

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22368Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: 1-SEP-2010

From: Deepika Arora, Ph.D., CMC Reviewer, Branch IX/ONDQA

To: NDA 22-368, Aridol (mannitol inhalation powder)

Through: Prasad Peri, Ph.D., Branch Chief (Acting), Branch VII/ONDQA

Subject: Approval recommendation. Updated labeling (submitted review 27-AUG-2010)

In the CMC review #4, dated 15-JUN-2010, the NDA is recommended for approval. Updated labeling has been provided following Agency's labeling comments dated 20-AUG-2010. Also the applicant's US office address has been updated to the following:

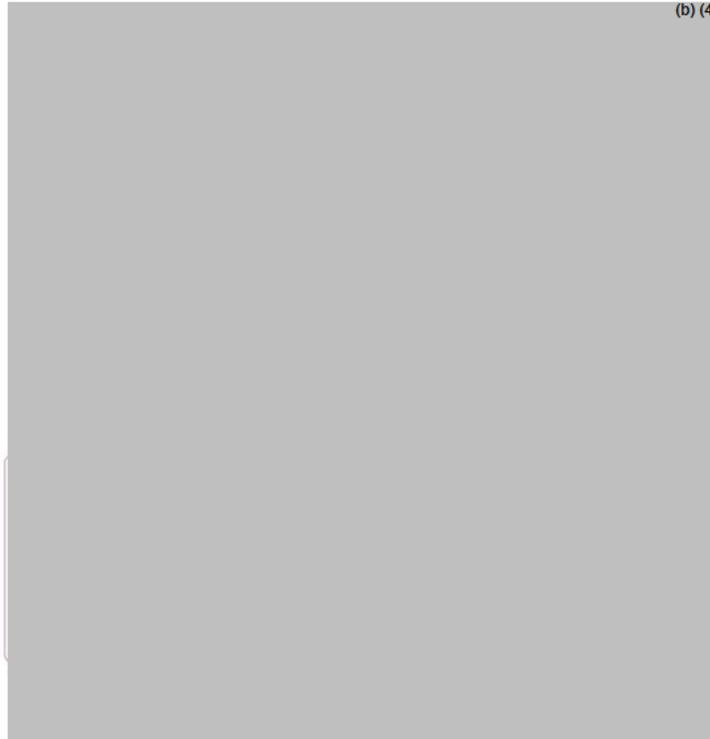
One East Uwchlan Avenue, Suite 405, Exton, PA 1934

Phone: (610) 363-5120; Fascimile: (610) 363-5926

Labeling Edits:

Carton Labeling

The carton has been modified to reflect the name ARIDOL refers to the entire bronchial challenge test kit.



Evaluation: Adequate.

ARIDOL Instructions Sheet

The instruction sheet has been modified to reflect the name ARIDOL refers to the entire bronchial challenge test kit.

Foil

The foil has been modified to include "Pharmaxis, Inc." per the requirements in 21 CFR 201.10(h)(2). A revised draft ARIDOL foil is provided.

Full Prescribing Information

Tracked changes show that all labeling recommendations have been incorporated.

In conclusion, NDA 22-368 is recommended for approval from CMC perspective. All recommended labeling edits have been incorporated.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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

/s/

DEEPIKA P ARORA
09/01/2010
Recommend approval from CMC perspective.

PRASAD PERI
09/01/2010
I concur

Aridol® (mannitol inhalation powder)

NDA 22368

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

Applicant: Pharmaxis Ltd.
Unit 2, 10 Rodborough Rd
Frenchs Forest NSW 2076
Australia

Representative: Ms. Valerie Waltman,
403 Gordon Drive, Exton, PA 19341
Phone: (610) 363-5120 ext 103, Fax: (610) 363-5926

Indication: Assessment of bronchial hyper responsiveness (BHR) to aid in the diagnosis of patients 6 yrs age and older with symptoms of or suggestive of asthma.

Presentation: Each ARIDOL™ kit contains an Aridol Device and nineteen mannitol capsules of different strengths identified by their color. The number of capsules needed for one complete inhalation challenge test is one placebo (empty) capsule, one 5 mg, one 10 mg, one 20 mg, and fifteen 40 mg capsules. Inhaling all the capsules through the Aridol device provides a maximum cumulative dose of 635 mg. The drug product is only to be administered under the supervision of a trained professional in a clinic. This drug product will not be available in retail pharmacies.

EER Status: ACCEPTABLE (22-FEB-2010)

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Assessment of methods by Agency laboratories not deemed necessary
Pharm/toxicology – Acceptable

Resubmission: 7-APR-2010

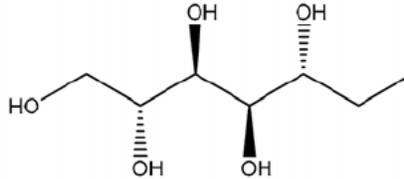
Original Submission: 27-FEB-2009

Post-Approval CMC Commitments:

- The applicant (Pharmaxis) commits to test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and will evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Pharmaxis further proposes to submit a changes-being-effected (CBE) supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meet the proposed specification) to either remove or finalize the test specification.

- The proposed specifications for Aerodynamic particle Size Distribution (APSD) are interim and the applicant will review/revise (if necessary) the APSD specifications based on the first 10 Aridol (Mannitol Inhalation Powder) U.S. commercial batches by means of a prior-approval supplement (PAS).

Drug Substance:



The IUPAC name for the drug substance is (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN is mannitol. The drug substance is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are three morp hic forms of mannitol denoted as α , β , δ -mannitol. The DS has a melting range of 164-169°C with a pKa of 13.5 at 18°C. It is not hygroscopic (resists moisture sorption even at high relative humidity). The retest period of the drug substance is (b) (4) years and is supported by the stability information.

The drug substance is synthesized, tested and packaged by (b) (4) referenced in a DMF (b) (4). The drug substance was found to be adequate in a review dated 02-NOV-2009.

The critical steps in the process are identified to be (b) (4).
The specification for the drug substance includes (b) (4).
(b) (4)

The drug substance is stored in (b) (4). Stability and retest period information are all referenced to the Drug Master File.

Conclusion: The drug substance is adequate.

Drug Product:

The drug product kit consists of pre-metered mannitol as the only ingredient as the formulation contained in hard-gelatin capsules along with an Aridol inhalation device. There are 5 different strengths of this product contained in different capsules of same size (identified by different cap colors): 0, 5, 10, 20 and 40 mg per capsule. The mannitol obtained from (b) (4) is spray dried by Pharmaxis Inc. Australia, to give the specific properties desired for the inhalation grade of mannitol.

Insertion of these capsules into the inhalation device (RS01 Inhaler Model 7), enables the capsule contents to be orally inhaled upon breathing maneuver by the subject. The device is (b) (4)

(b) (4) marketed outside the US for many years. The device causes the capsule piercing and inhalation from the mouthpiece results in spinning of the capsule, releasing the powder from the capsule followed by entrainment into the air-stream resulting in an emitted dose from the device.

The use of this drug product is different in that one kit of the drug product (includes 1 device and 19 capsules of five different strengths) is used for one inhalation challenge test, i.e., 1 x 0 mg capsule, 1 x 5 mg, 1 x 10 mg, 1 x 20 mg and 15 x 40 mg capsules (theoretical total cumulative dose of mannitol that can be delivered = 635 mg following one inhalation challenge). Thus, when tested for delivered dose uniformity at 60 L/min for 2 s per capsule, the *in vitro* dose delivery targets (mean cumulative delivered doses) are (b) (4) mg of mannitol.

The regulatory specification for the drug product includes the parameters of purity of mannitol and testing for related substances, identification by infrared spectroscopy, (b) (4) (b) (4) appearance (of capsules, capsule contents, blisters and packs), bacterial endotoxins, microbial limits, aerodynamic particle size distribution, and uniformity of delivered dose. All methods and acceptance criteria were found acceptable except for the uniformity of dosage content (capsule content not delivered dose) acceptance criterion. A comment was forwarded to the sponsor to tighten the acceptance criterion for uniformity of dosage content and comply with the USP criterion. The applicant agreed with the Agency's recommendations and this acceptance criterion has been deemed adequate.

Note that the APSD and delivered or emitted dose are measured by a challenge type test which actually simulates the patient use.

The applicant proposes a shelf life of 12 months which is supported.

Conclusion: The drug product is adequate.

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. Thus no method assessment by the Agency laboratory is deemed necessary. The additional items in the re-submission were replacement of (b) (4) facility for testing (b) (4) (b) (4) (b) (4) by Pharmaxis. (b) (4) was included as an additional specification for the drug substance.

The Office of Compliance has provided an acceptable recommendation for the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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

/s/

CRAIG M BERTHA

08/05/2010

Signing for Dr. Prasad Peri, Acting Branch Chief

NDA 22-368

Aridol™ (Mannitol Inhalation Powder)

Pharmaxis Ltd.

Deepika Arora, Ph.D.
Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA # **22-368**
2. REVIEW # 4
3. REVIEW DATE: 09-JUN-2010
4. REVIEWER: Deepika Arora, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-FEB-2009
CMC Filing Review	26-FEB-2009
CMC Review #1	18-NOV-2009
CMC Review #2	08-DEC-2009
CMC Review#3	22-DEC-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
23 (Resubmission)	07-APRIL-2010

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: ARIDOL™ (proposed)

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Mannitol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Diagnostic (Assessment of Bronchial Hyperresponsiveness to aid in the diagnosis of patients >/6 yrs age with symptoms of or suggestive of asthma)

11. DOSAGE FORM: Dry powder capsules

12. STRENGTH/POTENCY: 0, 5, 10, 20, 40 mg

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

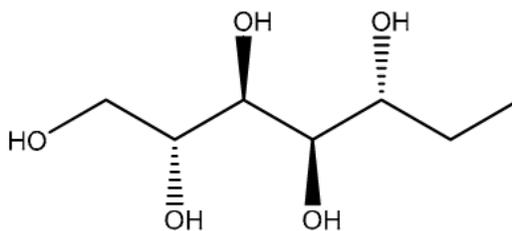
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular formula: C₆H₁₄O₆

Relative molecular mass: 182.17

Chemistry Review Data Sheet



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)	Mannitol	1	Adequate	11/02/2009	AroraD for NDA 22-368	LOA date June-25-2008
	III	(b) (4)	RS01 Dry Powder Inhaler Model 7	1	Adequate	10/23/2009	AroraD for NDA 22-368	LOA date May-12-2008
	III	(b) (4)	(b) (4)	1	Adequate	10/30/2009	AroraD for NDA 22-368	LOA date Feb-11-2008
	IV	(b) (4)	(b) (4)	3	Adequate	04/22/2009	BerthaC for (b) (4) (Inhalation Powder)	LOA date June-06-2008
	IV	(b) (4)	(b) (4)	3	Adequate	08/30/2001	FrankewichR for Entocort Capsules (Solid Oral)	LOA date June-06-2008
	III	(b) (4) (b) (4)	(b) (4)	3	Adequate	09/15/2005	ShawA for NDA 21-868 (Inhalation Powder)	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:

Chemistry Review Data Sheet

Document	Application Number	Description
IND	70,277	Aridol™ (Mannitol as broncho-provocative agent)

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biopharm/ClinPharm	N/A		
CDRH	Not required as device does not have any software or electronics		
EA	Exclusion requested. Certification is provided		
EES	Pending		Acceptable
OSE/DMEPA/DDMAC Consult	Labeling consult sent		
Methods Validation	Not validated		
Microbiology	Recommend Approval (Evaluated for microbial and endotoxin limits, methods)	10/07/2009	JW Metcalfe, Ph.D.
Pharm/Tox	Recommend Approval (Evaluated for drug substance and product impurities)	08/06/2009	L Pei, Ph.D.

The Chemistry Review for NDA 22-368

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC perspective, the NDA is recommended for approval.

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

- The applicant (Pharmaxis) commits to test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and will evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Pharmaxis further proposes to submit a changes-being-effected (CBE) supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalize the test specification.
- The Aerodynamic particle Size Distribution (APSD) proposed specifications by the applicant (after recommendations from the Agency to revise the APSD specifications in the original NDA) are interim to ensure that these ranges are reflective of batch to batch variability for the product. Therefore, the applicant has proposed interim specifications in an amendment to the application and will review/revise the APSD specifications based on the first 10 Aridol (Mannitol BCT) U.S. commercial batches by means of a prior-approval supplement (PAS). For any confirmed out-of-specification (OOS) result in marketed drug product, Pharmaxis will submit a Field Alert report to FDA per 21 CFR 314.81(b)(1). If Pharmaxis has evidence that the OOS result does not affect the safety and efficacy of the drug product, Pharmaxis will discuss it with the appropriate FDA chemistry team and provide justification for the continued distribution of that batch. If deemed necessary by Pharmaxis or FDA, drug product batches with confirmed OOS results will be withdrawn from the market.

II. Summary of Chemistry Assessments

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

The drug product is ARIDOL™ (Mannitol Inhalation Powder), a (b) (4) (b) (4) dry powder inhaler formulation, proposed for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients with symptoms of or suggestive of asthma. The drug product is pre-metered and the formulation is contained in hard-gelatin capsules. There are 5 different strengths of this product contained in different capsules of same size (identified by different cap colors): 0, 5, 10, 20 and 40 mg per capsule. Insertion of these capsules into the inhalation device RS01 Inhaler

Executive Summary Section

Model 7, enables the capsule contents to be orally inhaled upon breathing maneuver by the subject. The device is (b) (4) marketed outside the US for many years. The device causes the capsule piercing and inhalation from the mouthpiece results in spinning of the capsule, releasing the powder from the capsule followed by entrainment into the air-stream resulting in an emitted dose from the device. The drug product consists of mannitol as the only ingredient and no formulation comparability studies were necessary or included in the application. The use of this drug product is different in that one kit of the drug product (includes 1 device and 19 capsules of five different strengths) is used for one inhalation challenge test, i.e., 1 x 0 mg capsule, 1 x 5 mg, 1 x 10 mg, 1 x 20 mg and 15 x 40 mg capsules (theoretical total cumulative dose of mannitol that can be delivered = 635 mg following one inhalation challenge). Thus, when tested for delivered dose uniformity at 60 L/min for 2 s per capsule, the *in vitro* dose delivery targets (mean cumulative delivered doses) are (b) (4) of mannitol.

The IUPAC name for the drug substance is (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN is mannitol. The structural details of this compound are provided in p. 6. The drug substance is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are three morpnic forms of mannitol denoted as α , β , δ -mannitol. The DS has a melting range of 164-169°C with a pKa of 13.5 at 18°C. It is not hygroscopic (resists moisture sorption even at high relative humidity). The retest period of the drug substance is (b) (4) years and is supported by the stability information of the same. The drug substance is synthesized, tested and packaged by (b) (4) and for the drug product manufacture, (b) (4)

The manufacturing process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the Phase 3 clinical studies. The regulatory specifications on 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 were found acceptable for the drug substance and drug product. However, the methods and their validation have not been evaluated in FDA laboratories.

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

ARIDOL™ is intended to be used as a bronchial challenge test to aid the assessment of bronchial hyperresponsiveness in the diagnosis of patients with symptoms of or suggestive of asthma. Each ARIDOL™ contains the number of capsules needed for one inhalation challenge test: one

Executive Summary Section

placebo (empty) capsule as well as 1, 1, 1, and 15 of the 5 mg, 10 mg, 20 mg, and 40 mg mannitol capsules, respectively, thus, maximum cumulative dose is 635 mg. The drug product is only to be administered under the supervision of a suitably trained professional in a clinic setting. This drug product will not be available in retail pharmacies.

C. Basis for Approvability or Not-Approval Recommendation

The NDA resubmission submitted in response to the complete response letter issued by FDA (23-DEC-2009) addressed following changes in the Quality section:

1. [REDACTED] (b) (4)
[REDACTED] (b) (4) (b) (4) (b) (4) (b) (4) optical rotation testing has been replaced with Pharmaxis (acceptable cGMP status). The site still does testing for [REDACTED] (b) (4) [REDACTED] (b) (4) for which it has acceptable cGMP status by the Office of Compliance (22-FEB-2010).
2. Specifications were changed under the drug substance section to include a new method for testing [REDACTED] (b) (4) [REDACTED] (b) (4)
3. Updated manufacturers information
4. Updated labeling in response to the edits and recommendations communicated during the review cycle of the original submission. The updated information was reviewed and found to be adequate. Based upon the previous CMC reviews of the original submission (Reviews by D Arora, 18-Nov-2009, 8-Dec-2009 and 22-Dec-2009) and the review of the information in the resubmission, the application is recommended for approval from CMC perspective.

III. Administrative

A. Reviewer's Signature**B. Endorsement Block**

DArora/ONDQA/Reviewer/06/09/10

Prasad Peri/ONDQA/DIV3/BRANCH9Acting Branch Chief _____

C. CC Block

MRaggio/DPAP/Regulatory PM

AHarry/DPAP/Medical Officer

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CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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/s/

DEEPIKA P ARORA

06/15/2010

NDA is recommended for approval from CMC perspective.

PRASAD PERI

06/15/2010

I concur

NDA 22-368

Aridol™ (Mannitol Inhalation Powder)

Pharmaxis Ltd.

Deepika Arora, Ph.D.
Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA # **22-368**
2. REVIEW # 3
3. REVIEW DATE: 22-DEC-2009
4. REVIEWER: Deepika Arora, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-FEB-2009
CMC Filing Review	26-FEB-2009
CMC Review #1	18-NOV-2009
CMC Review #2	08-DEC-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	27-FEB-2009
Amendment 1	11-JUN-2009
Amendment 2	17-JULY-2009
Amendment 5	08-SEP-2009
Amendment 6	14-OCT-2009
Amendment 8	30-OCT-2009
Amendment 9	3-NOV-2009
Amendment 10	13-NOV-2009
Amendment 11	01-DEC-2009
Amendment 13	14-DEC-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Pharmaxis Ltd.

Chemistry Review Data Sheet

Address: 403 Gordon Grive, Exton, PA 19341

Representative: Valerie Waltman

Telephone: (610) 363-5120

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ARIDOL™ (proposed)
- b) Non-Proprietary Name (USAN): Mannitol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Diagnostic (Assessment of Bronchial Hyperresponsiveness to aid in the diagnosis of patients >/6 yrs age with symptoms of or suggestive of asthma)

11. DOSAGE FORM: Dry powder capsules

12. STRENGTH/POTENCY: 0, 5, 10, 20, 40 mg

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

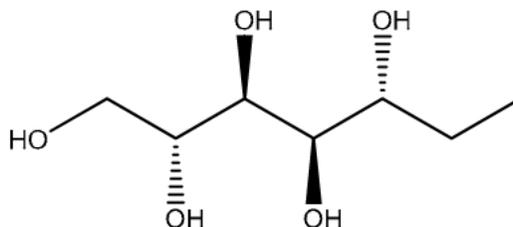
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Chemistry Review Data Sheet

Molecular formula: C₆H₁₄O₆

Relative molecular mass: 182.17



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)	Mannitol	1	Adequate	11/02/2009	AroraD for NDA 22-368	LOA date June-25-2008
(b) (4)	III	(b) (4)	RS01 Dry Powder Inhaler Model 7	1	Adequate	10/23/2009	AroraD for NDA 22-368	LOA date May-12-2008
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	10/30/2009	AroraD for NDA 22-368	LOA date Feb-11-2008
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	04/22/2009	BerthaC for (b) (4) (Inhalation Powder)	LOA date June-06-2008
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	08/30/2001	FrankewichR for Entocort Capsules (Solid Oral)	LOA date June-06-2008
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	09/15/2005	ShawA for NDA 21-868 (Inhalation Powder)	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")

Chemistry Review Data Sheet

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
IND	70,277	Aridol™ (Mannitol as broncho-provocative agent)

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biopharm/ClinPharm	N/A		
CDRH	Not required as device does not have any software or electronics		
EA	Exclusion requested. Certification is provided		
EES	Foreign sites are pending		
OSE/DMEPA/DDMAC Consult	Labeling consult sent		
Methods Validation	Not validated		
Microbiology	Recommend Approval (Evaluated for microbial and endotoxin limits, methods)	10/07/2009	JW Metcalfe, Ph.D.
Pharm/Tox	Recommend Approval (Evaluated for drug substance and product impurities)	08/06/2009	L Pei, Ph.D.

The Chemistry Review for NDA 22-368

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC perspective, the NDA is recommended for approval pending acceptable cGMP recommendation from the Office of Compliance (see attachment of the review for current status).

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

- The applicant (Pharmaxis) commits to test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and will evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Pharmaxis further proposes to submit a changes-being-effected (CBE) supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalize the test specification.
- The Aerodynamic particle Size Distribution (APSD) proposed specifications by the applicant (after recommendations from the Agency to revise the APSD specifications in the original NDA) are interim to ensure that these ranges are reflective of batch to batch variability for the product. Therefore, the applicant has proposed interim specifications in an amendment to the application and will review/revise the APSD specifications based on the first 10 Aridol (Mannitol BCT) U.S. commercial batches by means of a prior-approval supplement (PAS). For any confirmed out-of-specification (OOS) result in marketed drug product, Pharmaxis will submit a Field Alert report to FDA per 21 CFR 314.81(b)(1). If Pharmaxis has evidence that the OOS result does not affect the safety and efficacy of the drug product, Pharmaxis will discuss it with the appropriate FDA chemistry team and provide justification for the continued distribution of that batch. If deemed necessary by Pharmaxis or FDA, drug product batches with confirmed OOS results will be withdrawn from the market.

II. Summary of Chemistry Assessments

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

The drug product is ARIDOL™ (Mannitol Inhalation Powder), a (b) (4) (b) (4) dry powder inhaler formulation, proposed for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients with symptoms of or suggestive of asthma. The drug product is pre-metered

Executive Summary Section

and the formulation is contained in hard-gelatin capsules. There are 5 different strengths of this product contained in different capsules of same size (identified by different cap colors): 0, 5, 10, 20 and 40 mg per capsule. Insertion of these capsules into the inhalation device RS01 Inhaler Model 7, enables the capsule contents to be orally inhaled upon breathing maneuver by the subject. The device is (b) (4)

(b) (4) marketed outside the US for many years. The device causes the capsule piercing and inhalation from the mouthpiece results in spinning of the capsule, releasing the powder from the capsule followed by entrainment into the air-stream resulting in an emitted dose from the device. The drug product consists of mannitol as the only ingredient and no formulation comparability studies were necessary or included in the application. The use of this drug product is different in that one kit of the drug product (includes 1 device and 19 capsules of five different strengths) is used for one inhalation challenge test, i.e., 1 x 0 mg capsule, 1 x 5 mg, 1 x 10 mg, 1 x 20 mg and 15 x 40 mg capsules (theoretical total cumulative dose of mannitol that can be delivered = 635 mg following one inhalation challenge). Thus, when tested for delivered dose uniformity at 60 L/min for 2 s per capsule, the *in vitro* dose delivery targets (mean cumulative delivered doses) are (b) (4) of mannitol.

The IUPAC name for the drug substance is (2R,3R,4R,5R)-Hexane-1,2,3,4,5,6-hexol and the USAN is mannitol. The structural details of this compound are provided in p. 6. The drug substance is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are three morpnic forms of mannitol denoted as α , β , δ -mannitol. The DS has a melting range of 164-169°C with a pKa of 13.5 at 18°C. It is not hygroscopic (resists moisture sorption even at high relative humidity). The retest period of the drug substance is (b) (4) years and is supported by the stability information of the same. The drug substance is synthesized, tested and packaged by (b) (4) and for the drug product manufacture, (b) (4)

The manufacturing process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the Phase 3 clinical studies. The regulatory specifications on the drug product include purity of mannitol and testing for related substances, identification by infrared, (b) (4) (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 were found acceptable for the drug substance and drug product. However, the methods and their validation have not been evaluated in FDA laboratories.

Executive Summary Section

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

ARIDOL™ is intended to be used as a bronchial challenge test to aid the assessment of bronchial hyperresponsiveness in the diagnosis of patients with symptoms of or suggestive of asthma. Each ARIDOL™ contains the number of capsules needed for one inhalation challenge test: one placebo (empty) capsule as well as 1, 1, 1, and 15 of the 5 mg, 10 mg, 20 mg, and 40 mg mannitol capsules, respectively, thus, maximum cumulative dose is 635 mg. The drug product is only to be administered under the supervision of a suitably trained professional in a clinic setting. This drug product will not be available in retail pharmacies.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided adequate information on the chemistry, manufacturing and controls for the production of ARIDOL™ (mannitol) inhalation powder.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

DArora/ONDQA/Reviewer/12/22/09

Prasad Peri/ONDQA/DIV1/Acting Branch Chief _____

C. CC Block

MRaggio/DPAP/Regulatory PM

AHarry/DPAP/Medical Officer

YFan/OCP/Clinical Pharmacologist

LPei/DPAP/Pharmacologist

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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/s/

DEEPIKA P ARORA

12/22/2009

From CMC perspective, the NDA is recommended for approval pending acceptable cGMP recommendation from the Office of Compliance

PRASAD PERI

12/22/2009

I concur

Aridol® (mannitol inhalation powder)

NDA 22-368

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

Applicant: Pharmaxis Ltd.
Unit 2, 10 Rodborough Rd
Frenchs Forest NSW 2076
Australia

Representative: Ms. Valerie Waltman,
403 Gordon Drive, Exton, PA 19341
Phone: (610) 363-5120 ext 103, Fax: (610) 363-5926

Indication: Assessment of bronchial hyper responsiveness (BHR) to aid in the diagnosis of patients 6 yrs age and older with symptoms of or suggestive of asthma.

Presentation: Each ARIDOL™ kit contains an Aridol Device and nineteen mannitol capsules of different strengths identified by their color. The number of capsules needed for one complete inhalation challenge test is one placebo (empty) capsule, one 5 mg, one 10 mg, one 20 mg, and fifteen 40 mg capsules. Inhaling all the capsules through the Aridol device provides a maximum cumulative dose of 635 mg. The drug product is only to be administered under the supervision of a trained professional in a clinic. This drug product will not be available in retail pharmacies

EER Status: Recommendation Pending

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency may be requested to get similar results as provided in the applicant.
Pharm/toxicology – Acceptable

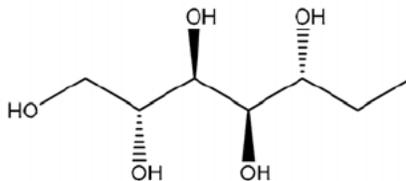
Original Submission: 27-Feb-2009

Post-Approval CMC Commitments:

- The applicant (Pharmaxis) commits to test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and will evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Pharmaxis further proposes to submit a changes-being-effected (CBE) supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalize the test specification.
- The proposed specifications for Aerodynamic particle Size Distribution (APSD) are interim and the applicant will review/revise the APSD specifications based on the first 10

Aridol (Mannitol Inhalation Powder) U.S. commercial batches by means of a prior-approval supplement (PAS).

Drug Substance:



The IUPAC name for the drug substance is (2R,3R,4R,5R)-Hexane-1,2,3,4,5,6-hexol and the USAN is mannitol. The drug substance is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are three morphic forms of mannitol denoted as α , β , δ -mannitol. The DS has a melting range of 164-169°C with a pKa of 13.5 at 18°C. It is not hygroscopic (resists moisture sorption even at high relative humidity). The retest period of the drug substance is (b) (4) years and is supported by the stability information.

The drug substance is synthesized, tested and packaged by (b) (4) (b) (4) (b) (4) and referenced in a DMF (b) (4). The drug substance was found to be adequate in a review dated 11/2/09.

The critical steps in the process are identified to be (b) (4). The specifications on the drug substance include (b) (4).

(b) (4)

The drug substance is stored in (b) (4). Stability and retest period information are all referenced to the Drug Master File.

Conclusion: The drug substance is satisfactory

Drug Product:

The drug product kit consists of pre-metered mannitol as the only ingredient as the formulation contained in hard-gelatin capsules along with an Aridol inhalation device. There are 5 different strengths of this product contained in different capsules of same size (identified by different cap colors): 0, 5, 10, 20 and 40 mg per capsule. The mannitol obtained from (b) (4) (b) (4) (b) (4) is (b) (4) (b) (4) by Pharmaxis Inc. Australia, to give the specific properties desired for the inhalation grade of mannitol.

Insertion of these capsules into the inhalation device (RS01 Inhaler Model 7), enables the capsule contents to be orally inhaled upon breathing maneuver by the subject. The device is (b) (4) (b) (4) marketed outside the US for many years. The device causes the capsule piercing and inhalation from the

mouthpiece results in spinning of the capsule, releasing the powder from the capsule followed by entrainment into the air-stream resulting in an emitted dose from the device.

The use of this drug product is different in that one kit of the drug product (includes 1 device and 19 capsules of five different strengths) is used for one inhalation challenge test, i.e., 1 x 0 mg capsule, 1 x 5 mg, 1 x 10 mg, 1 x 20 mg and 15 x 40 mg capsules (theoretical total cumulative dose of mannitol that can be delivered = 635 mg following one inhalation challenge). Thus, when tested for delivered dose uniformity at 60 L/min for 2 s per capsule, the *in vitro* dose delivery targets (mean cumulative delivered doses) are (b) (4) mg of mannitol.

The regulatory specifications on the drug product include purity of mannitol and testing for related substances, identification by infrared, (b) (4) (b) (4) appearance (of capsules, capsule contents, blisters and packs), bacterial endotoxins, microbial limits, aerodynamic particle size distribution, and uniformity of delivered dose. All methods and acceptance criteria were found acceptable except for the Uniformity of Dosage Content acceptance criterion. A comment was forwarded to the sponsor to tighten the acceptance criterion for Uniformity of dosage content and comply with the USP criterion. The response to this comment is pending.

Note that the APSD and Emitted dose are measured by a challenge type test which actually simulates the patient use.

The applicant proposes a shelf life of 12 months which is supported.

Conclusion: The drug product is acceptable pending the acceptance criterion for uniformity of dose content and acceptable status from the Office of Compliance for all establishments.

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 because of the unusual nature of the methods.

Acceptable compliance status has not been provided (until the writing of this review) by the Office of Compliance for all sites.

Overall Conclusion:

From a CMC perspective, the application is approvable pending acceptable cGMP recommendation from the Office of Compliance and resolution of acceptance criterion issues for Uniformity of Dosage Content.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22368

ORIG-1

PHARMAXIS LTD

ARIDOL POWDER FOR
INHALATION

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/s/

PRASAD PERI
12/09/2009

NDA 22-368

Aridol™ (Mannitol, Bronchial Challenge Test)

Pharmaxis Ltd.

Deepika Arora, Ph.D.
Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA # **22-368**
2. REVIEW # 2
3. REVIEW DATE: 07-DEC-2009
4. REVIEWER: Deepika Arora, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-FEB-2009
CMC Filing Review	26-FEB-2009
CMC Review #1	18-NOV-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	27-FEB-2009
Amendment 1	11-JUN-2009
Amendment 2	17-JULY-2009
Amendment 5	08-SEP-2009
Amendment 6	14-OCT-2009
Amendment 8	30-OCT-2009
Amendment 9	3-NOV-2009
Amendment 10	13-NOV-2009
Amendment 11	01-DEC-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Pharmaxis Ltd.
Address: 403 Gordon Grive, Exton, PA 19341
Representative: Valerie Waltman

Chemistry Review Data Sheet

Telephone: (610) 363-5120

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ARIDOL™ (proposed)
- b) Non-Proprietary Name (USAN): Mannitol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Diagnostic (Assessment of Bronchial Hyperresponsiveness to aid in the diagnosis of patients >/6 yrs age with symptoms of or suggestive of asthma)

11. DOSAGE FORM: Dry powder capsules

12. STRENGTH/POTENCY: 0, 5, 10, 20, 40 mg

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

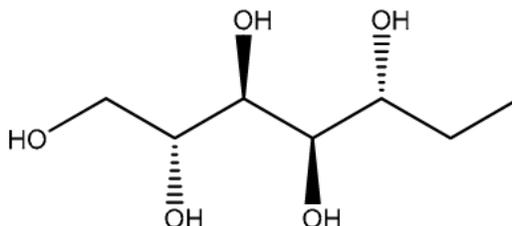
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular formula: C₆H₁₄O₆

Chemistry Review Data Sheet

Relative molecular mass: 182.17



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) SA	Mannitol	1	Adequate	11/02/2009	AroraD for NDA 22-368	LOA date June-25-2008
(b) (4)	III	(b) (4)	RS01 Dry Powder Inhaler Model 7	1	Adequate	10/23/2009	AroraD for NDA 22-368	LOA date May-12-2008
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	10/30/2009	AroraD for NDA 22-368	LOA date Feb-11-2008
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	04/22/2009	BerthaC for (b) (4) (Inhalation Powder)	LOA date June-06-2008
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	08/30/2001	FrankewichR for Entocort Capsules (Solid Oral)	LOA date June-06-2008
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	09/15/2005	ShawA for NDA 21-868 (Inhalation Powder)	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)

Chemistry Review Data Sheet

B. Other Documents:

Document	Application Number	Description
IND	70,277	Aridol™ (Mannitol as broncho-provocative agent)

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biopharm/ClinPharm	N/A		
CDRH	Not required as device does not have any software or electronics		
EA	Exclusion requested. Certification is provided		
EES	Foreign sites are pending		
OSE/DMEPA/DDMAC Consult	Labeling consult sent		
Methods Validation	Not validated		
Microbiology	Recommend Approval (Evaluated for microbial and endotoxin limits, methods)	10/07/2009	JW Metcalfe, Ph.D.
Pharm/Tox	Recommend Approval (Evaluated for drug substance and product impurities)	08/06/2009	L Pei, Ph.D.

The Chemistry Review for NDA 22-368

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC perspective, the NDA is recommended for approval pending satisfactory compliance recommendation for manufacturing and testing facilities to be used and pending responses to the requests for clarifications and information detailed at the end of this review.

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

- The applicant (Pharmaxis) commits to test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and will evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Pharmaxis further proposes to submit a changes-being-effected (CBE) supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalise the test specification.
- The Aerodynamic particle Size Distribution (APSD) proposed specifications by the applicant (after recommendations from the Agency to revise the APSD specifications in the original NDA) are interim to ensure that these ranges are reflective of batch to batch variability for the product. Therefore, the applicant has proposed interim specifications in an amendment to the application and will review/revise the APSD specifications based on the first 10 Aridol (Mannitol BCT) U.S. commercial batches by means of a prior-approval supplement (PAS). For any confirmed out-of-specification (OOS) result in marketed drug product, Pharmaxis will submit a Field Alert report to FDA per 21 CFR 314.81(b)(1). If Pharmaxis has evidence that the OOS result does not affect the safety and efficacy of the drug product, Pharmaxis will discuss it with the appropriate FDA chemistry team and provide justification for the continued distribution of that batch. If deemed necessary by Pharmaxis or FDA, drug product batches with confirmed OOS results will be withdrawn from the market.

II. Summary of Chemistry Assessments

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

The drug product is ARIDOL™ (Mannitol Inhalation Powder), a (b) (4) (b) (4) dry powder inhaler formulation, proposed for the assessment of bronchial hyperresponsiveness to aid in the

Executive Summary Section

diagnosis of patients with symptoms of or suggestive of asthma. The drug product is pre-metered and the formulation is contained in hard-gelatin capsules. There are 5 different strengths of this product contained in different capsules of same size (identified by different cap colors): 0, 5, 10, 20 and 40 mg per capsule. Insertion of these capsules into the inhalation device RS01 Inhaler Model 7, enables the capsule contents to be orally inhaled upon breathing maneuver by the subject. The device is (b) (4) marketed outside the US for many years. The device causes the capsule piercing and inhalation from the mouthpiece results in spinning of the capsule, releasing the powder from the capsule followed by entrainment into the air-stream resulting in an emitted dose from the device. The drug product consists of mannitol as the only ingredient and no formulation comparability studies were necessary or included in the application. The use of this drug product is different in that one kit of the drug product (includes 1 device and 19 capsules of five different strengths) is used for one inhalation challenge test, i.e., 1 x 0 mg capsule, 1 x 5 mg, 1 x 10 mg, 1 x 20 mg and 15 x 40 mg capsules (theoretical total cumulative dose of mannitol that can be delivered = 635 mg following one inhalation challenge). Thus, when tested for delivered dose uniformity at 60 L/min for 2 s per capsule, the *in vitro* dose delivery targets (mean cumulative delivered doses) are (b) (4) of mannitol.

The IUPAC name for the drug substance is (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN is mannitol. The structural details of this compound are provided in (b) (4). The drug substance is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are three morpnic forms of mannitol denoted as α , β , δ -mannitol. The DS has a melting range of 164-169°C with a pKa of 13.5 at 18°C. It is not hygroscopic (resists moisture sorption even at high relative humidity). The retest period of the drug substance is (b) (4) years and is supported by the stability information of the same. The drug substance is synthesized, tested and packaged by (b) (4), (b) (4), (b) (4) and for the drug product manufacture, (b) (4).

The manufacturing process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the Phase 3 clinical studies. The regulatory specifications on the drug product include purity of mannitol and testing for related substances, identification by infrared, (b) (4), (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 were found acceptable for the drug substance and drug product. However, the methods and their validation have not been evaluated in FDA laboratories.

Executive Summary Section

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

ARIDOL™ is intended to be used as a bronchial challenge test to aid the assessment of bronchial hyperresponsiveness in the diagnosis of patients with symptoms of or suggestive of asthma. Each ARIDOL™ contains the number of capsules needed for one inhalation challenge test: one placebo (empty) capsule as well as 1, 1, 1, and 15 of the 5 mg, 10 mg, 20 mg, and 40 mg mannitol capsules, respectively, thus, maximum cumulative dose is 635 mg. The drug product is only to be administered under the supervision of a suitably trained professional in a clinic setting. This drug product will not be available in retail pharmacies.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided adequate information on the chemistry, manufacturing and controls for the production of ARIDOL™ (mannitol) inhalation powder.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

DArora/ONDQA/Reviewer/12/07/09

Prasad Peri/ONDQA/DIV1/Acting Branch Chief _____

C. CC Block

MRaggio/DPAP/Regulatory PM

AHarry/DPAP/Medical Officer

YFan/OCP/Clinical Pharmacologist

LPei/DPAP/Pharmacologist

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CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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/s/

DEEPIKA P ARORA
12/07/2009

PRASAD PERI
12/08/2009

NDA 22-368

Aridol™ (Mannitol, Bronchial Challenge Test)

Pharmaxis Ltd.

Deepika Arora, Ph.D.
Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA # **22-368**

2. REVIEW # 1

3. REVIEW DATE: 20-JULY-2009

4. REVIEWER: Deepika Arora, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-FEB-2009
CMC Filing Review	26-FEB-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	27-FEB-2009
Amendment 1	11-JUN-2009
Amendment 2	17-JULY-2009
Amendment 5	08-SEP-2009
Amendment 6	14-OCT-2009
Amendment 8	30-OCT-2009
Amendment 9	3-NOV-2009
Amendment 10	13-NOV-2009

7. NAME & ADDRESS OF APPLICANT:

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

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ARIDOL™ (proposed)
- b) Non-Proprietary Name (USAN): Mannitol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Diagnostic (Assessment of Bronchial Hyperresponsiveness to aid in the diagnosis of patients >/6 yrs age with symptoms of or suggestive of asthma)

11. DOSAGE FORM: Dry powder capsules

12. STRENGTH/POTENCY: 0, 5, 10, 20, 40 mg

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

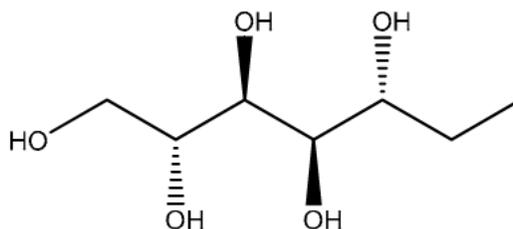
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular formula: C₆H₁₄O₆

Relative molecular mass: 182.17

Chemistry Review Data Sheet



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)	Mannitol	1	Adequate	11/02/2009	AroraD for NDA 22-368	LOA date June-25-2008
(b) (4)	III	(b) (4)	RS01 Dry Powder Inhaler Model 7	1	Adequate	10/23/2009	AroraD for NDA 22-368	LOA date May-12-2008
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	10/30/2009	AroraD for NDA 22-368	LOA date Feb-11-2008
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	04/22/2009	BerthaC for (b) (4) (Inhalation Powder)	LOA date June-06-2008
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	08/30/2001	FrankewichR for Entocort Capsules (Solid Oral)	LOA date June-06-2008
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	09/15/2005	ShawA for NDA 21-868 (Inhalation Powder)	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:

Chemistry Review Data Sheet

Document	Application Number	Description
IND	70,277	Aridol™ (Mannitol as broncho-provocative agent)

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biopharm/ClinPharm	N/A		
CDRH	Not required as device does not have any software or electronics		
EA	Exclusion requested. Certification is provided		
EES	Foreign sites are pending		
OSE/DMEPA/DDMAC Consult	Labeling consult sent		
Methods Validation	Not validated		
Microbiology	Recommend Approval (Evaluated for microbial and endotoxin limits, methods)	10/07/2009	JW Metcalfe, Ph.D.
Pharm/Tox	Recommend Approval (Evaluated for drug substance and product impurities)	08/06/2009	L Pei, Ph.D.

The Chemistry Review for NDA 22-368

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC perspective, the NDA is recommended for approval pending satisfactory compliance recommendation for manufacturing and testing facilities to be used and pending responses to the requests for clarifications and information detailed at the end of this review.

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

- The applicant (Pharmaxis) commits to test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and will evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Pharmaxis further proposes to submit a changes-being-effected (CBE) supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalise the test specification.
- The Aerodynamic particle Size Distribution (APSD) proposed specifications by the applicant (after recommendations from the Agency to revise the APSD specifications in the original NDA) are interim to ensure that these ranges are reflective of batch to batch variability for the product. Therefore, the applicant has proposed interim specifications in an amendment to the application and will review/revise the APSD specifications based on the first 10 Aridol (Mannitol BCT) U.S. commercial batches by means of a prior-approval supplement (PAS). For any confirmed out-of-specification (OOS) result in marketed drug product, Pharmaxis will submit a Field Alert report to FDA per 21 CFR 314.81(b)(1). If Pharmaxis has evidence that the OOS result does not affect the safety and efficacy of the drug product, Pharmaxis will discuss it with the appropriate FDA chemistry team and provide justification for the continued distribution of that batch. If deemed necessary by Pharmaxis or FDA, drug product batches with confirmed OOS results will be withdrawn from the market.

II. Summary of Chemistry Assessments

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

The drug product is ARIDOL™ (Mannitol Inhalation Powder), a (b) (4) (b) (4) dry powder inhaler formulation, proposed for the assessment of bronchial hyperresponsiveness to aid in the

Executive Summary Section

diagnosis of patients with symptoms of or suggestive of asthma. The drug product is pre-metered and the formulation is contained in hard-gelatin capsules. There are 5 different strengths of this product contained in different capsules of same size (identified by different cap colors): 0, 5, 10, 20 and 40 mg per capsule. Insertion of these capsules into the inhalation device RS01 Inhaler Model 7, enables the capsule contents to be orally inhaled upon breathing maneuver by the subject. The device is (b) (4) marketed outside the US for many years. The device causes the capsule piercing and inhalation from the mouthpiece results in spinning of the capsule, releasing the powder from the capsule followed by entrainment into the air-stream resulting in an emitted dose from the device. The drug product consists of mannitol as the only ingredient and no formulation comparability studies were necessary or included in the application. The use of this drug product is different in that one kit of the drug product (includes 1 device and 19 capsules of five different strengths) is used for one inhalation challenge test, i.e., 1 x 0 mg capsule, 1 x 5 mg, 1 x 10 mg, 1 x 20 mg and 15 x 40 mg capsules (theoretical total cumulative dose of mannitol that can be delivered = 635 mg following one inhalation challenge). Thus, when tested for delivered dose uniformity at 60 L/min for 2 s per capsule, the *in vitro* dose delivery targets (mean cumulative delivered doses) are (b) (4) of mannitol.

The IUPAC name for the drug substance is (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN is mannitol. The structural details of this compound are provided in p. 6. The drug substance is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are three morpnic forms of mannitol denoted as α , β , δ -mannitol. The DS has a melting range of 164-169°C with a pKa of 13.5 at 18°C. It is not hygroscopic (resists moisture sorption even at high relative humidity). The retest period of the drug substance is (b) (4) years and is supported by the stability information of the same. The drug substance is synthesized, tested and packaged by (b) (4), (b) (4), (b) (4) and for the drug product manufacture, a (b) (4)

The manufacturing process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the Phase 3 clinical studies. The regulatory specifications on the drug product include purity of mannitol and testing for related substances, identification by infrared, (b) (4), (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 were found acceptable for the drug substance and drug product. However, the methods and their validation have not been evaluated in FDA laboratories.

Executive Summary Section

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

ARIDOL™ is intended to be used as a bronchial challenge test to aid the assessment of bronchial hyperresponsiveness in the diagnosis of patients with symptoms of or suggestive of asthma. Each ARIDOL™ contains the number of capsules needed for one inhalation challenge test: one placebo (empty) capsule as well as 1, 1, 1, and 15 of the 5 mg, 10 mg, 20 mg, and 40 mg mannitol capsules, respectively, thus, maximum cumulative dose is 635 mg. The drug product is only to be administered under the supervision of a suitably trained professional in a clinic setting. This drug product will not be available in retail pharmacies.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided adequate information on the chemistry, manufacturing and controls for the production of ARIDOL™ (mannitol) inhalation powder. The labeling is currently under review and an advisory committee meeting is scheduled for November 20, 2009.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

DArora/ONDQA/Reviewer/11/12/09

Prasad Peri/ONDQA/DIV1/Acting Branch Chief _____

C. CC Block

MRaggio/DPAP/Regulatory PM

AHarry/DPAP/Medical Officer

YFan/OCP/Clinical Pharmacologist

LPei/DPAP/Pharmacologist

111 pages has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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

/s/

DEEPIKA P ARORA

11/18/2009

From CMC perspective, the NDA is recommended for approval pending satisfactory compliance recommendation for manufacturing and testing facilities to be used and pending responses to the requests for information detailed at the end of this review.

PRASAD PERI

11/18/2009

I Concur

OND Division of Pulmonary and Allergy Products

NDA: 22-368

Applicant: Pharmaxis, Ltd

Stamp Date: 27-Feb-2009

PDUFA Date: 27-Dec-2009

ONDQA 5 month date: 27-July-2009

Proposed Proprietary Name: Aridol® (mannitol) Inhalation powder

Established Name: (mannitol)

Dosage form and strength: Inhalation Powder, 0, 5, 10, 20 and 40 mg per capsule.

Route of Administration: oral inhalation

Indications: Assessment of hyper-responsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive asthma.

PAL: Prasad Peri, Ph.D. Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (Deepika Arora, Ph.D)

Time goals:

- **Initial Quality Assessment in DFS:** by 13-Apr-2009 (Filing meeting)
- **Chemistry filing memo in DFS:** by 13-Apr-2009
- Filing decision "Day 45": 13-Apr-2009 (set by Clinical Division)
- Filing review issues "Day 74": 12-May-2009 (set by Clinical Division)
- **Chemistry Review (DR/IR) letter:** by 27-Jul-2009
- Mid-cycle meeting "Month 5": 27-Jul-2009
- Wrap Up: 27-Oct-2009
- **Final Chemistry Review "Month 8" in DFS:** by 3-Nov-2009
- **Secondary Review Due:** 17-nov-2009
- Labeling Tcon: TBD
- CDTL Memo: TBD
- Action Package Readiness: TBD
- Division Director Memo: TBD
- Division Goal: TBD
- PDUFA: 27-Dec-2009

Relevant Applications/DMFs

IND 70,277 (Aridol and Bronchitol)

DMF (b) (4) (Mannitol USP from (b) (4) (b) (4)

DMF (b) (4) and DMF (b) (4)

DMF (b) (4)

DMF (b) (4)

DMF (b) (4)

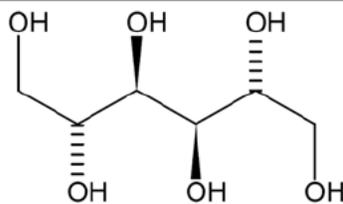
CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	Not applicable
CDRH	<i>Usually Not necessary since device does not have any software of electronics.</i>
EA	Exclusion requested. Certification provided.
EES	EER sent to Office of Compliance. Many foreign sites are pending.
OSE/DMEPA/DDMAC Consult	<i>Labeling consult request will be sent as part of DPAP's request.</i>
Methods Validation	<i>Per decision of reviewer but no critical tests identified.</i>
Microbiology	<i>Microbial limits, methods, and Endotoxins limits to be evaluated.</i>
Pharm/Tox	<i>DS and DP Impurities to be qualified</i>
Labeling and Nomenclature	<i>Trade name has been consulted to OSE/DMEPA. The drug product to be named Inhalation Powder.</i>

Summary:

- This is a standard (10 months) electronic NDA in eCTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary (divided into DS and DP sections). This NDA is filed as a 505(b)(1) application. The associated IND is 70,277. Several meeting with the sponsor are reported in DARRTS and by the applicant. CMC comments were sent to the sponsor in communications dated 7/3/2007 (CMC SPA), and 5/29/2008 (preNDA)
- Note that this is not an **NME**. Mannitol has been used in inhaled products before and is a part of the inhaled formulation in Exubera. A similar challenge agent (Methacholine) was approved a long time ago. Note that the drug product is approved in the European Union and Australia.

Drug Substance

- Mannitol is the drug substance and is used neat in the drug product. The drug substance is manufactured by (b) (4) (b) (4) (b) (4) and is referenced in a DMF (b) (4) (b) (4) is responsible for the manufacture, testing, and packaging.
- DMF (b) (4) is new and has never been reviewed. This DMF will need to be reviewed. A letter of authorization 25-Jun-2008 is issued to the Agency on behalf of the sponsor. The agent for the DMF holder is (b) (4). The drug substance is described in monographs of the USP, Ph. Eur., and BP.
- The drug substance is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are three morphic forms of mannitol denoted as α , β , δ -mannitol. The DS has a melting range of 164-169°C with a pKa of 13.5 at 18°C it is not hygroscopic (resists moisture sorption even at high relative humidity). The structure of the molecule is shown on the next page.



C₆H₁₄O₆

182.17

- The drug substance is controlled by the following tests: (b) (4)
(b) (4)
The drug substance manufacture states that (b) (4) (b) (4) is used in the preparation of the drug substance and (b) (4), no testing is required for Residual Solvents in accordance with USP Chapter <467>. (b) (4)
From the meeting minutes of Pharmaxis needs to add this to the drug substance specifications. The test method for impurities is stated to be derived from the USP and Ph.Eur. Exactly how they are used will need to be assessed. **It appears that there is no qualification results for the impurity** (b) (4) (b) (4). Highest levels seen at release is (b) (4). The level of (b) (4) is probably assumed based on the levels found in Ph. Eur. The mannitol assay method (by HPLC) described in the Ph. Eur./USP also specifies the detection of the related substances: (b) (4) listed in the Ph. Eur. as impurities (b) (4) respectively. Further descriptions of attempts to identify unknown impurities are provided by Pharmaxis.
- Mannitol was compared by HPLC with (b) (4) (b) (4)
(b) (4)
The remaining impurities have not been identified to date; however, all are at or below the limit of (b) (4) as required for identification of impurities by ICH Guidance for Industry Q3A.
- A vendor qualification program for the supplier of mannitol is provided. Currently all tests are performed by Pharmaxis and post approval appearance, appearance by solution, and ID by FTIR will be performed.
- Validation of analytical methods are provided for TM006 and Mannitol and Related Substances Assay. Brief descriptions and associated validation data for other methods are available for review at various other sites. Method for heavy metals by IEP-AES is reported as well.
- Pharmaxis provided results form three batches of mannitol as reproduced from the application in the following pages.
- Bulk drug substance is stored in (b) (4) Pharmaxis claims that all materials meet the FDA and EU regulations for materials in contact with food.
- Stability is referenced to the DMF for mannitol. (b) (4) has assigned a (b) (4) year retest period when stored in original packaging.
- The following stability data for the drug substance is available in addition to the stability data under stressed conditions.

Comment in the 74 day letter:

1. Provide a reference to 21CFR regulations for food contact materials or results from suitability tests for the (b) (4) used to store the drug substance.

ONDQA PAL's Initial Quality Assessment

Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

2. Provide safety qualification data to justify the proposed levels of (b) (4) in the drug product. Reference to USP or Ph. Eur. is not sufficient to justify the proposed levels of (b) (4) in the drug substance for the inhaled formulation. The pharmtox group may have additional comments on the necessary data for qualification.
3. Update the Specifications for mannitol to include testing for particle size distribution with acceptance criterion.

Drug Product

- The drug product consists of hard gelatin capsules (b) (4) containing 0 mg, 5 mg, 10 mg, 20 mg, and 40 mg of spray-dried mannitol. No excipients are included in the contents of the capsules (the 0 mg capsules are empty). The capsules are administered using the dry powder inhalation device provided. The inhalation device is the RS01 Inhaler Model 7, (b) (4) marketed outside the US for many years. (b) (4)
- A TRADENAME (mannitol BCT) contains the number of capsules needed for one inhalation challenge test, i.e., 1 x 0 mg capsule, 1 x 5 mg, 1 x 10 mg, 1 x 20 mg and 15 x 40 mg capsules. The capsule body is clear for all strengths, whereas the cap is colored for identification (except for the 0 mg capsule, which is also clear). The 5 mg capsule cap is white (titanium dioxide), 10 mg is yellow (yellow iron oxide and titanium dioxide), 20 mg is pink (red iron oxide and titanium dioxide), and 40 mg is red (red iron oxide and titanium dioxide). The capsule strength is imprinted using black ink.
- There are no excipients. The proposed specifications are listed at the end of this document. All excipients used for the manufacture of the printing inks are USP or NF grades.
- PSD for the bulk (b) (4) (b) (4) product is controlled (b) (4)

Table 2.3.P.1-5: Complete composition: mannitol, 40 mg, hard capsule (clear body, red cap)

Name of ingredient	Function	Reference to standard	Quantity (mg or % of capsule component)
Capsule content			
Mannitol	Drug substance	Ph. Eur. ; USP	40 mg
Capsule body			
Gelatin	Capsule shell	Ph. Eur. ; NF	100%
Capsule cap			
Red iron oxide (b) (4)	(b) (4)	(b) (4); NF	(b) (4)
Titanium dioxide (b) (4)	(b) (4)	Ph. Eur.; USP	
Gelatin	Capsule shell	Ph. Eur.; NF	

ONDQA PAL's Initial Quality Assessment

Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

Table 2.3.P.1-3: Complete composition: mannitol, 10 mg, hard capsule (clear body, yellow cap)

Name of ingredient	Function	Reference to standard	Quantity (mg or % of capsule component)
Capsule content			
Mannitol	Drug substance	Ph. Eur. ; USP	10 mg
Capsule body			
Gelatin	Capsule shell	Ph. Eur. ; NF	100%
Capsule cap			
Yellow iron oxide (b) (4)	(b) (4)	(b) (4); NF	(b) (4)
Titanium dioxide (b) (4)	(b) (4)	Ph. Eur. ; USP	
Gelatin	Capsule shell	Ph. Eur. ; NF	

Table 2.3.P.1-4: Complete composition: mannitol, 20 mg, hard capsule (clear body, pink cap)

Name of ingredient	Function	Reference to standard	Quantity (mg or % of capsule component)
Capsule content			
Mannitol	Drug substance	Ph. Eur.; USP	20 mg
Capsule body			
Gelatin	Capsule shell	Ph. Eur.; NF	100%
Capsule cap			
Red iron oxide (b) (4)	(b) (4)	(b) (4); NF	(b) (4)
Titanium dioxide (b) (4)	(b) (4)	Ph. Eur.; USP	
Gelatin	Capsule shell	Ph. Eur.; NF	

Table 2.3.P.1-1: Complete composition: mannitol, 0 mg, hard capsule (clear body and cap)

Name of ingredient	Function	Reference to standard	Quantity (mg / % of capsule component)
Capsule content			
Mannitol	Drug substance	not applicable	0
Capsule body			
Gelatin	Capsule shell	Ph. Eur.; NF	100%
Capsule cap			
Gelatin	Capsule shell	Ph. Eur.; NF	100%

Table 2.3.P.1-2: Complete composition: mannitol, 5 mg, hard capsule (clear body, white cap)

Name of ingredient	Function	Reference to standard	Quantity (mg or % of capsule component)
Capsule content			
Mannitol	Drug substance	Ph. Eur.; USP	5 mg
Capsule body			
Gelatin	Capsule shell	Ph. Eur.; NF	100%
Capsule cap			
Titanium dioxide (b) (4)	(b) (4)	Ph. Eur.; USP	(b) (4)
Gelatin	Capsule shell	Ph. Eur.; NF	

- The device is referenced to a DMF (b) (4) and (b) (4) from (b) (4). The actual device is referenced in DMF (b) (4) and the safety information of extractables and leachables is referenced in DMF (b) (4). Note that the materials of composition are the same for the devices in both the DMFs. **Both DMFs will need to be reviewed.** However it is noted that (b) (4) has other devices that were approved in Europe and Asia.
- During development there are changes made to the devices used in the clinical trials. Five different inhaler devices were used. (b) (4)

The table indicates the devices and size of capsules used. (b) (4)

- Two phase three studies are reported (one performed ex US DPM-A-301 and one within the US DPM-A-305). Following the DPM-A-301 study, a (b) (4) procedure was introduced within the sub batches. Also production was scaled up by the addition of two (b) (4) and the (b) (4) (b) (4) was replaced.
- Note that the Gelatin Capsules are referenced to DMF (b) (4). The empty gelatin capsule is manufactured by (b) (4). This DMF was recently reviewed and found adequate.
- The manufacturing process involves (b) (4)

CRITICAL ISSUES

**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
5/5/2009 10:06:32 PM
CHEMIST

Ali Al-Hakim
5/6/2009 03:54:26 PM
CHEMIST

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	NDA 22368/000	Action Goal:	
Date:	27-FEB-2009	District Goal:	08-APR-2010
Regulatory:	07-OCT-2010		
Applicant:	PHARMAXIS LTD 403 GORDON DR EXTON, PA 19341	Brand Name:	ARIDOL POWDER FOR INHALATION
		Estab. Name:	
		Generic Name:	MANNITOL(CAPS CONTAINING POWDER FOR INHA
Priority:	3S	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	570		001; CAPSULE; MANNITOL; 40MG 002; CAPSULE; MANNITOL; 20MG 003; CAPSULE; MANNITOL; 10MG 004; CAPSULE; MANNITOL; 5MG 005; CAPSULE; MANNITOL; 0MG

Application Comment: THIS NDA IS FOR AN ENCAPSULATED MANNITOL. THE CAPSULES CONTAIN 0, 5, 10, 20 AND 40 MG MANNITOL PER CAPSULE EACH. IT (b) (4). THE NDA IS HELD BY PHARMAXIS LTD. WHICH IS THE FIRST TIME SUBMITTING AN APPLICATION TO THE USA. IT DOES NOT APPEAR TO BE INSPECTED ANYTIME. MANNITOL IS BEING USED AS A CHALLENGE AGENT TO INDUCE BRONCHOCONSTRICTION. THE ADDRESS FOR PHARMAXIS IS UNIT 2, 10 RODBOROUGH ROAD, FRENCHS FOREST NSW, 2086 AUSTRALIA, PHONE +61 2 9454 7211.

(b) (4)

FDA Contacts:	M. RAGGIO	Project Manager	301-796-2109
	P. PERI	Review Chemist (HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader	301-796-1323

Overall Recommendation:	ACCEPTABLE	on 09-JUN-2010	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on 17-DEC-2009	by M. STOCK	(HFD-320)	301-796-4753

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: [REDACTED] (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	15-APR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	15-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI:
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-MAR-2009				PERIP
OC RECOMMENDATION	24-MAR-2009			ACCEPTABLE BASED ON PROFILE	KIEL

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR DRUG PRODUCT PACKAGING AND LABELING. [REDACTED] (b) (4)

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	15-APR-2009	Product Specific			JOHNSONE
INSPECTION PERFORMED	03-SEP-2009		03-SEP-2009		IRIVERA
INSPECTION SCHEDULED	01-OCT-2009		26-OCT-2009		IRIVERA
INSPECTION PERFORMED	26-OCT-2009		26-OCT-2009		JOSE.CRUZ

[REDACTED] (b) (4)

DO RECOMMENDATION 22-FEB-2010 ACCEPTABLE INSPECTION JOHNSONE

OC RECOMMENDATION 22-FEB-2010 ACCEPTABLE DISTRICT RECOMMENDATION INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: POTENTIAL OAI

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	15-APR-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	01-OCT-2009		29-OCT-2009		IRIVERA
INSPECTION PERFORMED	28-OCT-2009		28-OCT-2009		JOSE.CRUIZ

(b) (4)

DO RECOMMENDATION	17-DEC-2009			WITHHOLD	STOCKM PEND REG ACTION - WARNING LTR
OC RECOMMENDATION	17-DEC-2009			WITHHOLD	STOCKM DISTRICT RECOMMENDATION
SUBMITTED TO OC	09-APR-2010				HENRYD
REQUEST CANCELLED	09-APR-2010				HENRYD FACILITY WITHDRAWN
SUBMITTED TO OC	12-APR-2010				HENRYD
SUBMITTED TO DO	13-APR-2010	Product Specific			INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

DC RECOMMENDATION 27-APR-2010
FIRM ONLY ACCEPTABLE FOR TESTS NOTED IN COMMENTS FOR THIS APPLICATION.
WOULD NEED TO REINSPECT FOR OTHER TESTS OR OTHER APPLICATIONS.

ACCEPTABLE JOHNSONE
ADEQUATE FIRM RESPONSE

OC RECOMMENDATION 27-APR-2010
SEE DO REC. COMMENTS

ACCEPTABLE INYARDA
DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-OCT-2009				PERIP
OC RECOMMENDATION	27-OCT-2009			ACCEPTABLE BASED ON PROFILE	KIEL

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: THIS SITE MANUFACTURES MANNITOL WHICH IS THE ACTIVE INGREDIENT. (on 17-MAR-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-MAR-2009				PERIP
SUBMITTED TO DO	24-MAR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	23-APR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	24-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: [REDACTED] (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	23-APR-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	01-OCT-2009		21-OCT-2009		IRIVERA
INSPECTION PERFORMED	21-OCT-2009		21-OCT-2009		JOSE.CRUZ

[REDACTED] (b) (4)

DO RECOMMENDATION	22-FEB-2010			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	22-FEB-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-OCT-2009				PERIP
SUBMITTED TO DO	09-OCT-2009	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	20-OCT-2009	Product Specific			PDOMINGO
INSPECTION PERFORMED	22-OCT-2009		22-OCT-2009		PDOMINGO
DO RECOMMENDATION	03-NOV-2009			ACCEPTABLE	PDOMINGO
INSPECTION DATED (b) (4) WILL BE CLASSIFIED NAI. FIRM IS ACCEPTABLE.				INSPECTION	
OC RECOMMENDATION	03-NOV-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 22368/000
S Date: 27-FEB-2009
Regulatory: 27-DEC-2009

Action Goal:
District Goal: 28-OCT-2009

Applicant: PHARMAXIS LTD
 403 GORDON DR
 EXTON, PA 19341

Brand Name: ARIDOL POWDER FOR INHALATION
Estab. Name:
Generic Name: MANNITOL(CAPS CONTAINING POWDER FOR INHA

Priority: 3S
Org. Code: 570

Product Number; Dosage Form; Ingredient; Strengths

001; CAPSULE; MANNITOL; 40MG
 002; CAPSULE; MANNITOL; 20MG
 003; CAPSULE; MANNITOL; 10MG
 004; CAPSULE; MANNITOL; 5MG
 005; CAPSULE; MANNITOL; 0MG

Application Comment: THIS NDA IS FOR AN ENCAPSULATED MANNITOL. THE CAPSULES CONTAIN 0. 5. 10. 20 AND 40 MG MANNIOTL PER CAPSULE EACH. (b) (4). THE NDA IS HELD BY PHARMAXIS LTD. WHICH IS THE FIRST TIME SUBMITTING AN APPLICATION TO THE USA.IT DOES NOT APPEAR TO BE INSPECTED ANYTIME. MANNITOL IS BEING USED AS A CHALLENGE AGENT TO INDUCE BRONCHOCONSTRICTION. THE ADDRESS FOR PHARMAXIS IS UNIT 2, 10 RODBOROUGH ROAD, FRENCHS FOREST NSW, 2086 AUSTRALIA, PHONE +61 2 9454 7211.

(b) (4)

FDA Contacts:	M. RAGGIO	Project Manager	301-796-2109
	P. PERI	Review Chemist (HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader	301-796-1323

Overall Recommendation: WITHHOLD on 17-DEC-2009 by M. STOCK (HFD-320) 301-796-4753

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
 [REDACTED] (b) (4)
 [REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: [REDACTED] (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	15-APR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	15-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI:
(b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-MAR-2009				PERIP
OC RECOMMENDATION	24-MAR-2009			ACCEPTABLE BASED ON PROFILE	KIEL

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: (b) (4)
[REDACTED] (b) (4)

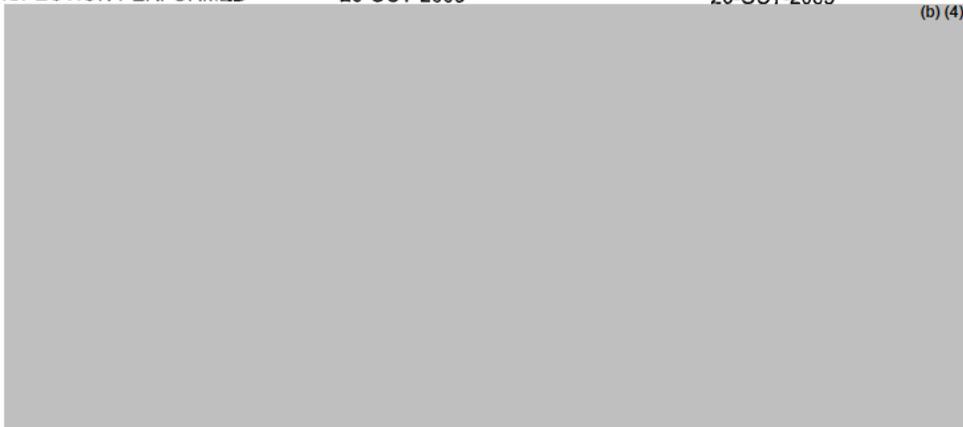
DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR DRUG PRODUCT PACKAGING AND LABELING. IN AN AMENDMENT DATED 9-SEPT-2009, THE FULL STREET ADDRESS HAS BEEN PROVIDED. [REDACTED] (b) (4)

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	15-APR-2009	Product Specific			JOHNSONE
INSPECTION PERFORMED	03-SEP-2009		03-SEP-2009		IRIVERA
INSPECTION SCHEDULED	01-OCT-2009		26-OCT-2009		IRIVERA
INSPECTION PERFORMED	26-OCT-2009		26-OCT-2009		JOSE.CRUZ



**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: POTENTIAL OAI

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	15-APR-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	01-OCT-2009		29-OCT-2009		IRIVERA
INSPECTION PERFORMED	28-OCT-2009		28-OCT-2009		JOSE.CRUIZ



DO RECOMMENDATION	17-DEC-2009			WITHHOLD	STOCKM
				PEND REG ACTION - WARNING LTR	
OC RECOMMENDATION	17-DEC-2009			WITHHOLD	STOCKM
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-OCT-2009				PERIP
OC RECOMMENDATION	27-OCT-2009			ACCEPTABLE BASED ON PROFILE	KIEL

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: THIS SITE MANUFACTURES MANNITOL WHICH IS THE ACTIVE INGREDIENT. (on 17-MAR-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-MAR-2009				PERIP
SUBMITTED TO DO	24-MAR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	23-APR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	24-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: [REDACTED] (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-APR-2009				PERIP
SUBMITTED TO DO	06-APR-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	23-APR-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	01-OCT-2009		21-OCT-2009		IRIVERA
INSPECTION PERFORMED	21-OCT-2009		21-OCT-2009		JOSE.CRUIZ

[REDACTED] (b) (4)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-OCT-2009				PERIP
SUBMITTED TO DO	09-OCT-2009	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	20-OCT-2009	Product Specific			PDOMINGO
INSPECTION PERFORMED	22-OCT-2009		22-OCT-2009		PDOMINGO
DO RECOMMENDATION	03-NOV-2009			ACCEPTABLE	PDOMINGO
INSPECTION DATED (b) (4) WILL BE CLASSIFIED NAI. FIRM IS ACCEPTABLE.				INSPECTION	
OC RECOMMENDATION	03-NOV-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	