

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22368Orig1s000**

**OTHER REVIEW(S)**

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: A clinical trial with Aridol (mannitol inhalation powder) in subjects/patients older than 50 years of age who have significant co-morbidities common in an elderly population (e.g., COPD, obesity, cardiac risk factors, etc.) or reanalyze the data from completed clinical trials in which Aridol (mannitol inhalation powder) was administered to an elderly population with co-morbidities. A substantial number of the total population should be 65 years of age or greater. The trial should include the following objectives: 1) evaluate the degree of bronchoconstriction defined as a fall in FEV1 in the older subject/patient population and 2) evaluate the overall adverse event profile in subjects over 50 years of age.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2012</u>
	Study/Trial Completion:	<u>09/30/2013</u>
	Final Report Submission:	<u>02/28/2014</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Patients older than 50 years of age were not enrolled in the pivotal clinical trial submitted to the NDA. There was a limited number of patients in this age group evaluated in one supportive study and therefore it is appropriate for a postmarketing requirement. Only a clinical trial rather than a nonclinical or observational study will be sufficient to identify any unexpected serious risks in patients older than 50 years of age with co-morbid conditions common in older populations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To identify any unexpected serious risks of Aridol in patients 50 years of age and older who have significant co-morbid conditions common in the elderly (i.e. Chronic Obstructive Pulmonary Disease, obesity, cardiac risk factors). The trial will include the following objectives:

1. Evaluate the degree of bronchoconstriction in the older patient population
2. Evaluate the overall adverse event profile in subjects over 50 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial should be undertaken in patients 50 years of age and older with co-morbidities common in the older population. A substantial number of the total sample population should be 65 years of age and older. Alternatively, the sponsor may reanalyze the data from completed clinical trials in which Aridol (mannitol inhalation powder) was administered to an elderly population with co-morbidities.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  
As an alternative to the clinical trial, the sponsor may instead reanalyze the data from completed clinical trials in which Aridol was administered to an elderly population with co-morbidities.

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  - Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)

---

  - Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
-

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Test and evaluate aerodynamic particle size distribution (APSD) in the first 10 US commercial batches of Aridol. Revise the APSD specifications based on the the commercial batch data.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>July 2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Data from multiple commercial batches is needed to set APSD specifications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The proposed specifications for the Aerodynamic Particle Size Distribution (APSD) are interim and the applicant will review/revise the APSD specifications based on the first 10 U.S. commercial batches of ARIDOL by means of a prior-approval supplement

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Test and evaluate foreign particulate matter in the first 6 US commercial batches of Aridol and evaluate the data to either remove or finalize the foreign particulate drug product specifications.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>July 2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Data from multiple commercial batches is needed to make a scientific judgement regarding whether foreign particulate matter specification is required.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The applicant commits to test foreign particulate matter for the first 6 U.S. commercial batches of ARIDOL and evaluate the results from this testing to either remove or finalize the foreign particulate drug product specifications.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

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***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
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- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

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- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

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SALLY M SEYMOUR  
10/05/2010

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** July 9, 2010

**To:** Miranda Raggio, Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)

**From:** Roberta Szydlo, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Through:** Kathleen Klemm, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**CC:** Lisa Hubbard, Professional Group Leader  
Shefali Doshi, DTC Group Leader  
Robyn Tyler, Regulatory Review Officer  
Wayne Amchin, Regulatory Health Project Manager  
(DDMAC)

**Subject:** NDA 022368  
DDMAC labeling comments for ARIDOL™ (mannitol inhalation powder)

---

DDMAC has reviewed the proposed product labeling (PI) and proposed physician instruction sheet for ARIDOL™ (mannitol inhalation powder) submitted for consult on May 12, 2010. DDMAC's comments are based on the following:

- proposed draft marked-up labeling titled "Aridol CR label tracked 06-29-10.doc" that was sent via email from DPARP to DDMAC on June 29, 2010
- proposed physician instruction sheet titled "7-2-10 AHdraft-instructions\_Trackchanges.pdf" that was sent vial email from DPARP to DDMAC on July 2, 2010.

DDMAC's comments on the PI and physician instruction sheet are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials. If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or [roberta.szydlo@fda.hhs.gov](mailto:roberta.szydlo@fda.hhs.gov).

18 pages of draft labeling 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

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/s/

ROBERTA T SZYDLO  
07/09/2010

**REGULATORY PROJECT MANAGER LABELING REVIEW  
(PHYSICIAN LABELING RULE)**

**Division of Pulmonary and Allergy Products**

**Application Number:** NDA 22-368 Class 2 Resubmission

**Name of Drug:** Aridol® (mannitol inhalation powder)

**Material Reviewed:**

**Submission Date:** 4-7-10

**Receipt Date(s):** 4-7-10

**Submission Date of Structure Product Labeling (SPL):** Not yet submitted

**Type of Labeling Reviewed:** Track Changes Word Version

**Background**

Pharmaxis submitted an original NDA on February 26, 2009, for Aridol (mannitol inhalation powder) as a diagnostic test for asthma. On December 23, 2009, a Complete Response (CR) action was taken on this application. Pharmaxis submitted a Class 2 Resubmission on April 7, 2010. The PLR review of the label submitted on April 7, 2010, is found below.

**Review**

The following issues/deficiencies have been identified in the proposed labeling. The following comments should be conveyed to the sponsor for resolution prior to action:

**Highlights**

1. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
2. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Refer to the “Guidance for Industry: Determining Established a Pharmacologic Class for Use in Highlights of Prescribing Information”

3. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57(a)(11)]. Provide an email address, phone number, or company website which is dedicated to the reporting of adverse reactions.
4. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
5. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
6. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

### **Table of Contents**

7. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]. Indent all subsection headings, as some are not indented in the proposed label.
8. Remove the extra spaces after subsections 8.6 and 13.1 prior to the subsection heading.

### **Full Prescribing Information (FPI)**

9. Remove the extra spaces after subsections 8.6 and 13.1 prior to the subsection heading.
10. If a Boxed Warning is included, the same title from the Boxed Warning must be inserted at the beginning of the TOC, in bold type and upper case letters.
11. Do not refer to adverse reactions as (b) (4) Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.  
(b) (4)
12. Section 8 USE IN SPECIFIC POPULATIONS, subsection 8.1 Pregnancy states [See Nonclinical Toxicology (13.2)]. Correct this to match the 13.2 subsection heading of Animal Toxicology and/or Pharmacology in the FPI.

13. The revision date at the end of the Highlights section replaced the revision date at the end of the labeling and should not appear in both places. Delete the revision date at the end of the FPI.

### **Inhaler Instructions Sheet**

14. The photos on the instruction sheet in Steps 6-8 show an individual with a nose-clip in place. However, there is no mention of having the subject put on nose-clip in the instructional text. Insert this step, as appropriate.

### **Recommendations**

The labeling comments will be sent to the sponsor in a labeling fax. Pharmaxis should address the identified deficiencies/issues and re-submit labeling. This updated version of labeling will be used for further labeling discussions.

---

Miranda Raggio  
Regulatory Project Manager  
Finalized

Supervisory Comment/Concurrence:

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Sandy Barnes  
Chief, Project Management Staff  
Initialed 5-20-10

Drafted: Miranda Raggio/5-7-10

Revised/Initialed:Sandy Barnes/5-20-10

Finalized:Miranda Raggio/ 5-21-10

**CSO LABELING REVIEW OF PLR FORMAT**

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22368

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ORIG-1

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PHARMAXIS LTD

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ARIDOL POWDER FOR  
INHALATION

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/s/  
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MIRANDA B RAGGIO

05/21/2010

## SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-368
APPLICANT	Pharmaxis Limited
DRUG NAME	ARIDOL (mannitol inhalation powder)
SUBMISSION DATE	February 27, 2009
SEALD REVIEW DATE	December 9, 2009
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

18 pages of draft labeling 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

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/s/

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DEBRA C BEITZELL  
12/09/2009

LAURIE B BURKE  
12/14/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 8, 2009

To: Badrul Chowdhury, MD, Director  
Division of Pulmonary and Allergy Products

Through: Carlos Mena-Grillasca, RPh, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Judy Park, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Aridol (Mannitol) Inhalation Powder

Application Type/Number: NDA 022368

Applicant: Pharmaxis, Ltd.

OSE RCM #: 2009-532 & 2008-1714

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## **1 INTRODUCTION**

This review is written in response to a March 17, 2009 request from the Division of Pulmonary and Allergy Products for an evaluation of the Aridol container labels, carton and insert labeling to identify areas that could lead to medication errors.

## **2 METHODS AND MATERIALS**

Using Failure Mode and Effects Analysis,<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton and insert labeling submitted on February 27, 2009 to identify vulnerabilities that could lead to medication errors.

## **3 RECOMMENDATION**

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1, *Comments to the Division* for consideration in labeling discussions with the review team. Section 3.2 *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Carolyn Volpe, OSE Project Manager, at 301-796-5204.

### **3.1 COMMENTS TO THE DIVISION**

#### **A. General**

1. Revise the established name and dosage form to the proper format and dosage form [i.e. (mannitol) inhalation powder] in all areas of the package insert that list the name.
2. Based on the discussion with the clinical team, remove the box on the first page of the insert labeling. Per 21 CFR 201.57(e), the boxed warning is reserved for “special problems, particularly those that may lead to death or serious injury.”

#### **B. Highlights, Dosage and Administration Section:**

1. Revise the terms “dry powder mannitol” to read “mannitol capsules” to correctly reflect the kit content.
2. Revise the statement “Capsules are to be administered” to read “Inhale capsule content...” in order to correctly reflect the actual route of administration (i.e. oral inhalation).
3. Include a statement that the capsules need to be used with the inhaler device.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4. The “indicated arrow” that describes the direction to twist open the inhaler is missing from the picture. Please include it.



**C. Highlights, Dosage Forms and Strengths Section:**

1. Include the total number of capsules in the kit and the quantity of capsules per strength (e.g. 0 mg – 1 capsule).
2. Revise the “single-use inhaler” statement to read “single patient use inhaler” to clarify that the inhaler should be used for one patient and not shared and to clarify that the inhaler can be used for all the doses contained in the package, not just for a single dose. Additionally, include instructions to discard the inhaler after single patient use.

**D. Full Prescribing Information, Dosage and Administration Section 2:**

1. Revise the statement “capsules of dry powder” under Basic Dosing Information (first paragraph) to read “capsules for oral inhalation.”
2. Revise the Test Implementation section to include numbered steps. As currently presented, after the instruction for the removal of the empty capsule from the inhaler the following instruction states “Repeat Steps 3 – 5”. However, there are no numbered step in this section.

**E. Full Prescribing Information, Dosage Forms and Strengths Section 3:**

1. Revise the “single-use inhaler” statement to read “single patient use inhaler” to clarify that the inhaler should be used for one patient and not shared and to clarify that the inhaler can be used for all the doses contained in the package, not just for a single dose. Additionally, include instructions to discard the inhaler after single patient use.
2. Revise the presentation of the contents of the blister packs in alignment with our recommendation in Section 3.2 B. 2.

### **3.2 COMMENTS TO THE APPLICANT**

**A. General Comment for All Labels and Labeling**

1. “Mannitol bronchial challenge test” is not the correct established name for this product. Additionally, “Capsule for Oral Inhalation” is not a recognized, proper designation of the dosage form. Revise the established name and dosage form to read as follows [i.e. (mannitol) inhalation powder].
2. Revise the statement “Single Use Only” throughout all labels, labeling, and instructions for use to read “Single Patient Use Only”.
3. Consider revising the pictures to include a closer view that clearly represents the applicable step.

**B. Blister Label**

1. Since there have been many postmarketing cases of patients ingesting capsules intended for oral inhalation, include the statement “For Oral Inhalation Only”.
2. Remove the watermarked numbering system in the background that indicates the number of blister packs (i.e. 1, 2, 3) and keep the numbering of the 9 steps. Two different numbering systems on the same label can be confusing and it is unnecessary.

**C. Carton Labeling**

1. The presentation of the first letter of the proprietary name (‘a’) resembles the letter ‘O’ and the name may be read incorrectly. Revise the font to clearly present it as the capital letter “A” to diminish the potential confusion.
2. We note that the product is described as a “test kit” and will be used for diagnostic use. However, this description is not prominently displayed on the carton labeling. The description (e.g. “Diagnostic Kit”) should be prominently displayed to clarify that it is only intended for diagnostic use and not for treatment.
3. Include the discard statement (e.g. Discard after single patient use) after the “For single patient use only” statement to ensure the unused capsules will not be reused.
4. Include the usual or recommended dosage statement per 21 CFR 201.100(b)(2) and 21 CFR 201.55.

**D. Bronchial Challenge Test Guidelines**

1. Revise the statement “Single use only” to “Single patient use only” throughout the guidelines.

3 pages of draft labeling 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

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/s/

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JUDY J PARK  
12/08/2009

DENISE P TOYER  
12/08/2009

CAROL A HOLQUIST  
12/08/2009

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: December 2, 2009

TO: Miranda Raggio, Regulatory Project Manager  
Anya Harry, M.D., Ph.D., Medical Officer  
Division of Pulmonary and Allergy Products Products

THROUGH: Tejashri Purohit-Sheth, MD, FAAAI  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-368

APPLICANT: Pharmaxis

DRUG: mannitol (Aridol, Bronchitol)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients greater than 6 years of age with symptoms of, or suggestive of asthma

CONSULTATION REQUEST DATE: December 7, 2009

DIVISION ACTION GOAL DATE: December 23, 2009

PDUFA DATE: December 27, 2010

## I. BACKGROUND:

Provocation tests that use indirect stimuli have a high specificity for asthma causing smooth muscle contraction by release of endogenous mediators including prostaglandins, leukotrienes, and histamines. Evaporative water loss occurs in conditioning the inspired air and causes exercise-induced bronchoconstriction by inflammatory mediators of mast cell origin. Exercise is generally recognized as having a low sensitivity to identify bronchial hyperresponsiveness. Exercise-induced bronchospasm is consistent with a diagnosis of asthma, and responds to chronic treatment with inhaled corticosteroids and other therapeutic regimens used in the treatment of asthma. A dry powder of mannitol has been developed as an indirect bronchial provocation challenge test and is available as a standardized test kit. The test kit contained pre-filled mannitol capsules in escalating doses and a hand-held dry powder inhaler device.

**Protocol DPM-A-305** was a phase III, multicenter, blinded, clinical diagnostic test utility study to assess the sensitivity and specificity of mannitol (Aridol) challenge as compared with methacholine challenge. The purpose was to predict bronchial hyperresponsiveness, as manifested by a positive exercise challenge in subjects presenting with signs and symptoms suggestive of asthma, but without a definitive diagnosis.

The total number of enrolled subjects and sites constituted 509 unique subjects and 27 sites (N.B. 25 sites enrolled subjects), respectively, across the United States. A total of 418 subjects completed the study, and 375 subjects performed all tests (i.e., “per protocol” population). The “per protocol” population included 111 children (6-17 years old) and 264 adults (18-50 years old). The primary objectives for this diagnostic test performance study were threefold: (1) to estimate accurately the sensitivity and specificity of mannitol bronchial challenge test to detect exercise-induced bronchospasm as a manifestation of bronchial hyperresponsiveness, (2) to demonstrate whether mannitol had clinically acceptable sensitivity to detect exercise induced bronchospasm as a manifestation of bronchial hyperresponsiveness, and (3) to demonstrate whether the specificity of mannitol was superior to that of methacholine to detect exercise-induced bronchospasm as a manifestation of bronchial hyperresponsiveness.

Two clinical sites (Dr. Ratner and Dr. Rundell) were inspected for this study, as well as the sponsor, Pharmaxis.

## II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Paul Ratner, MD /Site #29	San Antonio, TX	DPM-A-305	September 9-15, 2009	October 1, 2009	NAI
Kenneth Rundell, PhD /Site #15	Scranton, PA	DPM-A-305	September 8-11, 2009	September 23, 2009	NAI
Pharmaxis	Exton, PA	Sponsor	September 28-29, 2009	October 7, 2009	NAI

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

## **PROTOCOL DPM-A-305**

### **1. Paul Ratner, MD/Site #29**

7711 Louis Pasteur Drive Suite 407  
San Antonio, TX 78229

#### **a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from September 9 to 15, 2009. A total of 40 subjects were screened, and 36 subjects were randomized, and completed the study. The inspection evaluated the following documents: comparison of medical records to electronic case report forms, audit trails for spirometry testing electronic data, study drug accountability logs, informed consent documents, study monitoring visits and correspondence. Source documents were verified for consistency with data listings.

#### **b. Limitations of inspection:**

None.

#### **c. General observations/commentary:**

Study randomization and blinding procedures were followed. No significant regulatory violations were noted and no Form FDA 483 was issued.

#### **d. Data acceptability/reliability for consideration in the NDA review decision:**

The data in support of clinical efficacy and safety at this clinical site appear acceptable.



(b) (4) The field investigator also confirmed the subjects that were enrolled, terminated and completed the study.

**b. Limitations of inspection:**

None.

**c. General observations/commentary:**

No Form FDA 483 was issued, and no significant regulatory violations were noted.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

The data in support of clinical efficacy and safety at this clinical site appear acceptable.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Two domestic clinical investigator sites and the sponsor were inspected in support of this application for study Protocol # **DPM-A-305**, in support of mannitol approval for the assessment of bronchial hyper-responsiveness in the diagnosis of patients greater than 6 years of age with symptoms of or suggestive of asthma

Inspection findings for DPM-A-305 documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. No significant discrepancies were noted upon inspection at the clinical sites. The data generated by these inspected sites appear reliable in support of the application.

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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/

ANTHONY J ORENCIA  
12/02/2009

TEJASHRI S PUROHIT-SHETH  
12/02/2009

## DSI CONSULT: Request for Clinical Inspections

**Date:** July 23, 2009

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2  
Anthony Orenca MD, Medical Officer OC/DSI  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Anya Harry MD, PhD., Medical Officer DPAP  
Anthony Durmowicz MD Clinical Team Leader, DPAP  
Badrul Chowdhury MD. PhD, Division Director, DPAP

**From:** Miranda Raggio, Senior Regulatory Project Manager

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA-21368

Applicant/ Applicant contact information (to include phone/email):

Pharmaxis

Valerie Waltman, Senior Manager, Regulatory Affairs

[Valerie.waltman@pharmaxis.com](mailto:Valerie.waltman@pharmaxis.com)

403 Gordon Drive

Exton, PA 19341

Phone: 610-363-5120 ext. 103

Fax: 610-363-5926

Drug Proprietary Name: (b) (4) (mannitol) Powder for Inhalation

NME or Original BLA (Yes/No): YES

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): The assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients > 6 years of age with symptoms of or suggestive of asthma

PDUFA: 12-27-09

Action Goal Date: 12-23-09

DSI Consult

version: 5/08/2008

Inspection Summary Goal Date: 12-07-2009

**II. Protocol/Site Identification**

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
Paul Ratner, MD Sylvana Research Associates, PA 7711 Louis Pasteur Drive, Ste. 406 San Antonio, TX 78229 Tel 219-614-6673 Fax 219-614-7892	DPM-A-305	40	Assessment of bronchial hyper-responsiveness
Kenneth Rundell, PhD Keith J. O'Neil Center for Healthy Families, Marywood University 2300 Adams Ave. Scranton, PA 18509 Tel 570-340-6059 Fax 570-340-6067	DPM-A-305	36	Same

**III. Site Selection/Rationale**

DSI audits are being requested for two of the high enrolling sites for this unique NDA for an in vivo diagnostic test (inhaled mannitol) to assess for bronchial hyperreactivity in patients suspected of having asthma. We have not identified any specific safety concern with any of the sites.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**IV. Tables of Specific Data to be Verified (if applicable)**

NA

Should you require any additional information, please contact Miranda Raggio RPM at 301-796-2109 or Anya Harry MD PhD at 301-796-3954

Concurrence: NA

\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

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Miranda Raggio  
7/23/2009 01:54:52 PM

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-368 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Aridol Established/Proper Name: mannitol bronchial challenge test Dosage Form: dry powder capsules Strengths: 0,5,10,20,40		
Applicant: Pharmaxis, Ltd. Agent for Applicant (if applicable):		
Date of Application: 2-26-09 Date of Receipt: 2-27-09 Date clock started after UN:		
PDUFA Goal Date: 12-27-09		Action Goal Date (if different): 12-10-09
Filing Date: 5-12-09 Date of Filing Meeting: 4-13-09		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3S		
Proposed Indication(s): the assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients > 6 years of age with symptoms of or suggestive of asthma.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b>Refer to Appendix A for further information.</b>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input checked="" type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 70,277	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  <b>If yes, explain:</b>  <b>If yes, has OC/DMPQ been notified of the submission?</b>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
User Fee Status  <b>Comments:</b> Waiver letter on file	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i><b>Note:</b> 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes</b>, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  # years requested: 3  <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>

**Note:** If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? **Check the Electronic Orange Book at:**  
<http://www.fda.gov/cder/ob/default.htm>

YES  
 NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

**Format and Content**

**Do not check mixed submission if the only electronic component is the content of labeling (COL).**

**Comments:**

All paper (except for COL)  
 All electronic  
 Mixed (paper/electronic)

CTD  
 Non-CTD  
 Mixed (CTD/non-CTD)

**If mixed (paper/electronic) submission**, which parts of the application are submitted in electronic format?

**If electronic submission:**  
paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

YES  
 NO

**Forms include:** 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications include:** debarment certification, patent certification(s), field copy certification, and pediatric certification.

**Comments:**

**If electronic submission**, does it follow the eCTD guidance? (<http://www.fda.gov/cder/guidance/7087rev.pdf>)

YES  
 NO

**If not**, explain (e.g., waiver granted):

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b> no registration number</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<b><u>PREA</u></b>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>Comments:</b></p>	

<p><b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<b>Prescription Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> <b>Not applicable</b>  <input checked="" type="checkbox"/> Package Insert (PI)  <input type="checkbox"/> Patient Package Insert (PPI)  <input type="checkbox"/> Instructions for Use  <input type="checkbox"/> MedGuide  <input checked="" type="checkbox"/> Carton labels  <input type="checkbox"/> Immediate container labels  <input type="checkbox"/> Diluent  <input type="checkbox"/> Other (specify)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p> <p><b>If no</b>, was a waiver or deferral requested before the application was received or in the submission?  <b>If before</b>, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>REMS consulted to OSE/DRISK?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b> Trade Name review submitted to OSE 10/08</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s):3-12-09; 3-13-09 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** April 13, 2009

**NDA/BLA #:** 22-368

**PROPRIETARY/ESTABLISHED NAMES:** Aridol

**APPLICANT:** Pharmaxis, Ltd.

**BACKGROUND:** The applicant is requesting approval of inhaled mannitol for the diagnosis of bronchial hyper-responsiveness. This is the first NDA submission by Pharmaxis.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Miranda Raggio	yes
	CPMS/TL:	Sandy Barnes	no
Cross-Discipline Team Leader (CDTL)	Tony Durmowicz		yes
Clinical	Reviewer:	Anya Harry	yes
	TL:	Tony Durmowicz	
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:	Sean Bradley	no
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ying Fan	yes
	TL:	Sally Choe	yes
Biostatistics	Reviewer:	Ruthie Davi	no
	TL:	Qian Li	yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	yes
	TL:	Molly Shea	yes
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Deepika Arora	yes
	TL:	Prasad Peri	yes
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b> cCTD format</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul> <p><b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<b>FACILITY (BLAs only)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority: Miranda J. Raggio</b>  <b>GRMP Timeline Milestones:</b> Mid-Cycle Meeting: 8-3-09; Labeling Meeting 9-28-09; Wrap Up Meeting 10-27-09; Primary Reviews due 11-3-09; Secondary Reviews due 10-27-09; PeRC 10-7-09  <b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other Signed off by Sandy Barnes on 5-11-09

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

-----  
Miranda Raggio  
5/12/2009 02:53:37 PM  
CSO

**REGULATORY PROJECT MANAGER LABELING REVIEW  
(PHYSICIAN LABELING RULE)**

**Division of Pulmonary and Allergy Products**

**Application Number:** NDA 22-368

**Name of Drug:** Aridol (mannitol bronchial challenge test)

**Material Reviewed:**

**Submission Date:** 2-27-09

**Receipt Date(s):** 2-27-09

**Submission Date of Structure Product Labeling (SPL):** 2-27-09

**Type of Labeling Reviewed:** Highlighted Word

**Background and Summary**

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

**Review**

The following issues/deficiencies have been identified in your proposed labeling.

**Highlights**

No deficiencies noted.

**Full Prescribing Information**

No deficiencies noted.

**Recommendations**

No action is required at this time. This original version of labeling will be used for further labeling discussions.

---

Miranda Raggio  
Regulatory Project Manager  
Finalized 4-10-09

Supervisory Comment/Concurrence:

---

Sandy Barnes  
Chief, Project Management Staff  
Intialed 4-9-09

Drafted: Miranda Raggio/March 17, 2009

Revised/Initialed:Sandy Barnes/4-9-09

Finalized:Miranda Raggio/ 4-10-09

**CSO LABELING REVIEW OF PLR FORMAT**

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

-----  
Miranda Raggio  
4/10/2009 01:06:49 PM  
CSO

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

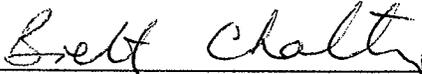
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Brett Charlton, PhD, MD	TITLE Medical Director
FIRM/ORGANIZATION Pharmaxis Ltd.	
SIGNATURE 	DATE 12 JAN 2009

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

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