Cyclmedica has done (see pp. 25-26, Drug Product Review, Ravi Kasliwal), a result of their addressing the Characterization and control of the aerosol drug product issue, cycling back to the carbon crucible wherein lies controls of the aerosol drug product from a product quality perspective rest. In the interest of closing the loop, updated crucible specifications and associated information and this has been received. Together with all responses from Cyclomedica regards Characterization and control of the aerosol drug product these issues are considered **Resolved**.

- **Summary of Assessments (Manufacturing – Process/Facilities):**

Here is a High-Level Summary for Manufacturing – Process/Facilities, reproduced from an email (9/08/2023) from Dr. Krishnakali Ghosh, and is signed as final in Panorama (9/08/2023) as adequate.

Technegas™ (kit for the preparation of Technetium Tc-99m Labeled Carbon Aerosol) is prepared using the carbon crucible and the automated synthesis module referred as the TechnegasPlus system. The generation of the Technegas™ aerosol occurs within the Technegas Plus™ system. This is an electrically powered equipment operated at clinical point of use, by nuclear medicine professionals. The automated system first dries the Sodium Pertechnetate Tc-99m Injection eluate by removing the water from the saline carrier solution then raises the temperature of the carbon crucible to 2750°C ± 100°C within 2 seconds and maintains this temperature for a period of 15 ± 1 second(s) to produce Technegas™ aerosol. The patient needs to inhale the aerosol within 10 minutes of production of the aerosol. Cyclomedica Australia is responsible for manufacturing of the carbon crucible, Technegas system components and the PAS delivery unit used by patients. This manufacturing site was deemed unacceptable for commercial manufacturing of Technegas™ due to

lack of product specific manufacturing process and facility controls. Hence this site was re-inspected during the resubmission of NDA 022335 due to inadequate responses to the FDA 483 observations during the initial PAI inspection in 2021.

In response to the CR deficiencies related to the manufacturing process and FDA 483 observations issued during the original submission preapproval inspection, the firm has implemented major "Corrective actions" along with establishment of acceptable in-process and final specifications and testing for the carbon crucible and the Technegas aerosol. New exhibit batches were executed with US crucible specifications and newly established quality attributed for the Technegas aerosol. OPQ/OPMA has completed its review of multiple FDA Post Action Letter deficiency responses and supportive GMP compliant procedures and closures of CAPA activities. The firm has executed multiple training sessions of personnel to ensure that the newly developed GMP manufacturing and testing procedures are adequately executed to support commercial manufacturing. A follow up PAI inspection was conducted during this resubmission to inspect the effectiveness of the implemented corrective actions which resulted in a VAI classification with easily correctable FDA 483 deficiencies. Based on the detailed review of all the corrective actions from the re-inspection, Cyclomedica facility is acceptable for manufacturing of the TechnegasPlus system, aerosol and the PAS unit at the facility and is recommended for application approval.

- **Summary of Assessments (CDRH):**

The Device components consist of the TechnegasPlus System and a Patient Administration Set (PAS). There is a recertification date for the TechnegasPlus System of one year. Upon recertification, the applicant verifies the product (aerosol) attributes.

Of the issues in the CR letter, those for CDRH focused on exposure doses and threshold values in the calculation of margin values for all detected chemicals. These concerns involved concentrations of [redacted] (b) (4) and other low molecular weight [redacted] (b) (4) compounds, and an unlabeled peak in a chromatogram for which there is lack of identity which needs a toxicological risk assessment. In an email from Berk Oktem (9/08/2023), the information to address these concerns has been evaluated. The following is from this email (in quote) with conclusions indicating that the device biocompatibility concerns are addressed at this time:

I reviewed the information we received in Sequence 51 and 54. Along with additional literature search and further discussion with Dr. Alan Hood (cc'd), we determined that the reported VOC amounts will present a tolerable risk to patients 6 years and older- based on patient population in the proposed label.

We consider the device biocompatibility concerns addressed at this time.

RE_ CMC- CDRH concerns for Techneg

A copy of this email is as follows:

- **Summary of Assessments (Microbiology):** No Action Indicated and no document in Panorama

- **Summary of Assessments (Biopharmaceutics):** No Action Indicated and no document in Panorama

- **Summary of Assessments (Labeling – CMC):**

From the Labeling Review (9/14/2023), Ravi Kasliwal:
The **Overall Assessment** is "Adequate with the indicated revisions to the container and carton labels." These revisions are enumerated in the Labeling Review.

The **established name** is "TECHNEGAS® (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol)

How Supplied section of PI:
TECHNEGAS (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol) is a 1.25 gram black to dark grey oval shape graphite carbon crucible packaged into thermoformed blister packs. Each carton contains five blister packs of 10 single-use Technegas Crucibles (NDC 73814-986-20).

Storage and Handling section of PI:
Storage and Handling Store Technegas Crucibles at 15°C to 30°C (59°F to 86° F). Store unused crucibles in the original package to prevent contamination of crucibles.

(The "kit" refers to the carbon crucible. Pertechnetate and argon, etc. are items supplied separately from the kit)

And from the Drug Product Review (within the section on Container Closure, p. 29 -30):
The container closure system for the Technegas crucible is a blister pack. (b) (4) 10-unit blister pack where each blister pack has pre-formed slots to accommodate individual crucibles. Each filled blister pack is closed using a backing card to form a 10-unit blister pack. Five (5) packs are then packed in a Cardboard Carton with the USPI, the carton is closed and labelled with the Batch Number and Expiry Date of the product.

The maximum use period for the Technegas Plus System is one year or 500 burn cycles, whichever occurs first. After this period, ask Cyclomedica to perform maintenance and recertify the Technegas Plus System for use.

For an example of the label see Labeling Review of 9/14/2023.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**N/A**

Environmental Assessment: Choose an item.
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

► Expiration Dating:
24 months for Technegas™(Kit for the preparation of technetium Tc 99m labeled carbon for inhalation aerosol) stored at 15-30^{0}C (59 – 86^{0}F) may be granted. Graphite of which the carbon crucibles are made is thermodynamically stable at normal temperatures and pressures and is not expected to change with time. The use period for the Technegas aerosol drug product is 10 min at 15-30^{0}C (59 – 86^{0}F).

► Assessment of Chemical Type and Drug Classification Code (ATL):
During review of the original submission, a designation of chemical type (NME) had temporarily been made but awaiting a more thorough analysis during review of the NDA and an updated determination. There are two considerations, the chemical entity (^{99m}Tc^0/C entity) as a whole, and the radionuclide (^{99m}Tc^0).

IN SUMMARY:
Firstly **(1)** consider the ^{99m}Tc^0/C entity. It is established that there is no chemical bond between ^{99m}Tc^0 and C, this by the finding in the T.J.Senden, et.al., in the seminal scientific and peer reviewed paper [*J. Nucl. Med, and38,1327-1333 (1997)*] of no carbides,

oxides, or discrete radiolabeled fullerenes as C_{60} or C_{70} in the aerosol. So, the carbon serves as a kind of carrier (**host in intercalation**) for the radionuclide.

Given that there is no chemical bond between $^{99m}Tc^0$, **(2)** it comes down to focusing on the $^{99m}Tc^0$, an excited state (energy state) of an isotope of Technetium (Tc) and a specific oxidation state of this isotope. MAPP 5018.2 excludes it from an NME because being ^{99m}Tc does not qualify it as a new isotope of Tc among the already approved products with the same isotope. Now as **for the oxidation state ($^{99m}Tc^0$), it can be considered within the scope of a formulation change**, although it is a prime factor in determining type of binding and stoichiometry in an organic-based technetium derivative. However, Technegas, an **aerosol drug product is also a different dosage form** than injectable dosage forms previously approved for Tc 99m products. The one administered by a nebulizer is a solution and not as labeled particles in a gas. Based on these considerations, due to the uniqueness of this product, the appropriate chemical type is **Type 3** (New Dosage Form).

(**Absence of Chemical Bond Between $^{99m}Tc^0$ and Carbon of Technegas Aerosol**)
The finding by T.J.Senden [*J.Nucl. Med, 38,1327-1333 (1997)*], that (1) no carbides, oxides, or discrete radiolabeled fullerenes such as C_{60} or C_{70} are found in the aerosol, as well as the finding that (2) the technetium in the aerosol exists as hexagonal metal crystals are consistent with **^{99m}Tc in the technegas particle ($^{99m}T/C$) as $^{99m}Tc^0$, remaining in the zero-oxidation state after the reduction of $^{99m}TcO_4^-$ at the crucible interface in accordance with the following:**

$$\mathbf{2KTcO_4 + 3C \rightarrow CO_2\uparrow + 2CO\uparrow + 2KTcO_2 \rightarrow 2KO_2\uparrow + 2Tc^0}$$

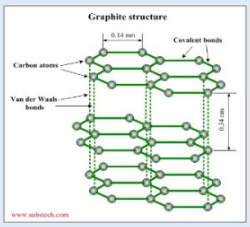
The product is $Tc^0/^{99m}Tc^0$ shown as the last entry in the above cascade of reactions. Senden uses $K^{99}TcO_4$ as a surrogate for $Na^{99m}TcO_4$ in these studies and its applicability is based on K and Na in the same Group in the Periodic Table (similar chemical and physical properties). $^{99m}TcO_4^-$ possesses the same chemistry as $^{99}TcO_4^-$ in either the K^+ or Na^+ salt because ^{99}Tc and ^{99m}Tc are isotopes of the same element and therefore possess the same chemistry, and there is no change in the chemical form (i.e., as pertechnetate, TcO_4^-). This paper is referenced in the NDA for the chemistry of production of $^{99m}Tc/C$ in the Technegas system.

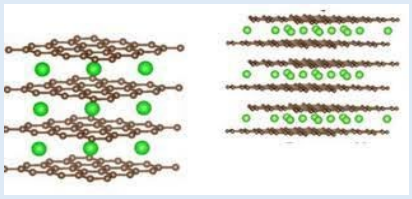
The conclusion (^{99m}Tc in the aerosol is in the zero-oxidation state ($^{99m}Tc^0$) is based on Electron diffraction of the aerosol together with EDXA (Electron-Dispersion X-Ray Analysis) from. EDXA is an analytical method that rapidly performs elemental analysis of a sample on different areas of the sample.

With Scanning Electron Microscopy (SEM) of the surface of the metallic technetium in the aerosol, **Senden showed that the shape of the crystals of $^{99m}Tc^0$ is hexagonal**

(platelets) covered with a thin layer of graphite. As a kind of carrier for $^{99m}Tc^0$, the latter is intercalated within graphene layers of graphite. And the intercalated $^{99m}Tc^0$ remains intercalated during aerosol product inhalation by patients. **Intercalation refers to the insertion of a guest molecule or ion into a host lattice.**

INTERCALATION:
The structure of graphite consists of honeycomb graphene sheets stacked together and held in place by van der Waals forces (left panel). In this illustration from the literature, think of this stack as the Host, and the green balls (right panel) as the hexagonal crystals of $^{99m}Tc^0$ caught between the sheets, the result (guest-host) for technegas being the ^{99m}Tc/C of the aerosol product.





Host Guest-Host

Intercalation is a well-established phenomenon in chemistry and mineralogy reaching far and wide into many diverse areas.

An associated corollary often met (but not always) and of great importance in intercalation is that of the **guest-host** entity being only slightly perturbed from the host lattice and the process is generally reversible. On this point, hexagonal Tc^0 (and the likeness in $^{99m}Tc^0$) crystal dimensions are far larger than those of the analogous single benzene molecule but would easily fit within honeycomb sheets (layers) of hexagons of carbon. And it may be a mutual flatness of hexagonal platelets of $^{99m}Tc^0$ and honeycomb structure of graphene that perhaps fuels a geometry-driven mode of interaction (in lieu of actual chemical bonding) to give these **inclusion structures** just enough stability in the aerosol to perform its function on inhalation by patients.

The experimental observation that ^{99m}Tc in the technegas particle ($^{99m}T/C$) remains in the zero-oxidation state, $^{99m}Tc^0$, after reduction of $^{99m}TcO_4^-$ (T.J.Senden, et.al) strongly suggests that a bond between $^{99m}Tc^0$ and C is not formed while intercalated. That it is highly unlikely (if not ruled out) is consistent with theory. Consider the valence electrons ($4d^5 5s^2$) in ^{99m}Tc. Electrons must be removed from the configuration for bonding to occur, and the schedule for that is in accordance with the energies in relation to that for filling the orbitals. No chemical bonds to Tc^0 can form until electrons are removed from these orbitals, the first starting from the orbital of lower energy ($5s^2$), requiring an input of 702 kJ/mol (the first ionization potential).

In accordance with the Senden paper (see section on structure, page 5), the coating of technetium occurs after its crystallization (melting point 2157^0C) and that form is crystalline technetium (Tc^0). But the pertinent temperature is that of the graphite vapor whose sublimation temperature we can assume to be that at the lit value of ~ 2700^0C. Therefore, we can calculate the amount of thermal energy in a mass of graphite (that is vaporized) at this temperature. Based on a 0.001 kg mass of graphite carbon, and assuming a specific heat capacity in joules per deg C (lit), there are [0.001 x 4180 x (2700 – 25)] joules, i.e., 11181.5 joules in one gram mass (11.2 kJ/g), or 134.2 kJ/mol, far less than the first ionization energy of 702 kJ/mol required to remove an electron from the $5s^2$ orbital. The ionization energies to remove successive electrons (5s) and the $4d^5$ electrons markedly increase, thus precluding any likelihood of chemical bonding of $^{99m}Tc^0$ with carbon while intercalated.

The "carbon" of Technegas is also in elemental form, $[He]2s^22p^2$. In this case the 2p shell is of lower energy than the 2s shell and thus also in a stable state; the only way it can form a covalent bond with either itself or with other elements is to receive enough energy to promote one of the $2s^2$ electrons to hybridize with the lower energy p-orbital. In this context, the first ionization potential of carbon is 1086.5 kJ/mol. That for the second ionization potential is 2352.6 kJ/mol, thus piggybacking on the same conclusions of the preceding paragraph, with theory thus supporting the experimental findings of the Senden paper.

In contrast to such an inclusion structure is a structure of two or more atoms that possesses sufficient strength to exist as an independent molecular entity. **The science here is clear; taking on a tag as an NME would imply that ^{99m}Tc/C of the aerosol would necessarily be an independent molecular entity (a distinct chemical unit whereby ^{99m}Tc and C are held together by a chemical bond or other mechanism to give it sufficient strength to exist as such). In conclusion, neither of these conditions is met in ^{99m}Tc/C for it to be such molecular entity.**

►Notes on Product Complexity (ATL)

For this, reference is made to N22335-OPQ-EL-1300 in Panorama (5/27/2021). But, in summary, **$^{99m}Tc^0$ in the ^{99m}Tc/C aerosol exists as hexagonal crystals intercalated between layers of graphene**, proven by EDXA (Electron-Dispersion X-Ray Analysis) and Scanning Electron Microscopy (SEM) [*T.J.Senden*, et.al., *J. Nucl. Med, 38, 1327-1333 (1997)*]. From the spectroscopic evidence in this paper and the finding that no carbides are found in the crucible sinter nor in the ^{99m}Tc/C aerosol, it is concluded that there are no chemical bonds between $^{99m}Tc^0$ and C. This is an important observation since carbides of Re do exist, and both Re and Tc are in the same Group 7 in the Periodic Table. The conclusion (*Senden*) is that if some TcC had formed and was initially present in the crucible sinter, it would be unstable (on grounds of energetics). Its instability is evidenced (lit) in a positive energy of formation (enthalpy non-negative with a large spread in ΔH^0 between energy of $^{99m}Tc^0$ and ^{99m}TcC in their standard states) and mechanistically ascribed (lit) to lattice distortion upon insertion of C atoms within the interstices of Tc metal at and above 2000^0C. **Chemical reactions that are favorable**

in general possess negative enthalpies (heat absorbed) and the fact that here we are talking about instability at such elevated temperatures leaves little question about the expectations and results at room temperature.

The carbon (C) in ^{99m}Tc/C aerosol originates from the carbon (graphite) crucible intercalating as graphene layers around $^{99m}Tc^{0}$ platelets (crystals). But this origination of the carbon (as graphene) **elevates the crucible to a critical material of the system, in theory connecting crucible quality with ^{99m}Tc/C aerosol product quality, a point brought out in the Action Letter of June 30, 2021**. In this context, crucible quality is a function not only of its dimensions, but also in terms of its constitution, including insertion of impurities during manufacture. Since the crucible is being consumed during the burn cycle and converted into graphene vapor (by sublimation), there is a theoretical risk for impurities (e.g., metal cations) in the carbon crucible to be carried into the aerosol and affect product quality.

On this point (ATL), pure graphite has a defined (theoretical) density of 2.26 g/cm^3. And mineralogy textbooks put's the mineral in the range of 2.1 – 2.3 g/cm^3. Also, it is known (lit) that synthetic graphite contains metallic impurities intercalated between sheets of graphene. In this context, the value obtained in the commercial sources of graphite (NDA) is in the range of (b) (4) g/cm^3, (b) (4) g/cm^3) in he mineral, suggesting two possibilities to account for the differences (impurities or porosity). **It's not just crucible dimensions, but also the degree of broadness of this density range ((b) (4) g/cm^3) which creates the link between crucible quality to ^{99m}Tc/C aerosol and that of its safety and effectiveness**. This issue is embraced in a comment conveyed to the applicant and is resolved.

119 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Eldon Leutzinger

Digitally signed by Eldon Leutzinger
Date: 9/19/2023 02:48:47PM
GUID: 508da7210002a0781943eff6cc724d1f

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information on labeling submitted on 8/28/2023

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)1	Adequate	TECHNEGAS® (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol)
Route(s) of administration	Adequate	for oral inhalation use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	TECHNEGAS (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol) is a 1.25 gram black to dark grey oval shaped graphite carbon crucible (Technegas Crucible). Upon addition of sodium pertechnetate Tc 99m injection, USP to the Technegas Crucible, the Technegas Plus system provides Technegas Aerosol for oral inhalation. (3)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Inadequate	We have recommended that single -use be added to dosage form statement.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	

For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	It is a radioactive inhalation product which is produced in a closed chamber at bedside. Visual observation is not possible.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	There is no USP monograph.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	Adequate	It is included.
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	Adequate	Warning and precautions have been included regarding the use (b) (4).

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Dosage form is "inhalation aerosol".
Strength(s) in metric system	Adequate	Strength is 1.25 gram
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Single use is indicated.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	TECHNEGAS (kit for the preparation of technetium Tc 99m labeled carbon inhalation aerosol)
Dosage form(s) and route(s) of administration	Adequate	Dosage for "inhalation aerosol" is included. Route of administration "for oral inhalation" is included.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	The only inactive ingredient is argon gas, which is included.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	It is an oral inhalation product.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	There is no alcohol as inactive ingredient.

Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	“Radioactive diagnostic agent” is included.
Chemical name, structural formula, molecular weight	Adequate	The kit consists of Graphite carbon. The physical dimension of the kit and relevant properties of the Technegas aerosol are included.
If radioactive, statement of important nuclear characteristics.	Adequate	Properties of Tc-99m are Included in section 11.2.
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	**Items in Proposed Labeling** (choose “Adequate”, “Inadequate”, or “N/A”)	**Assessor’s Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling	N/A	There is no USP monograph.

requirement may be applicable to another section of the PI (e.g., Section 2).		

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	"inhalation aerosol" is included.
Strength(s) in metric system	Adequate	"1.25 gram" is included.
Available units (e.g., bottles of 100 tablets)	Adequate	Each carton contains five blister packs of 10 single-use Technegas Crucibles (NDC 73814-986-20).
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	"Black to dark grey oval shape graphite carbon crucible packaged into thermoformed blister packs", is included.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable drug product.

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store (b) (4) Technegas Crucibles at 15° to 30°C (15° to 86° F). Store unused crucibles in the original package to prevent contamination of crucibles. Graphite is very stable, and 15-30 degree is acceptable.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	There is no Latex.

Include information about child-resistant packaging	Choose an item.	

1.2.5 Other Sections of Labeling

None

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured by: Cyclomedica Australia Pty Ltd Unit 4, 1 The Crescent Kingsgrove NSW 2208 Australia Website: www.cyclopharm.com

2.0 PATIENT LABELING

There is no patient labeling. The product is administered in Hospital or Imaging Centers by a qualified person.

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(b) (4)

3.2 Carton Labeling

70666 Technegas Crucible 50 Pack Carton Label

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Inadequate	The proprietary and established name should be as follows in container label: **Technegas™** (Kit for the Preparation of Technetium Tc 99m labeled Carbon Inhalation Aerosol)
Strength(s) in metric system	Adequate	Strength is included. "Weight: 1.25 gram per crucible" However, it should be relocated to below the established name.
Route(s) of administration	Inadequate	It is not indicated. Include following below the Strength Statement. "For Oral Inhalation after radiolabeling with Technetium Tc 99m in Technegas Plus System"
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Inadequate	Revise the statement to statement "Contains 10 Single-Use Graphite Carbon Crucibles"
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	A separate sticker is affixed to the label for batch number and expiration date.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	Revise the Storage Statement: "Store at 15°C-30°C (59°F-86°F) in Original Container."

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	Not an injectable product.
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	There is no alcohol inactive ingredient
Linear Bar code	Adequate	Bar code is included.

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap Overseal unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	There is no USP monograph.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	There is no USP monograph.
And others if space is available.	Inadequate	Include Statements: Do not use broken / fractured crucible.

Provide revised Technegas Crucible container and carton Labels with following revisions:

Technegas Crucible backing Card:

- Remove the word Crucible and place Kit for the preparation of technetium Tc 99m labeled carbon in halation aerosol in the brackets, as follows:
  Technegas®
  (Kit for the preparation of technetium Tc 99m labeled carbon in halation aerosol)

- Place the strength statement "Weight: 1.25 gram per crucible" below the established name.

- Route of administration is not included. Include statement "For Oral Inhalation after radiolabeling with Technetium Tc 99m in Technegas Plus System".

- Revise the content statement to "Content: 10 single-use crucibles of high purity Graphite."
- Revise the storage statement "Store at [redacted] (b) (4)' to "Store at 15°C-30°C (59°F – 86°F)"
- Add statement ""Do not use broken / fractured crucible" in bold.

Technegas Crucible 50 pack Carton label:

- The dosage form for this product is "for inhalation aerosol" and not "Kit". Remove "Dosage form: Kit" from the label. The established name contains the dosage form.
- Change the route of administration to "For Oral Inhalation after radiolabeling with Technetium Tc 99m in Technegas Plus System".
- Revise the storage statement "Store at [redacted] (b) (4) to "Store at 15°C-30°C (59°F – 86°F)"

Assessment of Carton and Container Labeling: *Inadequate*

ITEMS FOR ADDITIONAL ASSESSMENT

Technegas Crucible backing Card:

- Remove the word Crucible and place Kit for the preparation of technetium Tc 99m labeled carbon in halation aerosol in the brackets, as follows:
  Technegas®
  (Kit for the preparation of technetium Tc 99m labeled carbon in halation aerosol)
- Place the strength statement "Weight: 1.25 gram per crucible" below the established name.
- Route of administration is not included. Include statement "For Oral Inhalation after radiolabeling with Technetium Tc 99m in Technegas Plus System".
- Revise the content statement to "Content: 10 single-use crucibles of high purity Graphite."
- Revise the storage statement "Store at [redacted] (b) (4) to "Store at 15°C-30°C (59°F – 86°F)"
- Add statement ""Do not use broken / fractured crucible" in bold.

Technegas Crucible 50 pack Carton label:

- The dosage form for this product is "for inhalation aerosol" and not "Kit". Remove "Dosage form: Kit" from the label. The established name contains the dosage form.
- Change the route of administration to "For Oral Inhalation after radiolabeling with Technetium Tc 99m in Technegas Plus System".

- Revise the storage statement "Store at (b) (4), to "Store at 15°C-30°C (59°F – 86°F)"

Overall Assessment and Recommendation:

Adequate with the indicated revision to the container and carton labels.

Primary Labeling Assessor Name and Date:

Ravindra K. Kasliwal, Ph.D. *06-Sep-2023*

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Danae D. Christodoulou, Ph.D. *14-Sep-2023*

Ravindra Kasliwal

Digitally signed by Ravindra Kasliwal
Date: 9/18/2023 07:51:56AM
GUID: 508da7220002a0e4e2c176d5eddcbe42

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 9/18/2023 09:51:36AM
GUID: 5050dd27000012a4c69bfc70b47660b7

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

/s/

ANIKA A LALMANSINGH
09/20/2023 10:56:04 AM

ELDON E LEUTZINGER
09/20/2023 01:51:41 PM

NDA 022335 Integrated Quality Assessment (IQA)

Table of Contents

QUALITY ASSESSMENT

Recommendation: ***Complete Response***

NDA [22335]

Technegas

Review #[FINAL]

Drug Name/Dosage Form	Technegas (technetium Tc 99m carbon aerosol)
Strength(s)	(b) (4)
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Applicant	Cyclomedica Australia, Ltd
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED (seq. no.)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Origional	03/26/2020	OPQ-CMC, Microbiology, OPMA

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	N/A	N/A
Drug Product	Anne Marie Russell	Danae Christodoulou
Process/Facilities	Krishnakali Ghosh	Vidya Pai
Microbiology	Maritere Carattini	John Metcalfe
Environmental	Anne Marie Russell	Danae Christodoulou
RBPM	Anika Lalminsingh	N/A
Application Technical Lead	Eldon E. Leutzinger	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: N/A

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments

B.

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS

DISCIPLINE	RECOMMENDATION	DATE	REVIEWER
N/A			

Executive Summary

I. Overall Recommendation on Approvability

OPQ recommends [**COMPLETE RESPONSE**] of NDA [022335] for commercialization of [Technetium (technetium Tc 99m carbon), aerosol of technetium Tc 99m carbon particles in (b) (4) gas of undefined strength] with an expiration dating period of [10] minutes:

- The applicant [has not] provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The aerosol product has not been adequately characterized, and the individual deficiencies are summarized in this executive summary (see Parts III and IV).

- The Office of Process and Facility has made a recommendation of [CR] for all the facilities involved in this application. A high-level summary is provided in Part III (Process and Facilities Inspection) and is as follows (from Krishnakali Ghosh, Ph.D., OPQ-OPMA).

CR language for Facility – Cyclomedica Australia Pty Ltd
During a recent inspection of the Cyclomedica Australia Pty Ltd (FEI#3009638066) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility 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, noted at the facility.

II. The proposed labeling and labels [do not have] adequate information to meet the regulatory requirements. Labeling issues cannot be resolved because of the lack of CMC data.

III. Product Quality Review Context

Drug Product:
Technegas (Technetium Tc 99m carbon aerosol) for inhalation. It is a radioactive drug/device combination product. The aerosol is produced on-site in a TechnegasPlus Generator and inhaled by the patient (directly from the generator through a mouthpiece). Inhalation must be within 10 minutes of End of Synthesis.

Indication and Intended Population:
Technegas (Technetium Tc 99m carbon aerosol) is indicated for lung ventilation scintigraphy in adults and pediatric patients 6 years of age or older for:

- Visualization of pulmonary ventilation
- Evaluation of pulmonary embolism when paired with perfusion imaging

Regulatory Context - Designation of Drug Substance:
The Drug Substance in Technegas is that substance which is radioactive, **technetium Tc 99m carbon (^{99m}Tc-Carbon)** that *"is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, …of disease…"* (21 CFR 314.3)]. The image result is driven by both biodistribution of the chemical system (containing the radionuclide), and the radionuclidic properties of ^{99m}Tc. Based on these considerations and the fact that there is no other molecule radiolabeled with $^{99m}Tc^0$ existent as an FDA-approved product, it has been designated Type 1 (NME) in accordance to the principles in MAPP 5018.2.

Analysis by ATL:
The science is clear here, creating a basis for *technetium Tc 99m carbon* as the entity furnishing the "action" expected of a drug substance.

Technetium, [Kr]**$4d^5 5s^2$**, exists in oxidation states of – 1 to + 7, inclusively (and bracketing Tc^0 as the metallic state). Its ^{99m}Tc radionuclide (physical half-life of 6 hours) in the oxidation state 0 is ($^{99m}Tc^0$), the elemental form of the radionuclide, and is also metallic. As such, $^{99m}Tc^0$ possesses the same half-filled 4d shell. Referring to the electronic basis for the Periodic Table, with increasing atomic number the expectation for filling-in the orbitals occurs in accordance to the Pauli Exclusion principle, in the order of increasing energy (1s < 2s < 2p < 3s < …….< 4d < 4f < 5s…). However, after a certain point in the buildup, there are crossovers in this order. For example, with Tc, the 5s (lower energy) is filled before 4d (higher energy). So,

the electron configuration $4d^5 5s^2$ is more stable than $4d^6 5s^1$. **Filled and half-filled subshells turn out to provide the more stable electron configurations and are explainable on the basis of factors beyond the scope for discussion in this document**. Since chemical bonding involves valence electrons (e.g., $4d^5 5s^2$), electrons must be removed from the configuration, and the schedule for that is in accordance to the energies in relation to that for filling the orbitals. The upshot from all this is that no chemical bonds to Tc^0 can form until electrons are removed from these orbitals, the first starting from the orbital of lower energy ($5s^2$), requiring an input of 702 kJ/mol (the first ionization potential).

In accordance to the Senden paper (see section on structure, page 5), the coating of technetium occurs after its crystallization (melting point 2157^0C) and that form is crystalline technetium (Tc^0). But the pertinent temperature is that of the graphite vapor whose sublimation temperature we can assume to be that at the lit value of ~ 2700^0C. Therefore, we can calculate the amount of thermal energy in a mass of graphite (that is vaporized) at this temperature. Based on a 0.001 kg mass of graphite carbon, and assuming a specific heat capacity of joules per deg C (lit), there are [0.001 x 4180 x (2700 – 25)] joules, i.e., 11181.5 joules in one gram mass (11.2 kJ/g), or 134.2 kJ/mol, far less than the first ionization energy of 702 kJ/mol required to remove an electron from the $5s^2$ orbital. The ionization energies to remove successive electrons (5s) and the $4d^5$ electrons markedly increase, thus precluding any likelihood of chemical bonding of $^{99m}Tc^0$ with carbon from the graphite crucible of the Technegas generator.

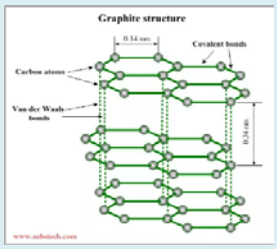
The "carbon" of Technegas is also in elemental form, $[He]2s^2 2p^2$. In this case the 2p shell is of lower energy than the 2s shell and thus also in a stable state; the only way it can form a covalent bond with either itself or with other elements is to receive enough energy to promote one of the $2s^2$ electrons to hybridize with the lower energy p-orbital. In this context, the first ionization potential of carbon is 1086.5 kJ/mol. That for the second ionization potential is 2352.6 kJ/mol, thus piggybacking on the same conclusions of the preceding paragraph.

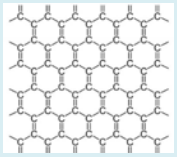
But, the unique structure of "graphite" imparts to this form of carbon some properties of a metal (electrical conduction). As explained later, this property holds the layers of graphene together in graphite, and in turn may be potentially responsible for the physical attractive force holding ($^{99m}Tc^0$-Carbon) together as a molecular 'assembly.' In this context, radiolabeling here is a process by which the two components are brought together by ignition of a graphite carbon crucible in the presence of $Na^{99m}TcO_4$ by which $^{99m}Tc^{7+}$ is first reduced to $^{99m}Tc^0$ followed by being enclosed with a layer of graphene (generated through its sublimation as vapor from the crucible).

Elemental carbon exists in two physical forms, graphite and diamond. The physical form of diamond exists in the face-centered cubic (fcc) structure. By comparison, graphite (the form present in the Technegas carbon crucible) is an unusual form, a structure of layers (of 'graphene'), distinctly unique. As such, the physicochemical properties of graphite play an important role in determining the structure of ^{99m}Tc-

Carbon. Each sheet (layer) of graphene resembles a 'honeycomb,' a giant 2-dimensional sheet of carbon atoms arranged in hexagonal design (like chicken wire) and exists in a stacked configuration.

These structures are shown as follows:





Graphite One Graphene Layer

Radiolabeling of graphite carbon is a unique version from the standpoint of a "connection" of $^{99m}Tc^0$ to carbon and involves no chemical bond in the classical sense (covalent or ionic), reference to the foregoing discussion. Typical bond types that have been used for explaining that in graphite is van der Waals, a bond type that might be suitable for explaining ^{99m}Tc-Carbon. Metallic bonding is another that has been proposed for graphite, one theory of which – from the inorganic chemistry literature - stems from the concept that the valence electrons of a metal are completely delocalized in the cubic structure and so forms an 'electron sea.' Positively charged "ions" result from this delocalization. So, these metal ions float in the resultant electron sea creating the attractive force holding the system together. This has emerged in the inorganic chemistry literature as a late alternative to van der Waals attraction in graphite. It might also have a bearing on the bonding in ^{99m}Tc-Carbon, since $^{99m}Tc^0$ is a metal, and graphite possesses some properties of a metal (and classification as a metalloid).

Based on these considerations, radiolabeling is characterized as a process whereby crystals of $^{99m}Tc^0$ are covered with a thin layer of graphite (after the Senden paper, referenced under structure). The question remains regards the structural meaning of "covered with a thin layer of graphite (graphene)." What seems to give a clue here is the results (a Figure 3 in the Senden paper) from **Force Microscopy** of the surface of the particle, a hexagon-shaped crystal of technetium. There is a mutual geometry in the assembly, the flat layer of graphene and the platelet-shaped hexagonal crystal of Tc^0. This would seem to create a natural tendency to move toward a "flat on flat" disposition which would give aid to the attractive forces holding the assembly together and there is precedence for this in the literature.

(**Structure**)

A peer-reviewed scientific publication by T.J.Senden, et.al. [*J. Nucl. Med, 38, 1327-1333 (1997)*], a seminal paper on technegas (mechanism of formation,

structure), is referenced in the NDA for the principles upon which the process in the Technegas generator is based.

Analysis (by ATL):
From the Senden paper, it is shown by Electron diffraction of the aerosol ($K^{99}TcO_4$) together with EDXA (Electron-Dispersion X-Ray Analysis) that the **primary technegas particle (^{99m}Tc-Carbon) consists of the native metal**, i.e., the portion of the entity (^{99m}Tc-Carbon) that carries the radioactivity – the **first (1) key** ($^{99m}Tc^0$ as 'native metal' form in ^{99m}Tc-Carbon) to understanding the structure. EDXA is an analytical method that rapidly performs elemental analysis of a sample on different areas of the sample. Based on Scanning Electron Microscopy (SEM) of the surface of a metallic technetium platelet in the aerosol, **the results in the Senden paper showed that the shape of $^{99m}Tc^0$ is hexagonal (crystals) but covered with a thin layer of graphite, the second (2) key**.

(Mechanism of Formation)
Based on the Senden paper, reduction of TcO_4^- occurs at the crucible interface and in accordance to the following equation: **$2KTcO_4 + 3C \rightarrow CO_2\uparrow + 2CO\uparrow + 2KTcO_2 \rightarrow 2KO_2\uparrow + 2Tc$.**

The studies described by these authors were performed with $K^{99}TcO_4$ as a surrogate for $Na^{99m}TcO_4$, applicability based on (1) K and Na in the same Group in the Periodic Table (similar chemical and physical properties) and (2) isotopes (^{99}Tc, ^{99m}Tc) of the same element possesses the same chemistry. So, the Senden paper remains relevant to the NDA. At the crucible interface, there is formed on heating a sinter of micron-sized graphite particles; this point begins at the melting point of $K^{99}TcO_4$ (540^0C). From thermographic analysis, the first reduction occurs at 560 – 840^0C and results in loss of CO_2 and CO. In the continuing reaction (840 – 1050^0C), there is loss of one equivalent of KO_2. **Graphene does not melt, but sublimes between 2652^0C and 2692^0C, existing as a hot vapor (although there appears to be some variation in the figures in the literature).** The crucible in the Senden studies was heated in a range of temperatures up to 2550^0C. The NDA procedure sends the temperature of heating a little higher, to 2750^0C. However, between 2000 and 3000^0C, the vapor pressure increases 6 orders of magnitude to around 70 Torr for typical carbon crucibles [*Senden paper*]; 1 Torr = 1 mm of Hg. **They are saying that coating of technetium metal occurs after crystallization (of Tc(0)).** Evidence is presented with other metals providing precedence for their conclusions.

Adding another dimension to understanding of the Technetium-Carbon structure of ^{99m}Tc-C in the Technegas aerosol and its formation in the generator are the results from analysis of the crucible sinter (Senden paper). Something ascribed to 'TcC' was reported to be found by XRD (X-Ray Powder Diffraction) in the sinter material collected

from a crucible following a mg burn. As this is of fundamental importance, the following is a brief discussion of these findings. "Sinter" refers to a bonded mass of particles formed and partially fused below the melting point of the materials. But, the authors in this paper explain that any participation of 'TcC' in the mechanism is uncertain. **Furthermore, they go on to discuss the finding of the absence of any strong evidence for TcC [Technetium carbide] in the vapor phase (aerosol), suggesting that any TcC formed decomposes at the crucible operating temperature. So, based on the totality of evidence from the Senden paper, the authors conclude that the aerosol consists solely of metallic hexagonal platelets of Tc(0) within a thin layer of graphitic carbon (graphene). There is no evidence of carbides, oxides, or discrete radiolabeled fullerenes such as C_{60} or C_{70} (in the aerosol).**

Analysis by ATL:
After the crucible burn, there are two 'products' from the ensuing chemistry, the form in the aerosol that I am representing by the symbol, '**Tc/C**,' and that which is identified and represented in the Senden paper as '**TcC**,' the latter found in the crucible sinter.

Reiterating, the bonds between the carbon atoms in a graphene sheet are covalent, whereas the forces holding the sheets together are much weaker, generally referred to van der Waals. As a result of these bonding differences, the graphene sheets in graphite can slide over each other (and also be split). These differences in bonding are manifested in the physicochemical properties of graphite and play important roles in the crucible burn for Technegas. In this context, the implication from the Senden paper is that 'TcC' found in the crucible sinter is some kind of chemical form, as opposed to 'Tc/C' of the aerosol. Logic would have it that the carbon in 'TcC' had to come about by C-C bond breakage out of the honeycomb structure of graphene, a far different scenario from that for 'Tc/C,' where Tc crystal(s) are layered by sheets of graphene. The conclusion from these considerations is that temperature (in the context of bond energies) must play a fundamental role. In this context, it is known (lit) that the C-C bonds in graphene are broken at a temperature of around 4000^0C. Now, the burn temperature of 2750^0C is about 70% of the way to 4000^0C. So, it is expected that C-C bond breakage in a few carbon atoms will start to break out of the honeycomb structure of graphene at the burn temperature at the crucible surface (and would become more numerous as if the temperature were allowed to increase to 4000^0C). At the interface, these C and Tc atoms would combine somewhere after formation of Tc^0. What comes to mind is a solid solution, e.g., an **interstitial carbide** (subtype of solid solution).

As it turns out **carbides of the transition elements are principally interstitial**, meaning that **carbon atoms enter the interstices of the metal lattice without too great a distortion of the lattice structure**. Based on known chemistry of Group 7 (interstitial carbides, ReC or Re_2C) and the similarity between Tc and Re implies that Tc should also form an interstitial carbide (although there is a paucity of information on any carbides of Tc in the inorganic chemistry literature). Thus, it is reasonable to imagine that Tc (in concert with its family members in Group 7) had initially formed an interstitial carbide ('TcC' in the crucible sinter), but is unstable at the crucible

temperature, consistent with the conclusion in the Senden that 'TcC' is not found in the aerosol.

Formation of a carbide of Tc requires that the carbon portion of 'TcC' is a single carbon atom (analogous to ReC and Re_2C). This carbon, originating from graphene, could only have resulted via a small amount of C-C bond breaking in graphene. But, in the case for 'Tc/C," its carbon had to be that of '**intact graphene**' finding its way into the product in the aerosol. This realization is based on the known fact (lit) that **graphene does not melt, but rather sublimes between 2652^{0}C and 2692^{0}C, existing as a hot vapor**. **This in turn explains the observation in the Senden paper that between 2000 and 3000^{0}C, the vapor pressure increases 6 orders of magnitude to around 70 Torr for typical carbon crucibles; 1 Torr = 1 mm of Hg.**

The graphene vapor produced from sublimation becomes available to condense around the hexagonal crystals of Tc^0 as the latter crystalizes, consistent with the conclusion in the Senden paper that coating of technetium metal occurs after crystallization (of Tc(0)).

Regulatory Context - Regulatory Status of the Carbon Crucible:
The carbon crucible is serving as a source of the carbon that is radiolabeled. This carbon is generated from the carbon crucible upon its heating to high temperature, a process that results in graphene carbon sublimed out of the carbon crucible (at 2750^{0}C) and suspended in argon; while still a vapor, it collects over the crystalized $^{99m}Tc^0$ hexagons before it finally solidifies producing $^{99m}Tc^0$-labeled carbon particles. Because a radiolabeled entity is produced here *in situ* during production of the drug product, it is not isolated, purified (in isolated form) and characterized as such as it would be for a conventional drug.

There are additional restrictive circumstances with Technegas, some of them based on practical considerations due to the architecture of the generator. These restrictive circumstances intensify the criticality of the carbon crucible. **Adding to this is the potential for the carbon crucible as a conduit for bringing into the final drug product impurity substances originating from the crucible's manufacturing process**. **Together, all these factors raise the need for special attention given to the controls of the carbon crucible.**

Regulatory Context – Regulatory Status of the TechnegasPlus Generator:
(**Generator Description**)
The TechnegasPlus Generator is described as a miniature high temperature furnace. It consists of a carbon crucible (precursor to $^{99m}Tc(0)$-C) fixed between two electrodes all contained in a steel chamber that is filled with argon during operation. The carbon crucible possesses a well ((b) (4) µm) in which (in operation) is filled with Sodium Pertechnetate Tc99m Injection. The water of the pertechnetate is dried (6 min), then the crucible is heated to 2750^{0}C ± 100^{0}C within 2 seconds. This temperature is maintained for 15 ± 1 seconds with sensors. There is an operator-controlled exit port in the chamber allowing the Technegas to be transported out of the chamber and vented

through a patient administration set to the patient. The inhalation product produced by TechnegasPlus Generator is Technetium Tc 99m Carbon (^{99m}Tc(0)-C) in argon, administered within 10 min of production.

The electronic system of the generator interfaces with an operator to process operator commands. There are built-in sensors to monitor critical steps in real time. Accidental use of expired Technegas (after 10 min) is precluded by the generator and the latter is purged through a filter to trap any residual Technegas.

(**Regulatory Designations**)
From the Office of Combination Products, 'Technegas' was given (January 5, 2004) a designation of combination drug-device, the designation made within the meaning of 503(g) of the Act and 21 CFR 3.2(e)(1). CDER is the lead center with the designated devices consulted to CDRH.

Drug - Technetium Tc99m Carbon
Device - TechnetiumPlus Generator and Patient Administration Set (PAS)

Product Profile and Critical Quality Attributes (CQA's):
Technegas (technetium Tc 99m carbon) is an aerosol of ^{99m}Tc-labeled carbon particles in argon. The number particle size is indicated to be (b) (4) nm, and mass particle size of (b) (4) nm. Based on the amount of pertechnetate added to the crucible, the nominal **strength** is indicated to be (b) (4), where (b) (4) is the volume of the generator chamber. **Although strength for a radiopharmaceutical is a calculated value, it is a calculation based on measured values of radioactivity and volume**; but, this Strength would be an oversimplification in the case for Technegas, because there is no end-product testing (just prior to patient administration), and no measurement of a final product volume and measurement of radioactivity. So, based on this oversimplified strength, they are assuming that there is no loss of ^{99m}Tc radioactivity (or that it can be defined) in the conversion from input pertechnetate (which no proof is provided in the NDA). The fact is that some radioactivity is adsorbed to the surfaces of the administration set, and probably to the generator chamber, based on documented experience in radiochemistry (literature and this author's) with an array of radionuclides.

Since Technegas is a radiolabeled particle, as well as an inhalation product, **particle size and particle size distribution** are in principle CQA's. However, it is not practical to hold technegas in the chamber or in another suitable container while particle size and distribution are measured prior to patient administration. That relegates these CQA's to being determined by validation (although in a suitable configuration radioactivity could be measured in-line).

Areas of Unique Focus:
♦ **Functional**. This refers to the performance of this combination product in terms of attributes or actions leading to a resulting action from a **device perspective,** identified by CDRH reviewers. In theory, these would be measures (or indicators) of the working

order of the generator and to some presumed degree are linkable to product quality, reference to the previous section on CQA's.

♦ **Drug Product**

- **Control of Materials**:

Carbon Crucible

There are two aspects regards the carbon crucible, that of (1) its configuration (well volume of particular importance) and that (2) of the source of the carbon. The latter may not immediately raise any concerns, but herein it needs to be noted that the common impurities in graphenic carbon include metals (prominently transition metals, e.g., iron) and carbonaceous materials. Carbonaceous materials will be burned into the gases (CO_2, CO) and expected to add little (if not miniscule) to that from carbon itself. Because burning is carried out in an inert atmosphere, there should be no conversion of any metal impurities to the oxides, and so will just add to the metallic load in the aerosol. It is presumed that this metals-impurity load will be negligible.

Argon (Excipient)

Argon is not a medical gas and so there is not a public standard of quality of documented suitability for human use. Nor, is there a recognized commercial source of the gas with suitable standards for that purpose.

Sodium Pertechnetate Tc 99m Injection

Any critical issues for pertechnetate would rest with any significant differences in the formulations from each of the US-approved technetium generators. But, in all 3 generators (Technelite, Ultra-Technekow, Radiogenix System), the Sodium Pertechnetate Tc 99m Injection is contained in 0.9% Sodium Chloride for Injection with no preservatives. With effectively the same formulations, and the same substance ($Na^{99m}TcO_4$) the most prominent differences are in strengths. Also, Sodium Pertechnetate Tc 99m Injection from these generators must meet the USP monograph. So, any other differences would be theoretical in nature, and be largely due to minor differences in radionuclidic impurity profiles. Although it seems inconceivable that any such difference would be of any significance in performance in Technegas, nevertheless it is probably prudent that it be proven with all 3 US-approved generators to reduce the potential for surprises.

- **Quality Controls**

The nature of the furnace construction, and the process configuration for administration to patients, presents a framework not easily suited to end-product testing. And, that inherently hinders the capability to provide assurance of meeting the fundamental CQA's, one of which is **strength (mCi/mL) to control patient dose**. In this context, there is no actual dose in units of mCi/mL. In the way the generator is being used, when the count rate in the patient reaches a certain point for producing the image (determined by the number of breaths taken from the mouthpiece by a patient) whatever this translates to the amount of aerosol taken from the generator represents the dose.

Analysis by ATL:
Consider the quantity, **$[mCi/mL]_{stream}$**, as the output of the generator, equivalent to Strength (or radioactivity concentration); this is what reaches the mouthpiece, and what is controlled by the generator and which in theory is proportional to the count rate in the patient. To establish consistency from generator-to-generator, ideally it will be the combination of generator in-process controls, plus strength. At this point, we have only in-process controls, the relatively easy part of the equation. The more difficult part is the Strength. It is the Strength, along with the Volume of aerosol breathed by a patient, **$[mCi/mL]_{stream}$ x $[Vol, mL]_{breathed}$**, that provides the required quantity of aerosol to obtain sufficient count rate in the lungs to produce imaging. In principle, a link is needed from the crucible burn (to create the aerosol composition) to what is at the point of the mouthpiece to the count rate in the lung [crucible → mouthpiece → patient (count rate)]. Hence, in theory, $[count\ rate]_{required}$ = $f\{[mCi/mL]_{stream} \times [Vol, mL]_{breathed}\}$, where the function would be expected to be linear. If we knew this function, we could get the sought-for Strength, $[mCi/mL]_{stream}$. No such measurements are provided in the NDA.

The architecture of the generator complicates such measurements. Only the [crucible → mouthpiece] section in this chain has any practical realization of being achievable (as a result of discussions with Christy John, Ph.D., CDER/OTS/OCP/DCPII), since only very broadly values of activity (as mCi) can be associated with patient count rate for imaging.

Ideally, the Strength, $[mCi/mL]_{stream}$ should be uniform in every part of the aerosol stream from the generator chamber through the PAS. If it were, that would be a readily obtainable quantity from a determination based on the generator chamber. Unfortunately, that idealization will not hold up, due to agglomeration (the percent and distribution unknown) and deposition of some radioactive particles to the walls of the PAS (as well as generator chamber, which will be different from the PAS. It could conceivably be calculated from the amount of $^{99m}TcO_4^-$ loaded into the crucible, with percent yield of ^{99m}Tc radioactivity in the burn result and estimated (or measured) losses due to adhesion to walls (chamber and PAS). It might also be done by actual measurement in validation studies (the desirable approach).

♦ Manufacture

- **Radiolabeling Chemistry**:

Because ^{99m}Tc and C are brought together in an entity that is unique to any FDA-approved technetium radiopharmaceutical (technetium in the zero-oxidation state, $^{99m}Tc^0$ (a metal existing in the product as hexagons within a thin layer of graphene of graphite), it renders the radiochemistry for its formation and formulation into a final dosage form similarly. Also, the architecture of the generator renders drug product controls less than straightforward, creating regulatory challenges.

IV. Summary of Quality Assessments

Because of uniqueness of product and the architecture of the generator, this product and generator system belies establishment of a straightforward panel of drug product release specifications typical of radiopharmaceuticals, resisting approaches to quality controls of the dose to patients, e.g., not allowing for direct measurement of radioactivity and volume for strength of dose (units of mCi/mL).

Deficiencies identified during primary reviews were conveyed in two IR's (IR#1 – 7/1/2020, and IR#2 – 9/28/2020). Summarizing, the deficiencies can be organized into the categories of clinical supplies (ethanol, argon, $Na^{99m}TcO_4$, with argon receiving special attention since it is not a medical gas), crucible manufacture, drug product specifications for each attribute (including strength of aerosol – mCi/mL, aerosol particle size distribution – D10, D50 and D90-analytical methods, and stability attributes and testing/acceptance criteria), batch data, clinical site simulation, manufacturing, device, and Technegas generator release tests and specifications. Overall, the problem with this application from a CMC standpoint is the lack of sufficient characterization of the system (although structure of ^{99m}Tc-Carbon and its associated general characteristics are as investigated and determined in the Senden paper) to allow for defining specifications to allow for ready control of product quality. As a consequence of lack of characterization are certain critical pieces, including Strength, **$[mCi/mL]_{stream}$**, at the point of the mouthpiece. **This is the piece that together with the in-process controls comprises the equation enabling control of consistency across generator-to-generator**.

There is also an accompanying corollary - that at this established Strength, whatever volume of breaths taken from a given generator, the resulting amount of aerosol, **$[mCi/mL]_{stream}$ x $[Vol, mL]_{breathed}$**, taken in by a patient will be sufficient to obtain the necessary count rate in the lungs for imaging. The output of the generator must be sufficient to meet whatever number of patient breaths it takes {**$[mCi/mL]_{stream}$**, at the point of the mouthpiece} to get that count rate. This corresponds to the last part of [crucible → mouthpiece → patient count rate]. Given the several correction factors, this ultimately depends on crucible loading. Crucible loading and number of patient breaths needs to be made consistent with required count rate (to be established in validation studies), the results of which would become part of the labeling. In these regards, there are issues of what is to be done when Technetium generators are running low on pertechnetate yield (aging generators), and is it acceptable to employ multiple crucible loadings under those conditions.

After several sets of IR's (IR#1, 8/24/2020; IR#2, 9/28/2020) and the applicant's responses in amendments (7/24/2020, 10/14/2020, 10/30/2020), as well as internal discussions and TCONS (Mid-Cycle 9/8/2020 and CMC for IR#1; CMC for IR#2), the outstanding issues come down to those that are currently in the **Discipline Review Letter** (12/07/2020). These issues involve Drug Substance (crucible), Drug Product (composition, batch formula, manufacturing description, analytical methods, stability, argon gas, aerosol specifications, device – generator specifications), Manufacturing (crucible, technegas generator manufacture, final drug product manufacturing operator

manual) and the Device. In each of these categories of issues, there are multiple pieces that need to be addressed (primarily by new data).

A response was received February 26, 2021 but continued to be deficient in multiple areas. A tcon was held (following an IR, March 19, 2021 requesting additional information to review the (b) (4) test reports) with the applicant to discuss these remaining issues. The information amendment from the applicant was determined to constitute a major amendment. Accordingly, the clock was extended to June 26, 2021. A recent email (4/1/3021) was received from the applicant indicating that they would like a conference call for some clarifications. The TCON was granted, and there was an agenda of items to be discussed. In the memo of that TCON, Cyclomedica indicated that many of the comments in the IR cannot be addressed at this time and will require further testing. **FDA confirmed this and indicated that this new information cannot be submitted as a post-approval commitment as Cyclomedica had proposed**.

One of the problems in developing a strength for an aerosol (that would be that at the mouthpiece and inhaled by a patient) is an accurate measurement of radioactivity of material (as well as particle size distribution) collected in the impactor ((b) (4) particle distribution testing). **This information (radioactivity), plus particle size distribution are two critical pieces of information for adequate characterization of the product from this generator**, the essence of the issues with the (b) (4) **Impactor Study Question 4 and 8**. In these regards, it was learned in the TCON that their dose calibrator is a well-counter after all (not well described in previous information from Cyclomedica and sending FDA in the direction of the next best option). Cyclomedica indicated in their response that the impactor (b) (4) ; this is an important clarification and Cyclomedica will send information (including photographs) to address this issue.

With this information, the **Impactor Study Question 8** becomes moot (acknowledging the superiority of a well-type DC) since it was being offered as an alternative an instance where the DC would be severely handicapped by not being a well-type counting system. **Nevertheless, that there is no perceived notion that the standard well-type DC (typically used in radiopharmacies) is the ultimate, these DC's do not provide 4π counting. That capability requires placing the sample to be counted at the center of a sphere with a crystal detection system. Although these counting systems do exist, none of the commercial DC's have that capability**. Also, most commercially available DC's are ionization chambers which also contributes to the limitations with standard dose calibrators. **With standard well-counters in radiopharmacy practice there is no point in the positioning of a sample where 100% of all rays can be collected**. And, there may be a misconception that placement of a sample at the bottom of the well provides the optimal position for collecting all the rays. Quite to the contrary, **the so-called "sweet spot" is the actual, optimum placement for a sample in the typical well-type DC where the errors can be minimized; this is well-established as part of the criticality of geometric factors**

for radioactivity in dose calibrators. And, it waits to be seen in the new information how they handle these impactor plates in their well-type DC.

Guidance is also provided to Cyclomedica regards their development of suitable methods for characterizing Technegas (particle size distribution, strength and yield), along with specific attributes and acceptance criteria. Guidance was provided to Cyclomedica in this development work, referring to USP <610> and that from FDA for Metered Dose Inhalers (MDI) and Dry Powder Inhalers (DPI) in the continuing development work.

Hence, there are many issues from the Discipline Review letter that remain unresolved. These constitute approvability issues, which are summarized under Part IV.

- **Drug Product Labeling**

Revised instructions in PI and User Manual (February 26, 2021), but because of the lack of support from CMC data, the labeling was not completed in this cycle.

- **Microbiology**

A review from microbiology perspective determined not to be necessary.

- **Process/Facility Inspections**

One facility requires inspection in March 29 – April 6, 2021 (Cyclomedica, Australia). In accordance to an email from Krishnakali Ghosh (4/7/2021), the findings from the field are numerous issues and gaps that are major in content. Accordingly, the initial recommendation from the field is a CR, and Krishna's high level summary is as follows:

Summary for executive review- NDA

The following is a high level summary taken from this ICON (email by Krishnakali Ghosh, Ph.D.):

(Technegas™) is a gaseous suspension of carbon particles radiolabeled with Technetium-99m (^{99m}Tc) produced by the Technegas™ generator and is a combination drug/device product. the manufacturing process and facility evaluations have concluded that NDA 022335 cannot be recommended for approval at this time for manufacturing and testing of (b) (4) crucible, Technegas™ generator and patient delivery device unit (PAS) based on applications review and preapproval inspections. Major CGMP and product specific deficiencies were identified and a total of 13 deficiencies were cited during the pre-approval inspections conducted from 3/29-4/06/2021. A facility withhold recommendation has been made for Cyclomedica Pty Ltd (FEI#3009638066) by OPMA and ORA for NDA 022335.

The major deficiencies noted were due to inadequate manufacturing and equipment controls required under 21 CFR 211 and Part 820 regulations. The firm has failed to establish critical process parameters for the manufacturing process for the carbon crucible, final drug product aerosol and PAS device and failed to demonstrate documented evidence of exhibit batches produced under GMP regulations for the drug Product. The firm has implemented unvalidated analytical methods for product testing, inadequate stability testing program for (b) (4) crucible, deficient environmental controls, inadequate quality controls methods, inadequate acceptance of critical raw materials and inadequate quality system procedures failing to ensure final drug product can consistently and reliably be produced.

CR language for Facility – Cyclomedica Australia Pty Ltd
During a recent inspection of the Cyclomedica Australia Pty Ltd (FEI#3009638066) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility 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, noted at the facility.

V. Final Analysis of Product Quality Review Issues

There are a multitude of issues remaining from the Discipline Review letter and several TCON's with Cyclomedica that remain unresolved. In essence, all of this distills down to lack of characterization of the aerosol (containing ^{99m}Tc-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, 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 ((b) (4) reports). Needed are measurements at the mouthpiece which basically is analogous to strength for a drug dose. In response to this issue (in subsequent TCON's with Cyclomedica) have led to further problems involving how the measurements of particle size distribution and radioactivity were done, thus leaving amiss an understanding of these measurements, still confounding a meaningful figure for the strength of aerosol that is inhaled by patients.

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 (1) 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 (2) 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 (3) is **insufficient analytical methods** to characterize the aerosol particle size distribution and radioactivity, along with the aerosol yield. The fourth (4) approvability issue is an **insufficient control of critical components** (namely the carbon crucible) that produce the radioactive drug substance (^{99m}Tc-Carbon Particles).

VI. Summary Basis for Product Quality Recommendation (150 words)

There are a multitude of issues remaining from the Discipline Review letter and several TCON's with Cyclomedica that remain unresolved.

There are four major categories that make up the basis for the non-approvability of the NDA . The first (1) 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 (2) 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 (3) is **insufficient analytical methods** to characterize the aerosol particle size distribution and radioactivity, along with the aerosol yield. The fourth (4) approvability issue is an **insufficient control of critical components** (namely the carbon crucible) that produce the radioactive drug substance (^{99m}Tc-Carbon Particles).

IV. Lifecycle Considerations

Important future lifecycle considerations cannot be determined until the appropriate CMC data has been provided to resolve the CR.

105 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

M E M O R A N D U M

DATE: 14 August 2020

TO: NDA 022335

FROM: Maritere Carattini, MS
Review Microbiologist
CDER/OPQ/OPMA/DMA II/Branch VI

THROUGH: John W. Metcalfe, PhD
Quality Assessment Lead
CDER/OPQ/OPMA/DMA II/Branch VI

SUBJECT: Microbiology assessment for NDA 022335- Resub 6
Drug product: Technegas™ (Technetium (Tc-99m) carbon aerosol)
Applicant: Cyclomedica Australia Pty Ltd
Submission date: 26 March 2020

Technegas™ is a radiopharmaceutical nonsterile aerosol drug product for inhalation administration. The drug product's ultrafine particles are produced at a temperature of 2750 ºC ± 100 ºC (an inherently antimicrobial temperature) at the point of use by the TechnegasPlus Generator system and is delivered to patients using a separate Patient Administration Set (PAS). The PAS is the interface between the TechnegasPlus Generator chamber and the patient. The device consists of a delivery hose that connects to the TechnegasPlus Generator, a mouthpiece, and a filtered exhaust unit. The PAS is single-use and is designed to prevent the release of Technegas into the atmosphere. A 510(k) (K913416) for the PAS was cleared by the FDA on October 28, 1991. In addition, since the drug product is inhaled immediately after being produced in the nuclear medicine department, there is no container closure system.

There is no FDA requirement for non-aqueous drugs that are orally inhaled to be sterile.

The manufacturing process provides microbial control. The generator reaches extremely high temperatures > 2,700 °C and is therefore self-sterilizing during the manufacturing process. Consequently, DMA is not concerned with bioburden accumulating over time. In addition, the chamber (b) (4) maintenance (yearly).

In conclusion, due to the drug product dosage form and absence of microbiological concerns during the review of the application, no further microbiological assessment is required.

END

Maritere Carattini

Digitally signed by Maritere Carattini
Date: 8/14/2020 12:38:23PM
GUID: 5a99a9800059de20999699de06332d80

John Metcalfe

Digitally signed by John Metcalfe
Date: 8/14/2020 12:47:26PM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ANIKA A LALMANSINGH
05/28/2021 04:39:52 PM

ELDON E LEUTZINGER
05/28/2021 04:50:36 PM