CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202049Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 14-OCT-2020

TO: NDA 202049

FROM: Craig M. Bertha, ATL and CMC Lead for DPACC/DRTM
ONDP, DNDP II, Branch 4

SUBJECT: Recommendation from OPQ/CMC on action for the 2nd resubmission of NDA 202049 from Pharmaxis Ltd. – Bronchitol (mannitol) Inhalation Powder

RECOMMENDATION: APPROVAL

BACKGROUND:
As indicated in the previous review dated 19-MAY-2019, the applicant had adequately addressed the quality-related recommendations and the GMP issues were resolved. The application was recommended to be approved. However, as the clinical Division took a complete response action and the labeling evaluations were not completed at that time. The drug product reviewer has now evaluated the labels/labeling (see review dated 09-OCT-2020 in Panorama) and recommends approval. Note that the only remaining minor revision to section 11 (DESCRIPTION) of the package insert (PI) has been captured in the Agency-revised PI that was forwarded to the applicant on 13-OCT-2020.

RECOMMENDATION TO DPACC FROM OPQ/CMC: Approval

_____
Craig M. Bertha, CMC Lead
for DPACC/DRTM

cc:
DPACC/LDo
DPACC/KPuthawala/RLim
ONDP/DNDP II/Branch 4/WWilson-Lee/CBertha/VPavuluri
DRBPMI/RBPMBI/FAisida

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/

CRAIG M BERTHA
10/14/2020 08:31:26 AM

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: As submitted on 02-OCT-2020

(b) (4)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	BRONCHITOL®	Acceptable.
Established name(s)	(mannitol) inhalation powder	Acceptable.
Route(s) of administration	for oral inhalation use	Acceptable.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Inhalation Powder: 40 mg mannitol per capsule	Acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Applicable	

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.	Not Applicable	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	Instruct patients on safe hygiene practices (clean and dry hands thoroughly) and correct inhaler use, including loading of capsules and proper inhalation technique per the Patient Instructions for Use. The BRONCHITOL inhaler should be discarded and replaced after 7 days of use. If the inhaler does need to be washed, the patient should allow the inhaler to thoroughly air dry before next use.	Acceptable. Additional preparation and use instruction provided in "Instructions for Use" and "Quick Reference Guide".

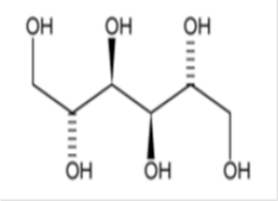
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Inhalation powder	Acceptable.
Strength(s) in metric system	40 mg mannitol per capsule	Acceptable.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not a salt	Not applicable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	clear, colorless hard gelatin capsule imprinted with "PXS 40 mg".	Acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet	Not applicable.
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not an injectable	Not applicable.

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION

BRONCHITOL contains D-Mannitol (referred to throughout as mannitol) as the active ingredient. Mannitol is a hexahydric sugar alcohol, with the following chemical name hexane-1,2,3,4,5,6-hexol and chemical structure:

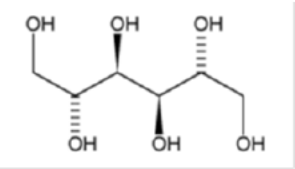


Mannitol is a white or almost white crystalline powder or free-flowing granules with an empirical formula of $C_6H_{14}O_6$ and molecular weight of 182.2. Mannitol is freely soluble in water, and very slightly soluble in alcohol. Mannitol shows polymorphism.

BRONCHITOL contains mannitol powder spray dried into particles of respirable size filled into clear, colorless hard gelatin capsules. There are no inactive ingredients in BRONCHITOL.

The accompanying white plastic inhaler is comprised of a mouthpiece, blue piercing buttons, capsule chamber, and a removable cap. A blister pack consists of 10 capsules, each containing 40 mg mannitol. After a capsule is placed in the capsule chamber and pierced by firmly pressing and releasing the buttons on the side of the device, the powder within the capsule becomes exposed and ready for dispersion into the airstream generated by the patient upon inhalation through the mouthpiece. Under standardized *in vitro* test conditions, the inhaler delivers 32.2 mg of mannitol per inhalation when tested at a flow rate of 60 L/min for 2 seconds. The actual amount of drug delivered to the lungs will depend on patient factors, such as inspiratory flow profile.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	BRONCHITOL contains D-Mannitol (referred to throughout as mannitol)	Acceptable. Established name may be included next to proprietary name by revising the 1st sentence as "BRONCHITOL (mannitol) inhalation powder contains D-Mannitol (referred to throughout as mannitol)…"
Dosage form(s) and route(s) of administration	No specific statement on dosage form or route of administration was included in section 11	Acceptable based on the descriptive statements in section 11 and elsewhere in the PI. To include "inhalation powder" after established name in first sentence, to comply with 21 CFR,201.57 (c)(12)(i)(B).
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not a salt	Not Applicable.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	No inactive ingredients	Not Applicable.
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.	Not an Injection	Not Applicable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No Alcohol present	Not Applicable.
Statement of being sterile (if applicable)	No applicable for inhalation powder	Not Applicable.
Pharmacological/ therapeutic class	Not stated	

Chemical name, structural formula, molecular weight	hexane-1,2,3,4,5,6-hexol;  $C_6H_{14}O_6$; 182.2	Acceptable.
If radioactive, statement of important nuclear characteristics.	Not a radioactive material	Not Applicable.
Other important chemical or physical properties (such as pKa or pH)		

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Not applicable	Not Applicable.
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	Not Applicable.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

BRONCHITOL (mannitol) inhalation powder:

- 40 mg of mannitol per capsule
- capsules are clear, colorless and imprinted in black with "PXS" on cap and "40 mg" on body.
- supplied in cartons containing 10, 140 or 560 capsules in blister packs co-packaged with 1, 1, and 4 inhalers respectively in a carton

BRONCHITOL is provided in 3 commercial presentations:

Pack Quantities	Inhalers	Capsules	NDC Number
4-week Treatment Pack (4 x 7-day treatment packs)	4	560	10122-210-56
7-day Treatment Pack	1	140	10122-211-14
Bronchitol Tolerance Test	1	10	10122-214-01

BRONCHITOL should be stored between 68°F-77°F (20°C-25°C) with excursions permitted between 59°F-86°F (15°C-30°C). [See USP Controlled Room Temperature]. Do not refrigerate. Do not freeze.

The Training Kit (NDC 10122-219-00), containing empty gelatin capsules, should be stored between 68°F-77°F (20°C-25°C) with excursions permitted from 59°F-86°F (15°C-30°C).

BRONCHITOL should only be used with the provided inhaler, which is a white plastic inhaler comprised of a mouthpiece, blue piercing buttons, capsule chamber, and a removable cap. All remaining unused (opened and unopened) blister packs and the inhalers should be properly discarded. Be sure to read the accompanying BRONCHITOL instructions completely before administration. If you have any questions, contact the supplier at 1-888-661-9260.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Inhalation powder	Acceptable.
Strength(s) in metric system	40 mg	Acceptable.
Available units (e.g., bottles of 100 tablets)	cartons containing 10, 140 or 560 capsules in blister packs	Acceptable.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	capsules are clear, colorless and imprinted in black with "PXS" on cap and "40 mg" on body. NDC numbers provided in a table.	Acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet	Not Applicable.
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.	Not an Injection	Not Applicable.

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

Item	Information Provided in the NDA	Assessor's Comments

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.)	Do not refrigerate. Do not freeze.	Acceptable.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	No Desiccant; Capsules are packaged in blisters	Not Applicable.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	stored between 68°F-77°F (20°C-25°C) with excursions permitted between 59°F-86°F (15°C-30°C). [See USP Controlled Room Temperature]. Do not refrigerate. Do not freeze.	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.”	Not Applicable	Not Applicable.
Include information about child-resistant packaging	Not a Child resistant package.	Acceptable.

1.2.5 Other Sections of Labeling

None

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Pharmaxis Ltd 20 Rodborough Rd Frenchs Forest NSW 2086 AUSTRALIA Manufactured for: Chiesi USA, Inc. Cary, NC 27518 USA BRONCHITOL® is a registered trademark of Pharmaxis Ltd.	Acceptable.

2.0 PATIENT LABELING

Patient Information and (IFU) were included at the end of PI contain the information on how to use Bronchitol:

How should I use BRONCHITOL?

See the step-by-step Instructions for Use at the end of this Patient Information leaflet.

- **BRONCHITOL is for oral inhalation only.**
- **Do not** use BRONCHITOL until your healthcare provider has given you the BTT and approved you for treatment. Ask your healthcare provider or pharmacist if you have any questions.
- Use BRONCHITOL exactly as your healthcare provider tells you to use it.
- **Do not** swallow BRONCHITOL capsules. BRONCHITOL capsules should be used only with the provided inhaler device.
- An inhaled short-acting bronchodilator should be used 5 to15 minutes before **every dose** of BRONCHITOL.
- Use BRONCHITOL **2 times** each day. Breathe in (inhale) through your mouth (oral inhalation) the capsule contents in 10 single BRONCHITOL capsules using the BRONCHITOL inhaler:
  - **1 time in the morning**
  - **1 time at least 2 to 3 hours before bedtime**
- If you use too much BRONCHITOL, call your healthcare provider or go to the nearest emergency room right away if you have any unusual symptoms, such as feelings that you cannot breathe, have wheezing, or cough a lot.
- Do not stop using BRONCHITOL or any other medicines unless told to do so by your healthcare provider because your symptoms might get worse.
- Your healthcare provider may change your medicines as needed.

Call your healthcare provider or get emergency medical care right away if your breathing problems get worse while taking BRONCHITOL.

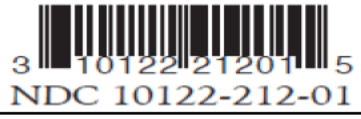
Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Blister foil (as updated on 02-OCT-2020)

Item	Information Provided in the NDA	Assessor's Comments about Container (Blister) Label
Proprietary name, established name, and dosage form (font size and prominence	Bronchitol® (mannitol) inhalation powder	Acceptable.
Dosage strength	40 mg per capsule	Acceptable.
Route of administration	for oral inhalation only	Acceptable.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	Not applicable.
Net contents (e.g. tablet count)	10 capsules	Acceptable.
"Rx only" displayed on the principal display	Rx only	Acceptable.
NDC number	NDC 10122-212-01	Acceptable.
Lot number and expiration date	LOT XXXXX EXP MM/YYYY	Acceptable.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Not included	Acceptable, given the limited space on blister foil. Storage statement included on the cartons holding the blisters and inhaler device: "Store at controlled room temperature 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F)" or a shortened version.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not for parenteral use	Not Applicable.

Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Don't swallow capsules	Acceptable. Required for inhalation powders in capsules
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No alcohol present	Not Applicable.
Bar code		Acceptable.

Item	Information Provided in the NDA	Assessor's Comments about Container (Blister) Label
Name of manufacturer/distributor	Chiesi USA, Inc.	Acceptable.
Medication Guide (if applicable)	Package insert and quick reference guide included in outer carton along with the blisters.	Acceptable.
No text on Ferrule and Cap overseal	Not an Injection or liquid	Not Applicable.
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.	Not a compendial drug product	Not Applicable.
And others, if space is available	"Use an inhaled bronchodilator 5-15 minutes before taking Mannitol Inhalation Powder". "Push capsule through foil at either corner".	Acceptable.

3.2 Carton Labeling

1 Week Carton (7-day treatment pack, as submitted on 02-OCT-2020)

(b) (4)

4 Week Carton (carton containing 4 x 7-day treatment packs, as submitted on 02-OCT-2020)

(b) (4)

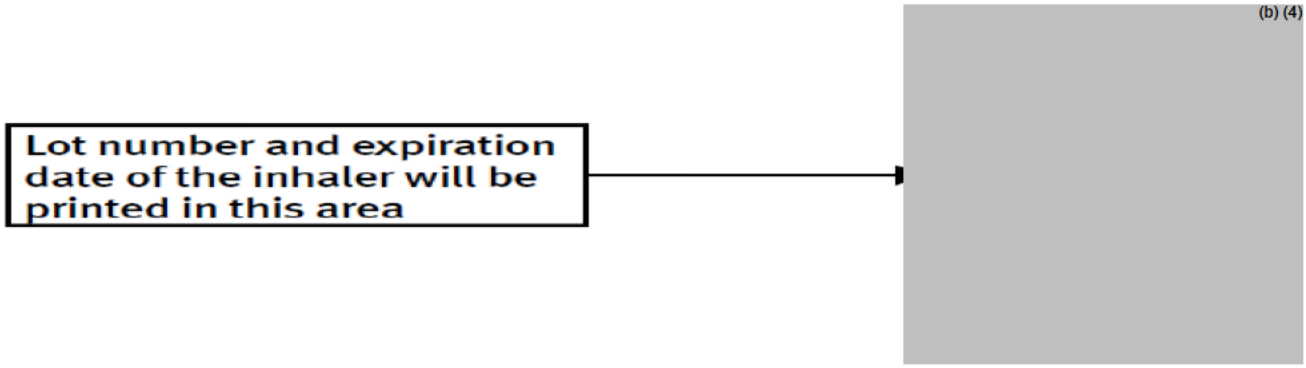
Item	Information Provided in the NDA	Assessor's Comments about 1-week and 4-week Cartons
Proprietary name, established name, and dosage form (font size and prominence	Bronchitol® (mannitol) inhalation powder	Acceptable.
Dosage strength	40 mg	Acceptable.
Route of administration	For inhalation use only	Acceptable.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	Not Applicable.
Net contents (e.g. tablet count)	7-day carton: (b) (4) [redacted] 4x7-day outer carton: (b) (4) [redacted]	Acceptable.
"Rx only" displayed on the principal display	Provided on both cartons **Rx Only**	Acceptable.
NDC number	**1-week carton**: NDC 10122-211-14 **4-week carton**: NDC 10122-210-56	Acceptable.
Lot number and expiration date	(b) (4) [redacted] **1-week carton:** **4-week carton:**	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	**1-week carton**: Store at controlled room temperature 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F). **4-week carton**: Store at controlled room temperature 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F).	**Acceptable.**

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not an injectable, but both cartons contains the following information: “For Single Patient Use Only Rx Only”. “Discard After Single Patient Use”.	Acceptable.
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Don’t swallow Bronchitol capsules	Acceptable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No alcohol present in formulation	Not Applicable.
Bar code	(b) (4)	Acceptable.

Item	Information Provided in the NDA	Assessor's Comments about 1-week and 4-week Cartons
Name of manufacturer/distributor	**Manufactured for**: Chiesi USA, Inc. 175 Regency Woods Place, Suite 600, Cary, NC 27518 **Manufactured by**: Pharmaxis Ltd 20 Rodborough Road, Frenchs Forest, NSW 2086 Australia	Acceptable.
Medication Guide (if applicable)	Package insert and quick reference guide included in outer carton along with the blisters.	Acceptable.
No text on Ferrule and Cap overseal	Not an injection or liquid.	Not Applicable.
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.	Not a compendial drug product.	Not Applicable.
And others, if space is available	1-week carton – Keep all medicines out of reach of children. **Do not remove capsules from blister until immediately before use.** 4-week carton – Keep all medicines out of reach of children. **Do not remove capsules from blister until immediately before use.**	Acceptable.

Assessment of Carton and Container (Blister foil) Labeling: Adequate

Label text for Inhaler (as submitted on 01-MAY-2020):



Assessment of Inhaler Label: **Adequate**

REQUEST FOR INFORMATION SENT TO SPONSOR DURING LABELING ASSESSMENT

Blister lid foil:

1. Bar code is required on primary container closure, per 21 CFR 201.25(b), unless exemption is requested per 21 CFR 201(d); and must meet the requirements specified under 21 CFR 201.25(c).
2. Proprietary name shall be included along with the established name.
3. Include the statement "(b) (4)".
4. Include term "10 capsules" as a distinct item on the lid foil, independent of other text; required per 21 CFR §201.51.
5. Include "Rx only" to appear on each blister card at top left side corner, above proprietary and established names, which otherwise deemed misbranded under 21 CFR §353(b)(4)(A).
6. Include the statement "Don't swallow capsules" after the route of administration.
7. Name of the manufacturer, packer, or distributor of the drug is required on labeling material, which otherwise would be deemed as misbranded drug per 21 CFR § 201.1(a). Provide revised labeling text for the blister foil, including name of the distributor.

1-week and 4-week cartons:

8. The established name font color should be of darker shade. Per 21 CFR 201.10(g)(2) established name shall have a prominence commensurate with the prominence with which proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
9. Use identical storage statements on all cartons used for packaging of Bronchitol capsules: "Store at controlled room temperature 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F)".

10. Under the name of Manufacturer / Distributor include street address, required per 21 CFR 201.1(i), along with the City, state and Zip code.
11. Use identical cautionary statements on all cartons used for packaging of Bronchitol capsules. Include the statement "Do not remove capsules from blister until immediately before use" on 1-week carton as well.
12. Include the statement "Keep all medicines out of reach of children" on both 1-week and 4-week cartons.

ITEMS FOR ADDITIONAL ASSESSMENT: None

Overall Assessment and Recommendation:

This application is deemed ready for "APPROVAL" up on revision of the 1st sentence under section 11 DESCRIPTION of the PI as *"BRONCHITOL (mannitol) inhalation powder contains D-Mannitol (referred to throughout as mannitol) as the active ingredient"*.

As of this review, all other deficiencies delineated under "REQUEST FOR INFORMATION SENT TO SPONSOR DURING LABELING ASSESSMENT" are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, P. D., R. Ph.,
Chemist, Br4/DNDPII/ONDP
05-OCT-2020

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

Wendy Wilson-Lee, Ph. D.,
08-OCT-2020,
Division Director, DNDPII/ONDP and Branch Chief (Acting)

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 10/08/2020 04:42:43PM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 10/09/2020 09:10:13AM
GUID: 50816dbc000085595ca3284bbca465a8

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 28-MAY-2019

TO: NDA 202049

FROM: Craig M. Bertha, ATL and CMC Lead for DPARP
ONDP, Division II, Branch IV

SUBJECT: Recommendation from OPQ/CMC on action for the resubmission of NDA 202049 from Pharmaxis Ltd. – Bronchitol (mannitol) Inhalation Powder

RECOMMENDATION: APPROVAL

BACKGROUND:
The drug product, Bronchitol (mannitol) Inhalation Powder, 40 mg, is proposed for treatment of cystic fibrosis. The same formulation (neat mannitol) was approved in 2010 with a diagnostic kit (also from Pharmaxis) for assessment of bronchial hyperresponsiveness in patients 6 yrs of age and older with symptoms of asthma (NDA 022368, Aridol Inhalation Powder).

The Bronchitol drug product is a non-sterile dry powder inhaler with formulation pre-metered in hard-gelatin capsules, each containing 40 mg of spray-dried mannitol. The capsules are packaged into aluminum foil-foil blisters and co-packaged with one or more inhalation devices, the Plastiape RS01 Inhaler Model 7 HR, which is a high-resistance inhaler. The to-be-marketed inhaler Model 7 HR is manufactured from the same plastic materials as inhaler Model 7 LR (low resistance) which is approved with Aridol Inhalation Powder diagnostic kit of NDA 022368, however there is difference in the air inlets (refer to page 59 of CMC review #1) to account for the difference in device resistances, and there are different color piercing buttons (blue for HR and red for LR). The mechanism of action for both inhaler models is the same and is described below, however the Aridol inhaler is labeled for less use (57 capsules) than the Bronchitol inhaler (140 capsules). Upon insertion of the capsule into the inhaler, it is pierced from both ends, and the patient inhales from the mouthpiece, which results in the spinning of the capsule and release of the powder by entrainment into the air-stream. The *in vitro* emitted dose, at 60 L/min for 2 L air volume, is 32.2 mg (target emitted delivery). Three package configurations are proposed for marketing, a Bronchitol Tolerance Test packaged with a Training Kit (10 capsules and a device), a 7-day Treatment Pack (140 capsules and 1 device), and a 4-week Treatment Pack (560 capsules and 4 devices). Daily dosage is inhalation of 10 capsules twice a day.

The drug substance, which comprises the entire formulation, is a sugar alcohol with IUPAC name (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN name mannitol. It is a white, crystalline powder of free flowing granules. It is freely soluble in water (22 g/100 mL) and very slightly soluble in alcohol. (b) (4) (b) (4)). There are three crystalline morphic forms of mannitol denoted as (b) (4) as well as (b) (4) The drug substance consists of predominantl (b) (4) and has a melting

range of 164-169°C, with a pKa of 13.5 at 18°C. It is not hygroscopic and known to resist moisture sorption at high relative humidity. The drug substance is synthesized, tested and packaged b (b) (4) (DMF (b) (4)). The retest period of the drug substance i (b) (4) years and is supported by the stability data. The specification controls for the drug substance include appearance, appearance of solution, assay, related substance (b) (4) melting range, conductivity, specific rotation, endotoxins, microbial limits (b) (4), (b) (4).

For the drug product manufacture, the mannito (b) (4) The regulatory specification controls for the drug product include purity of mannitol and testing for related substances, identification by infrared spectroscopy (b) (4), appearance, bacterial endotoxin limit, microbial limits, aerodynamic particle size distribution, and delivered dose uniformity (DDU).

At the end of the initial review cycle, the CMC team considered the application approvable pending a decision by the Office of Compliance regarding the GMP status of the various sites supporting the CMC for the drug product. Ultimately, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) issued a complete response (CR) letter to the applicant on 18-MAR-2013. The main issue leading to the CR letter was the GMP deficiencies found during investigation of a packaging and labeling facilit (b) (4)

The CMC team conveyed additional recommendations for the sponsor to consider for the resubmission, although it does not appear that the subjects of these were considered to be approvability issues. These comments and recommendations related to drug product specification (DDU), stability, manufacturing hold times (b) (4), device ruggedness, drug holdup and device cleaning, stability of fine particle fraction (b) (4) the post-approval stability protocol, and data supporting an improved foreign particulate method. Note that the applicant has now been producing their approved Aridol Inhalation Powder drug product for more than 8 years. This drug product also uses the same mannitol formulation prepared by the same process and the same device (but with a lower resistance) as for the Bronchitol Inhalation Powder drug product of this application. As a result, there is a substantially larger amount of data from process validation, clinical, and stability batches available now to gauge the production process and product stability, and these and other data provided in the resubmission mitigate the concerns outlined in the recommendation CMC comments included in the CR letter. In summary:

- The applicant has revised the DDU test acceptance criteria as requested.
- Regarding the Agency suggestion to consider adding (b) (4) to the manufacturing process, the applicant has provided additional data indicating that:

(b) (4)

- Regarding hold times for drug product intermediates, the applicant has updated the process description accordingly.
- Regarding device robustness and the drug hold-up issue, the applicant has revised the product presentation so that it now includes a device with each 7-day supply of capsules (no cleaning will be required).
- Updated stability data now support a 36 month expiry period and the applicant states that any extension of the expiry will be done via a prior-approval supplement as opposed to the typical submission via annual report.
- The post approval stability protocol is revised as requested, to include testing of assay and (b) (4) at the 3 month time-point.
- An updated and validated method for the determination of foreign particulates has now been provided as requested.

In summary, with this resubmission, the applicant has adequately addressed the quality-related recommendations and the GMP issues have been resolved. The evaluation of the resubmission is captured below in the reviews from the drug substance, drug product, process & facilities, and CDRH Office of Compliance teams.

RECOMMENDATION TO DPARP FROM OPQ/CMC: Approval

_____
Craig M. Bertha, CMC Lead
for DPARP

cc:
DPARP/LDo
DPARP/KPuthawala/RLim
ONDP/DNDPII/NDPIV/JPinto/CBertha/VPavuluri
OPF/DMA/MABII/XXu
OPF/DPAII/PABIV/RDandu/YHu
ONDP/NDBII/DNDAPI/FBurnett/DChristner
DRBPMI/RBPMBI/FAisida/ALalmansingh

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Reviewed By and For	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	01/28/2019	Friedrich Burnett, Ph.D. for NDA 202049	LOA date 09-NOV-2017
	III			4	N/A			LOA date 22-MAR-2018
	IV			4	N/A			LOA date 04-SEP-2018
	III			4	N/A			LOA date 02-NOV-2017
	III			4	N/A			LOA date 01-FEB-2016

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted 6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

MICROBIOLOGY

Product Background: Bronchitol is a sugar alcohol indicated for the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

NDA: 202049 (Resubmission)

Drug Product Name / Strength: Bronchitol (mannitol inhalation powder), 40 mg

Route of Administration: Oral inhalation

Applicant Name: Chiesi USA, 175 Regency Woods Place, Suite 600, Cary NC 27518

Manufacturing Site: Pharmaxis Ltd, 20 Rodborough Rd, Frenchs Forest, North South Wales 2086, Australia

Method of Sterilization: Drug product is not sterile.

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: This is a non-sterile dry powder product for oral inhalation administration. The manufacturing process is to be controlled for microbial quality and absence of specified microorganisms.

List Submissions Being Reviewed: 12/19/2018, 01/15/2019, 02/08/2019, 03/05/2019

Highlight Key Outstanding Issues from Last Cycle: None

Remarks: eCTD submission. This is a 505(b)(2) Class 2 resubmission. The Reference Listed Drug (RLD) is Aridol® (mannitol inhalation powder) bronchial challenge test kit indicated for the assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients 6 years of age or older who do not have clinically apparent asthma (NDA 022368). One RLD test kit contains dry powder mannitol capsules in graduated doses of 0 mg, 5 mg, 10 mg, 20 mg, and 40 mg and one, single patient use, dry powder inhaler device (RS01 low resistance version). The RLD is currently manufactured by Pharmaxis Ltd (20 Rodborough Rd, Frenchs Forest NSW 2086 Australia).

The initial submission of NDA 202049 received on 18 May 2012 was previously reviewed in microbiology review N202049r1.doc dated 06 February 2013 and

"Recommended for approval". The Complete Response Letter dated 18 March 2013 was issued due to deficiencies in clinical, product quality, and facility inspections. Information regarding the Mannitol Inhalation Powder Training Kit is summarized in this review, however, was not indicated in the previous microbiology review N202049r1.doc dated 06 February 2013.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: Microbiology review N202049r1.doc (Recommended for approval) dated 06 February 2013

S Drug Substance

The drug substance, mannitol, manufactured by (b) (4) is supplied as non-sterile. The drug substance, (b) (4) empty gelatin capsule and inhaler device are tested for microbial limits and bacterial endotoxins with the following acceptance criteria:

Drug Substance/ Excipient	Endotoxin Limit	Microbial Limits
Mannitol (b) (4)	(b) (4)	(b) (4)
Empty gelatin capsule	N/A	(b) (4)
Mouthpiece and capsule well of the inhaler device	N/A	

TVAC: Total Viable Aerobic Count
TYMC: Total Yeasts and Molds Count

Note to Reviewer: The acceptance criteria for quality microbiological tests for the drug substance are the same as the initial submission (5/18/2012). However, microbial controls for (b) (4) empty gelatin capsules and inhaler devices were not indicated in previous microbiology review N202049r1.doc dated 06 February 2013.

Reviewer's Assessment: Microbiological quality acceptance criteria for drug substance comply with those specified by USP <1111> for non-sterile substances for pharmaceutical use.

ADEQUATE

P.1 Description of the Composition of the Drug Product

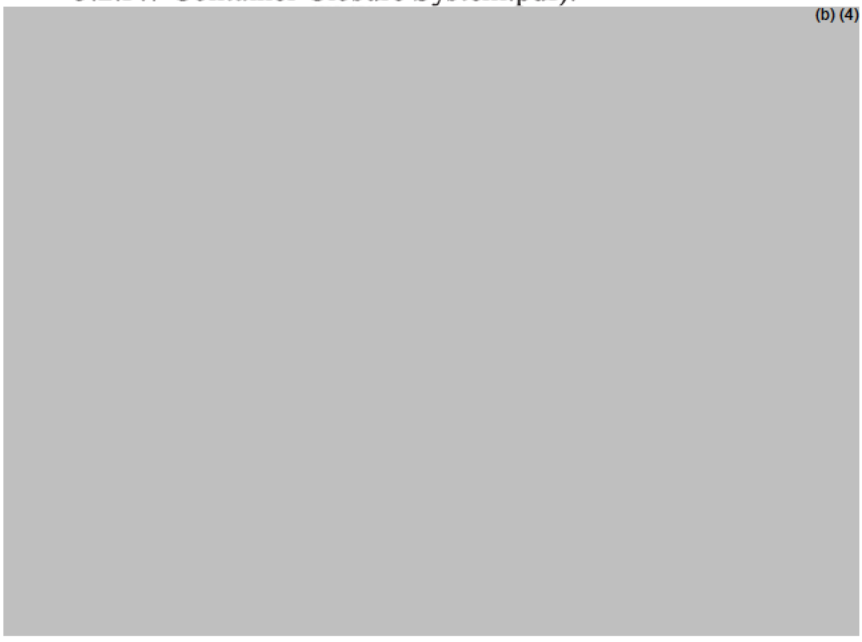
- **Description of drug product** – No change.
  Bronchitol (mannitol inhalation powder) is a combination drug product that consists of 40 mg of spray-dried Mannitol, USP filled into Size 3, hard gelatin capsules. Filled capsules are packed into aluminum blister cards and co-packaged with a dry powder inhalation device, the RS01 Inhaler Model 7 HR, a high-resistance inhaler. The capsule strength is imprinted by the capsule supplier, (b) (4) using black ink.

- **Drug product composition** – No change. No excipients are included in the contents of the capsule (b) (4) However, the drug product composition table is updated and duplicated below:

Component	Quality Standard	Function	Quantity per Capsule	Quantity per Inhalation
Mannitol	USP, Ph. Eur.	Drug substance	40 mg	32.2 mg
Size 3, clear, gelatin capsule	(b) (4)	Powder containment	NA	NA
(b) (4)		(b) (4)	NA	NA

- **Description of container closure system** – No change on the primary package and the inhaler device.

  The blister cards (the primary package) are composed of a double aluminum blister consisting of a bottom foil and a push-through foil manufactured by (b) (4) (3.2.P.1 Description and Composition of the Drug Product.pdf). The inhaler consists of three main components, the cap, mouthpiece, and inhaler body/perforating system. The diagram of the Bronchitol Inhaler is updated and duplicated below (page 5 of 13, 3.2.P.7 Container Closure System.pdf):



The commercial presentation of the Bronchitol drug product is updated in the resubmission. Bronchitol drug product will be supplied in the following three commercial presentations:

1. Bronchitol Tolerance Test co-packaged with a Training Kit
   - The Bronchitol Tolerance Test pack contains 1 blister (10 capsules) and one inhaler device. The Bronchitol Tolerance Test must be performed by a healthcare provider prior to beginning treatment with Bronchitol.
   - The Training Kit for use by health care providers consists of 1 blister (10 empty capsules) and one inhaler.
2. 7-day treatment pack (14 blisters/140 capsules and one inhaler device)
3. 4-week treatment pack (four 7-day packs)

Reviewer's Assessment: The drug product composition and container-closure system were adequately described. The container-closure system is adequate for the drug product oral inhalation route of administration.

Adequate

P.2 Pharmaceutical Development

(b) (4)

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

P.7 Container Closure – See P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability Summary.pdf)

Proposed Expiry: 3 years when stored not above 25°C.

Note to Reviewer: Expiry was not indicated in previous microbiology review N202049r1.doc dated 06 February 2013.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(3.2.P.8.2 Post Approval Stability.pdf)

Post Approval Stability Commitment

The applicant commits to placing the one batch of the subject drug product into their stability program annually. The microbial limits will be performed at initial, 12, 24, and 36 months at the 25°C/60% RH storage condition. Annually, a minimum of one batch of Mannitol, Inhalation Powder Training Kit will be tested for microbial limits at initial, 12, 24 and 36 months at the 25°C/60% RH storage condition.

Note to Reviewer: The previous microbiology review N202049r1.doc dated 06 February 2013 indicates that bacterial endotoxins testing was included in the stability program in the initial original submission (05/18/2012). Bacterial endotoxins stability testing is removed in the resubmission.

Reviewer's Assessment: Adequate

P.8.3 Stability Data

Microbiological stability data were not provided. However, the applicant states that microbiological stability results comply with specification for microbial limits and specified microorganisms for the test points and batches indicated below:

Batches	Manufacturing Site	25°C/60% RH and 30°C/65% RH	40°C/75% RH
The process validation batches EXP156, EXP162 and EXP166	(b) (4)	Initial, 24, 36 and 48 months	6 months
The pre-NDA exhibit batches 08274, 08344, 09092	(b) (4)	Initial, 6, 12, 18, 24, 36 and 48 months*	6 months
The clinical batch DPM-CF-303	(b) (4)	Initial and up to 32 months	12 months

* Batch 08274 was not tested at 48 months.

Note to Reviewer: Stability results for the pre-NDA exhibit batches were provided up to 24 months at 25ºC/60% RH and 30ºC/65% RH and up to 6 months at 40ºC/75% RH in the initial submission (05/18/2012).

Reviewer's Assessment: Adequate

A Appendices

A.2 Adventitious Agents Safety Evaluation

A.2.1 Materials of Biological Origin

The gelatin in the capsule is o (b) (4) The applicant states that Pharmaxis maintains complete documentation on the source and controls of the gelatin capsul (b) (4) (b) (4) (b) (4) The capsule is not inhaled or ingested. The capsule is discarded after the dose is delivered.

The applicant states tha (b) (4) used for the manufacture of the bottom foil and the push-through foil of the blister cards do not present a ris (b) (4)

Note to Reviewer: The (b) (4) statements for the gelatin capsules and bottom/push-through foils were not indicated in previous microbiology review N202049r1.doc dated 06 February 2013.

Reviewer's Assessment: Adequate

R Regional Information

Executed Batch Records

The batch record of batch# 16112BUK (batch size o (b) (4) kg, manufactured on 30 August 2016 (b) (4) R) are provided.

Reviewer's Assessment: Adequate

Comparability Protocols - No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Storage temperature: 68 °F -77°F (20 °C -25°C), with excursions permitted between 59 °F - 86°F (15 °C -30°C).
Route of administration: Oral inhalation
Container: Single dose

The drug product is non-sterile dry powder for oral inhalation administration, which is used directly without reconstitution or any further dilution. The proposed dose is 10 capsules (10×40 mg = 400 mg) twice daily. The product is not labeled as "single dose". However, ffter the patient inhales the spray-dried mannitol the empty capsules are discarded, which indicates the drug product is used as single dose. The inhaler device is discarded after 7 days of use. The Training Kit is stored at the same temperature as the drug product.

Note to Reviewer: The previous microbiology review N202049r1.doc dated 06 February 2013 did not indicate any information from the package insert.

Reviewer's Assessment: Adequate

Post-Approval Commitments: See P.8.2

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

Xia Xu, Ph.D. 03/12/2019

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

Nandini Bhattacharya, Ph.D. 03/12/2019

Xia Xu

Digitally signed by Xia Xu
Date: 3/12/2019 01:52:21PM
GUID: 585c30e50015a0ac941cb21671c188ce

Nandini Bhattacharya

Digitally signed by Nandini Bhattacharya
Date: 3/12/2019 01:54:24PM
GUID: 508da70c00028f454473851fced0e9d4

Bronchitol (mannitol inhalation powder)
NDA 202049

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Pharmaxis
403 Gordon Drive,
Exton PA 19341

Representative: Valerie Waltman

Indication: For the management of CF in patients 6 years of age or older to improve pulmonary function.

Presentation: Bronchitol is a drug delivery system for inhalation of mannitol using a plastic dry powder inhaler device and capsules containing mannitol. Bronchitol is supplied in cartons containing 10, 140 or (b) (4) capsules in blister strips. Each capsule contains 40 mg of mannitol. The capsules are clear and imprinted with "PXS 40 mg". The physician's initiation dose carton contains 10 capsules and 1 inhaler. The 14 day carton contains (b) (4) capsules and (b) (4) inhalers. The recommended dose is inhaling the contents of 10 capsules (400 mg) twice daily for a total dose of 800 mg per day.

The same formulation (neat mannitol) was approved in a diagnostic kit for assessment of bronchial hyperresponsiveness in patients 6 yrs of age and older with symptoms of asthma (NDA 22-368, Aridol Inhalation Powder).

The treatment kit should be stored below 25ºC (77ºF), with excursions permitted between 15ºC and 30ºC (59ºF to 86ºF). (b) (4).

The currently supported expiry period is (b) (4) months for storage at the described above conditions.

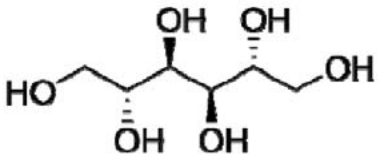
EER Status: Unacceptable.

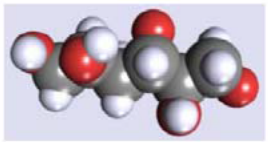
One of the contract testing facilities (b) (4) involved in protective packaging and labeling of the drug product has a withhold status as of March 4, 2013, based on inspection performed on (b) (4).

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Not necessary at this point
Pharmacology/Toxicology – Acceptable
CDRH Consult for Device –Based on previous devices from same site, ONDQA felt a consult was not necessary. A similar device approved for another NDA.

Original Submission: 18-May-2012

Drug Substance:





D-Mannitol M.W. 182. (b) (4) g/mol $C_6H_{14}O_6$

The drug substance is a sugar alcohol with IUPAC name (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN name mannitol. It is a white, crystalline powder or free flowing granules. It is freely soluble in water (22 g/100 mL) and very slightly soluble in alcohol. There are four morphic forms of mannitol denoted as (b) (4) The drug substance consists of predominantly (b) (4) and has a melting range of 164-169°C, with a pKa of 13.5 at 18°C. It is not hygroscopic and known to resist moisture sorption at high relative humidity.

The drug substance is synthesized, tested and packaged by (b) (4) (DMF (b) (4)). The retest period of the drug substance is (b) (4) years and is supported by the stability data. The specification controls for the drug substance include appearance, appearance of solution, assay, related substances, (b) (4), melting range, conductivity, specific rotation, endotoxins, microbial limits, (b) (4) (b) (4) and residue on ignition.

For the drug product manufacture, the mannitol (b) (4) As amended, all methods and acceptance criteria for the drug substance were found acceptable and all supporting DMFs have adequate status.

Conclusion: The drug substance is satisfactory

Drug Product:
The drug product is a combination of a dry powder inhaler and pre-metered hard-gelatin capsules containing mannitol. Each capsule contains 40 mg of spray-dried mannitol. The capsules are packaged into aluminum foil blisters and co-packaged with the inhalation device RS01 Inhaler Model 7 HR, a high-resistance inhaler manufactured by Plastiape S.p.A. (Italy). The to be marketed inhaler Model 7 HR is manufactured from the same plastic materials as inhaler Model 7 LR which is approved with the Aridol Inhalation Powder diagnostic kit, however there is difference in the air inlets to account for the higher air resistance, and different color piercing buttons which are blue for the HR inhaler proposed for Bronchitol Inhalation Powder versus red piercing buttons used in the LR inhaler approved with Aridol Inhalation Powder.

The device mechanism for both inhaler models is the same and is described below, however the Aridol inhaler was intended for significantly lesser use (maximum 57 capsules) than the proposed use of the Bronchitol inhaler (140 capsules within 7 days). Insertion of the capsule into

the inhaler, piercing it from both sides by pressing the blue buttons, followed by inhalation from the mouthpiece of the device results in the capsule spinning and releasing the powder by entraining it into the air-stream. The in vitro emitted dose, at 60 L/min for a 2 L aspiration volume, is 32.2 mg (target delivery). Two package configurations are proposed for marketing. The physician's initiation carton contains 1 blister strip (10 capsules) and 1 single-patient use inhaler device. The 14 day carton contains (b) (4) capsules ((b) (4) blister strips of 10 capsules) and (b) (4) single-patient use inhaler devices.

The drug product is controlled by the following specifications: Appearance (capsules and capsule content, blister strips), Identity, Purity, Related substance, (b) (4) Uniformity of Mass, Aerodynamic Particle Size Distribution, Uniformity of Delivered Dose, Mean Delivered Dose, and Microbial Limits. The sponsor is still developing a method for Foreign Particulate matter in the DPIs.

The following comments were recommended by Dr. Eugenia Nashed in her CMC review dated Feb 11, 2013. The implications of the comments were discussed internally again after the review was signed in DARRTS. The CMC reviewer and I recommend that these comments do not really rise to the level of a CR action from a CMC perspective, however the need for additional device durability studies and the agreement from the applicant to update methods and acceptance criteria for drug product are noted. Refer to the explanations and rationale provided under each recommendation.

1. Revise the specifications for drug product delivered dose uniformity (DDU) to comply with the recommendations of the FDA guidance document for metered dose inhalers (MDI) and dry powder inhalers (DPI), e.g., 9 of 10 within 85-115% of labeled claim and 10 of 10 to be within 75-125% of labeled claim, with the average of all values within 85-115% of labeled claim.

Evaluation: The specifications proposed are similar to the approved product for Aridol Inhalation Powder. The recommended acceptance criteria per the draft MDI/DPI guidance is for traditional dosage forms that usually employ 1-2 capsule per dose. The current product uses 10 capsules per dose each containing 40 mg of powder. Consequently, the delivered dose is an

average of 10 capsules. Since this is an exceptionally high number of capsules and mass, wider criteria for delivered dose uniformity (DDU) may be acceptable. However the drug product performance data indicate that the Applicant can meet the current guidance recommended criteria of 75-125% with an average of 85-115%. Hence even if the Applicant does not accept our recommendation, it is not a sufficient reason to hold up the approval.

2. We recommend that you explore the possibility of revising the drug product manufacturing process by including (b) (4) (b) (4)

Evaluation: The above recommendation is for the Applicant to explore improvements to the manufacturing process and subsequent implementation of the suggested (b) (4) (b) (4) (b) (4) Hence, even if the Applicant does not carry through our recommendation, it is not a reason to hold up an approval. Also, the Applicant may elect to pursue the recommended process improvements as a post-approval action.

3. We recommend tightening the processing and holding times for the drug product, (b) (4) (b) (4)

Evaluation: The recommendation of tightening the time controls [redacted] Since the current process and specification controls deliver repeatedly drug product with an acceptable dose performance, this comment does not rise to a hold recommendation from the CMC perspective

4. We recommend that you perform a study and submit data demonstrating the through-life (e.g., beginning and end of use life) ruggedness of the to-be-marketed HR device. Include results of drug product tested with repeatedly dropped devices to investigate potential changes in the delivered dose uniformity (DDU) and APSD [redacted].

[redacted]

[redacted]

6. We do not recommend extension of the [redacted] months expiry period *via* the annual report, [redacted]

7. Revise the post-approval stability protocol to include testing for the assay and the (b) (4) (b) (4) for the 3 months time point, since the submitted stability data suggests that change is occurring during the early stages of stability testing.

8. We acknowledge your previous post approval commitment provided in the NDA amendment dated November 29, 2012, to submit a validated improved method for the foreign particulate matter and data based acceptance criteria.

Evaluation: The last three comments above pertain to expiry, stability protocol, and a post market agreement that is already in place. These are to be addressed post approval.

Additional Items:
All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry; however the revalidation of the emitted dose and APSD may be requested by Agency labs as necessary because of the unusual nature of the device and methods, especially in the view the device performance to be used for a consecutive dose delivery of 140 (b) (4) capsules.

Note however that the Office of Compliance has found issues with one of the testing facilities and has provided a

Overall Conclusion: From a CMC perspective, the application is recommended for a Complete Response action. The drug product packaging and testing site does not have an acceptable recommendation from the Office of Compliance.

Comment for the CR Letter:

During an inspection on (b) (4), of the (b) (4) packaging and labeling facility for this application, our field investigator conveyed current Good Manufacturing Practices (cGMP) deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202049/000	**Sponsor:**	PHARMAXIS LTD
Org. Code:	570		1 EAST UWCHLAN AVE STE 405
Priority:			EXTON, PA 19341
Stamp Date:	18-MAY-2012	**Brand Name:**	Bronchitol (mannitol) Inhalation Powder
PDUFA Date:	18-MAR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	D-Mannitol
District Goal:	17-JAN-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; CAPSULE; MANNITOL; 40MG

FDA Contacts:	Y. LIU	Project Manager		3017961926
	E. NASHED	Review Chemist	(HFD-820)	3017961723
	A. SCHROEDER	Team Leader		3017961749

Overall Recommendation:	WITHHOLD	on 18-MAR-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 28-FEB-2013	by EES_PROD		
	PENDING	on 21-JUN-2012	by EES_PROD		
	PENDING	on 21-JUN-2012	by EES_PROD		

Establishment:	**CFN:**	**FEI:**	(b) (4)
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4)	**FEI:**	(b) (4)
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	22-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-MAR-2013		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:**	**FEI:** 3007428662	
	PHARMAXIS LTD UNIT 2, 10 RODBOROUGH ROAD FRENCHS FOREST, NSW, AUSTRALIA		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-FEB-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:**	(b) (4) (b) (4)
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	13-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRASAD PERI
03/18/2013

NDA 202-049

Bronchitol (mannitol) Inhalation Powder, 40 mg

Pharmaxis Ltd.

Eugenia M. Nashed, Ph.D.

Division of New Drug Quality Assessment III (ONDQA), for the Division of Pulmonary, Allergy and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA # **202-049**

2. REVIEW # 1

3. REVIEW DATE: 09-Feb-2013

4. REVIEWER: Eugenia M. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	18-May-2012
Amendment 1	06-JUN-2012
Amendment 2	15-JUN-2012
Amendment 5	06-SEP-2012
Amendment 6	29-Nov-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Pharmaxis Ltd.
Address: 403 Gordon Grive, Exton, PA 19341
Representative: Valerie Waltman
Telephone: (610) 363-5120

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: BRONCHITOL
b) Non-Proprietary Name (USAN): Mannitol Inhalation Powder
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Sugar Alcohol. XMannitol inhalation powder for treatment of cystic fibrosis. The same drug substance approved in a diagnostic kit for assessment of bronchial hyperresponsiveness in patients 6 yrs of age and older with symptoms of asthma (NDA 22-368, Aridol Inhalation Powder).

11. DOSAGE FORM: Inhalation powder

11. STRENGTH/POTENCY: 40 mg per capsule, 10 capsules per dose twice daily. Total daily dose 800 mg.

13. ROUTE OF ADMINISTRATION: Oral inhalation

14. Rx/OTC DISPENSED: _X_Rx ___OTC

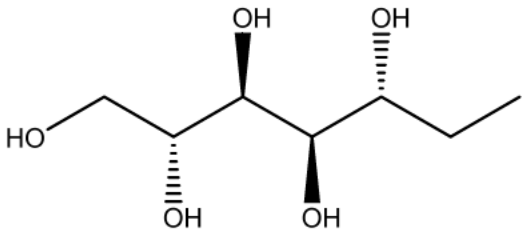
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X__SPOTS product – Form Completed

____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol

Molecular formula: $C_6H_{14}O_6$
Relative molecular mass: 182. (b) (4)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Reviewed By and For	Comments
(b) (4)	II	(b) (4	(b) (4)	1	Adequate	11/02/2009	AroraD for NDA 22-368	LOA date June-25-2008
	III			1	Adequate	10/23/2009	AroraD for NDA 22-368	LOA date Sep-13-2010
	III			1	Adequate	10/30/2009	AroraD for NDA 22-368	LOA date Feb-11-2008
	IV			3	Adequate	10/29/2010 04/22/2009	KellyS for oral capsules BerthaC for NDA 22-383 (Inhalation Powder)	LOA date June-06-2008
	IV			3	Adequate	08/30/2001	(b) (4)	LOA date June-06-2008
	III			3	Adequate	02/19/2010 09/15/2005	(b) (4)	LOA date Jan-14-2009

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application Number	Description
NDA	22-368	Aridol (mannitol) Inhalation Powder Diagnostic Kit
IND	70,277	Mannitol as broncho-provocative agent

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biopharm/ClinPharm	N/A		
CDRH	N/A, Device does not have any electronics or software		
EA	Acceptable		Exclusion requested. Certification is provided.
EES	Recommendation for 4 foreign sites are pending		5 testing sites AC; 4 sites (drug substance and drug product manufacturing) is pending
OSE/DMEPA/DDMAC Consult	Acceptable		Name Bronchitol is acceptable
Methods Validation			Not requested
Microbiology	Acceptable	Feb 7, 2013	Stephen Langille, Ph.D.
Pharm/Tox	Recommend Approval (Evaluated for drug substance and product impurities)	Feb 4, 2013	Luqi Pei, Ph.D.

The Chemistry Review for NDA 22-368

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, the NDA is approvable pending an acceptable recommendation from the Office of Compliance and pending satisfactory responses to the comments detailed at the end of this review. Also, the Microbiology team and the Pharmacology & Toxicology team recommend approval action for this NDA, in response to the CMC consult requests regarding the adequacy of microbiological safety controls and impurity controls, respectively.

At the conclusion of this review the establishment evaluation request (EER) is pending. The recommendation for 5 analytical testing sites is acceptable, however the evaluation of GMP status for the drug substance and the drug product manufacturing sites is not completed yet. The overall GMP recommendation for this NDA is pending as of Feb 11, 2013.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

However, there are two open CMC post-marketing commitments (PMC) pending for the cross-referenced NDA 22-368 for Aridol (mannitol) Inhalation Powder diagnostic kit. The Applicant provided a commitment to submit two supplemental applications with data and revised acceptance criteria for the foreign particulate matter and for the aerodynamic particle size distribution. The original commitment dates for submissions were July 2012 and July 2013, however based on the last report (Oct 2012), the Applicant is planning the responses by July 2013 and December 2014, respectively.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product, BRONCHITOL (mannitol) Inhalation Powder, 40 mg, is proposed for treatment of cystic fibrosis. The same formulation (neat mannitol) was approved in a diagnostic kit for assessment of bronchial hyperresponsiveness in patients 6 yrs of age and older with symptoms of asthma (NDA 22-368, Aridol Inhalation Powder).

The drug product is a non-sterile dry powder inhaler with formulation (neat mannitol) pre-metered in hard-gelatin capsules, each containing 40 mg of spray-dried mannitol. The capsules are packaged into aluminum foil blisters and co-packaged with the inhalation device RS01 Inhaler Model 7 HR, a high-resistance inhaler manufactured by Plastiape S.p.A. (Italy). The to-be-marketed inhaler Model 7 HR is manufactured from the same plastic materials as inhaler Model 7 LR which is approved with Aridol Inhalation Powder diagnostic kit, however there is difference in the air inlets (refer to page 59 of this review) to account for the higher air resistance, and different color piercing buttons which are blue for HR inhaler proposed for Bronchitol Inhalation Powder *versus* red piercing buttons used in LR inhaler approved with Aridol Inhalation Powder. The mechanism of action for both inhaler models are the same and is described below, however the Aridol inhaler was intended for significantly lesser use (maximum 57 capsules) than the use of the Bronchitol inhaler ((b) (4) capsules). Upon the insertion of the capsule into the inhaler and piercing it from both sides the inhalation from the mouthpiece results in spinning of the capsule and releasing the powder by entraining it into the air-stream. The *in-vitro* emitted dose, at 60 L/min for 2 L aspiration volume, is 32.2 mg (target delivery). Two package configurations are proposed for marketing. The physician's initiation carton contains 1 blister strip (10 capsules) and 1 single-patient use inhaler device. The 14 day carton contains (b) (4) capsules ((b) (4) blister strips of 10 capsules) and (b) (4) single-patient use inhaler devices.

The drug substance is a sugar alcohol with IUPAC name (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN name mannitol. It is a white, crystalline powder or free flowing granules. It is freely soluble in water (22 g/100 mL) and very slightly soluble in alcohol. (b) (4) (b) (4) There are four morphic forms of mannitol denoted as (b) (4). The drug substance consists of predominantly (b) (4) and has a melting range of 164-169°C, with a pKa of 13.5 at 18°C. It is not hygroscopic and known to resist moisture sorption at high relative humidity. The drug substance is synthesized, tested and packaged by (b) (4) (DMF (b) (4)). The retest period of the drug substance is (b) (4) years and is supported by the stability data. The specification controls for the drug substance include appearance, appearance of solution, assay, related substances, (b) (4), melting range, conductivity, specific rotation, endotoxins, microbial limits, (b) (4) (b) (4)

For the drug product manufacture, (b) (4) The regulatory specification controls for the drug product include purity of mannitol and testing for related substances, identification by infrared, (b) (4), appearance (of capsules, capsule contents, blisters and packs), bacterial endotoxins, microbial limits, aerodynamic particle size distribution and uniformity of delivered dose. As amended, all methods and acceptance criteria for the drug substance and drug product were found acceptable and all supporting DMFs have adequate status.

B. Description of How the Drug Product is Intended to be Used

BRONCHITOL Inhalation Powder is a combination drug product consisting of hard gelatin capsules containing 40 mg of respirable mannitol and a single-patient-use inhaler.
Two package configurations are proposed for marketing. The initiation carton contains 1 blister strip (10 capsules) and 1 single-patient-use inhaler device, and should be administered under the supervision of physician. The 14 day treatment carton contains (b) (4) capsules ((b) (4) blister strips of 10 capsules) and (b) (4) single-patient-use inhaler devices.

The proposed dosage is inhalation of the contents of 10 x 40 mg capsules, twice daily. Total daily dose is 800 mg (2 x 400 mg).

The treatment kit should be stored below 25ºC (77ºF), with excursions permitted between 15ºC and 30ºC (59ºF to 86ºF). (b) (4)

The currently supported expiry period is (b) (4) months for storage at the described above conditions. Due to the changes in fine particles observed on stability the extension of the expiry is limited to a prior approval supplement route.

C. Basis for Approvability or Not-Approval Recommendation

The NDA is considered approvable from the CMC perspective, pending acceptable recommendation from the Office of Compliance for the manufacturing and testing facilities and pending satisfactory responses to the comments detailed at the end of this review.

The original application was submitted on May 18, 2012, and several CMC information requests were forwarded to the Applicant on May 30, 2012 (complete list of manufacturing and testing facilities available for inspection), July 31, 2012 (LOA to DMF, revision of drug product specifications, analytical method for microbial limits, clarification of the expiry period), and October 19, 2012 (b) (4) (b) (4) (b) (4) The corresponding responses were received on June 6, September 6, and November 29, 2012, and they are included in this review.

The review of data submitted in the original NDA, subsequent NDA amendments and cross-referenced NDA 22-368 (Aridol diagnostic kit) support the approvable action for this NDA, with several remaining issues to be addressed by the Applicant in the forthcoming submission(s), as summarized below and listed in the CMC Comments to the Action Letter at the end of this review.

Summary of the remaining CMC issues:

- Revise the drug product manufacturing process [redacted]

- Submit an improved and validated method for the foreign particulate matter, based on the statement provided in amendment dated Nov 29, 2012.

- Perform through life device ruggedness study for the to-be-marketed device. Critically evaluate the number of inhalers supplied for the delivery of [redacted] capsules [redacted] in view of the intermittent high drug delivery, due to powder accumulation in the device, occurring 6 times more often for doses [redacted] in comparison to doses [redacted] and in view of the results from the requested ruggedness study. Support conclusions with data and revise labeling accordingly.

- The expiry period of [redacted] months can be extended only *via* prior-approval supplement (*versus* annual report) due to [redacted] The post-approval stability testing protocol needs to be revised to include 3 months testing point for the assay and the [redacted]

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ENashed/ONDQA/Reviewer/02/09/2013
Prasad Peri/ONDQA/DIV3/ Branch Chief / DARRTS date

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/s/

EUGENIA M NASHED
02/11/2013

PRASAD PERI
02/11/2013
I concur

Product Quality Microbiology Review

6 February 2013

NDA: **202-049**

Drug Product Name
Proprietary: Bronchitol
Non-proprietary: mannitol inhalation powder

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
17 May 2012	18 May 2012	9 August 2012	10 August 2012

Submission History (for amendments only): Not applicable

Applicant/Sponsor
Name: Pharmaxis Ltd.
Address: 20 Rodborough Rd.
Frenchs Forrest, NSW 2076
Australia

Representative: Stephen Beckman
Telephone: 610-363-5120

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original submission

2. SUBMISSION PROVIDES FOR: A new solid inhalation drug product

3. MANUFACTURING SITE: Pharmaxis Ltd,
Unit 2, 10 Rodborough Road,
Frenchs Forest NSW 2086, Australia

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Solid dry powder in a gelatin shell with an inhalation device
- Inhalation
- 40 mg/capsule

5. METHOD(S) OF STERILIZATION: Non-sterile drug product

6. PHARMACOLOGICAL CATEGORY: treatment for cystic fibrosis

B. SUPPORTING/RELATED DOCUMENTS: Not applicable

C. REMARKS: The application was provided in eCTD format.

filename: N202049r1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 202049 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The drug product is spray dried and packed into gelatin capsules for use with a dry powder inhaler.

B. Brief Description of Microbiology Deficiencies -

No product quality microbiology deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -

Not applicable

III. Administrative

A. Reviewer's Signature _____

Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block _____

Bryan Riley, Ph.D.
Acting Team Leader

C. CC Block

N/A

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/s/

STEPHEN E LANGILLE
02/06/2013

BRYAN S RILEY
02/06/2013
I concur.