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*APPLICATION NUMBER:*

**205636Orig1s000**

**PHARMACOLOGY REVIEW(S)**

## Secondary Pharmacology and Toxicology Review for NDA 205-636

TO: NDA 205-636 (Teva Branded Pharmaceutical Products, Inc.)

FROM: Marcie Wood, Ph.D.  
Supervisory Pharmacologist  
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: February 4, 2015

Overview: I concur with the recommendation of Dr. Nikunj Patel (detailed in a nonclinical review dated January 27, 2015) that the pharmacology and toxicology of ProAir RespiClick has been adequately studied and the drug product should be approved from a nonclinical perspective.

ProAir RespiClick, an albuterol sulfate (beta<sub>2</sub>-adrenergic agonist) dry powder inhaler, is indicated for the treatment or prevention of bronchospasm and for the prevention of exercise-induced bronchospasm in patients 12 years of age and older. For the treatment or prevention of bronchospasm, the proposed dosage is 2 inhalations repeated every 4 to 6 hours. For the prevention of exercise-induced bronchospasm, the proposed dosage is 2 inhalations 15 to 30 minutes before exercise. ProAir RespiClick meters 117 mcg and delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece per actuation. The proposed maximum recommended daily clinical dose of albuterol sulfate is 1080 mcg/day.

The nonclinical safety program of ProAir RespiClick is based upon complete albuterol pharmacology and toxicology studies that were previously submitted and reviewed under existing NDAs for ProAir HFA (NDA 21-457), Proventil HFA (NDA 20-503), and Proventil (NDA 17-559). No new, significant nonclinical data was included in the current submission, so a detailed pharmacology and toxicology review of albuterol sulfate was not needed for this NDA.

Labeling: The nonclinical sections of the labeling provided by the applicant were based on the approved ProAir HFA label. Changes to Section 8.1 (Pregnancy), Section 10 (Overdosage), and Section 13.2 (Animal Toxicology and/or Pharmacology) were proposed in Dr. Patel's review dated January 27, 2015, according to current nonclinical labeling practice. See Dr. Patel's review for details of recommended labeling changes. I agree with Dr. Patel's recommendations for labeling.

There are no outstanding Pharmacology and Toxicology issues for this product.

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/s/  
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MARCIE L WOOD  
02/04/2015

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

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 205-636  
Supporting document/s: SDN 1  
Applicant's letter date: May 5, 2014  
CDER stamp date: May 5, 2014  
Product: ProAir RespiClick (Albuterol Sulfate Inhalation Powder)  
Indication: Treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm  
Applicant: Teva Branded Pharmaceutical Products, Inc.  
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products  
Reviewer: Nikunj S. Patel, Ph.D.  
Supervisor/Team Leader: Marcie L. Wood, Ph.D.  
Division Director: Badrul Chowdhury, MD, Ph.D.  
Project Manager: Leila P. Hann

*Template Version: September 1, 2010*

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-636 are owned by Teva Pharmaceuticals or are data for which Teva Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 205-636 that Teva Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205-636.

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# 1 Executive Summary

## 1.1 Introduction

This review evaluates the nonclinical information to support safety of albuterol sulfate dry powder for inhalation. Albuterol is an agonist of beta-2 adrenergic receptors, which leads to the relaxation of smooth muscle in airways. Teva submitted a 505(b)(2) New Drug Application (NDA) on May 5, 2014, for albuterol multi-dose dry powder inhaler (albuterol MDPI, 108 µg of albuterol sulfate delivered per actuation). Teva proposes that the current drug product has the following 2 advantages over ProAir HFA: elimination of the need to coordinate actuation with inspiration, and the avoidance of ingestion of ethanol and HFA134a propellant. Albuterol MDPI (ProAir RespiClick) is being developed for the following 2 proposed indications:

1. The treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease.
2. The prevention of exercise-induced bronchospasm in patients 12 years of age and older.

## 1.2 Brief Discussion of Nonclinical Findings

No nonclinical pharmacology or toxicology studies were conducted with the proposed product. The sponsor provided a summary of publicly available literature on the nonclinical assessment for safety of albuterol and is referencing nonclinical information from previously approved albuterol products (see section 2.2 below for a list of referenced NDAs).

Nonclinical studies in rat and dog conducted in support of approved albuterol sulfate products have shown that the cardiovascular system is a major target organ. Clinically relevant cardiovascular toxicities observed in nonclinical studies include hypotension, tachycardia, changes in ECG wave parameters, and myocardial necrosis.

## 1.3 Recommendations

### 1.3.1 Approvability

From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

### 1.3.2 Additional Non Clinical Recommendations

### 1.3.3 Labeling

The labeling submitted by Teva mirrors the approved labeling for ProAir HFA (NDA 21-457), except for the absence of information on HFA-134a and dose ratios for children. The following nonclinical sections were reviewed and compared to the March 7, 2012, approved labeling for ProAir HFA. Since the proposed doses of albuterol sulfate in the proposed product are the same as those for ProAir HFA, the dose ratios for adults are unchanged. Proposed changes to labeling include the following: 1) Non-teratogenic reproductive toxicology information was moved from Section 13.2 (Animal Toxicology

and/or Pharmacology) to Section 8.1 (Pregnancy);

(b) (4)

Section 13.2 (Animal Toxicology and/or Pharmacology).

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled studies of ProAir RespiClick or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. ProAir RespiClick should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a mg/m<sup>2</sup> basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD.

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD.

Non-Teratogenic Effects: A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

### 10 OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of ProAir RespiClick.

Treatment consists of discontinuation of ProAir RespiClick together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of ProAir RespiClick.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Albuterol sulfate is a beta<sub>2</sub>-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta<sub>2</sub>-adrenergic receptors on airway smooth muscle. Activation of beta<sub>2</sub>-adrenergic receptors leads to the activation of adenylyl cyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that beta<sub>2</sub>-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta<sub>2</sub>-adrenergic receptors. The precise function of these receptors has not been established [see *Warnings and Precautions* (5.4)].

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [see *Warnings and Precautions* (5.4)].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 210 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 310 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

### 13.2 Animal Toxicology and/or Pharmacology

**Preclinical:** Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when  $\beta$ -agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 51022-70-9

Generic Name: Albuterol sulfate

Chemical Name:

Bis[(1RS)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3(hydroxymethyl)phenyl]ethanol] sulphate

or

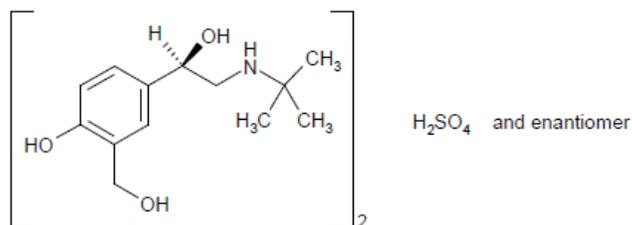
1,3-benzenedimethanol, alpha1-[[1,1-dimethylethyl)amino]methyl]-4-hydroxy-,sulfate (2:1) salt

or

alpha1-[(tert-Butylamino)methyl]-4-hydroxy-m-xylene-alpha, alpha1-diol sulfate (2:1) salt

Molecular Formula/Molecular Weight: (C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub>.H<sub>2</sub>SO<sub>4</sub> / 576.7 g/mol

Structure or Biochemical Description:



Pharmacologic Class: beta-2 adrenergic agonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

**Table 1 Summary of relevant NDAs**

NDA numbers	Product	US Approval Date
021457	ProAir HFA	10/29/2004
020503	Proventil HFA	8/15/1996
017559, 019243	Proventil CFC	5/1/1981, 1/14/1987
017853, 019383	Proventil tablets	5/7/1982, 7/13/1987

## 2.3 Drug Formulation

Each albuterol MDPI drug product container contains albuterol sulfate and lactose monohydrate in the following quantities (table excerpted from sponsor's submission):

**Table 2 Summary of drug product container contents**

Ingredients	Quantity	Function	Reference to standards
Albuterol sulfate	(b) (4)	Active substance	USP
Lactose monohydrate	(b) (4)	(b) (4)	USP NF
<i>Target fill weight per device</i>	0.65 g		
<i>Fraction of drug substance (%w/w)</i>	(b) (4)		

Each delivered dose (actuation) contains 108 µg of albuterol sulfate (90 µg albuterol base) and (b) (4) of lactose monohydrate.

## 2.4 Comments on Novel Excipients

There are no novel excipients in the drug product.

## **2.5 Comments on Impurities/Degradants of Concern**

All impurities in the proposed drug product are within acceptable limits. Impurity specification and qualification issues have been discussed with the chemistry review team.

## **2.6 Proposed Clinical Population and Dosing Regimen**

The proposed albuterol MDPI product is indicated for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 12 years of age and older. The proposed indications are the same as those for ProAir HFA.

## **2.7 Regulatory Background**

On December 10, 2009, Teva submitted IND 104532 for development of albuterol MDPI for the treatment or prevention of bronchospasm with reversible obstructive airway disease and exercise-induced bronchospasm. On May 15, 2014, Teva submitted a 505(b)(2) NDA for albuterol MDPI with the proposed indications for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise induced bronchospasm.

## **3 Studies Submitted**

None

## **4 Pharmacology**

No studies were submitted or reviewed.

## **5 Pharmacokinetics/ADME/Toxicokinetics**

No studies were submitted or reviewed.

## **6 General Toxicology**

No studies were submitted or reviewed.

## **7 Genetic Toxicology**

No studies were submitted or reviewed.

## **8 Carcinogenicity**

No studies were submitted or reviewed.

## **9 Reproductive and Developmental Toxicology**

No studies were submitted or reviewed.

## **10 Special Toxicology Studies**

No studies were submitted or reviewed.

## 11 Integrated Summary and Safety Evaluation

The proposed product in the current 505(b)(2) NDA is a MDPI containing albuterol sulfate and lactose monohydrate. Albuterol is a recognized agonist of beta-2 adrenergic receptors that is widely used in the United States. The interaction of albuterol with beta-2 adrenergic receptors leads to an increase in intracellular cAMP and consequently bronchodilation of smooth muscle tissues. No nonclinical pharmacology and toxicology studies were conducted with the proposed drug product. The sponsor is relying on demonstration of safety and efficacy from NDAs of previously approved albuterol products. The proposed product is the same as ProAir HFA (Teva) except that the HFA134a propellant and ethanol excipients have been replaced with lactose monohydrate.

Albuterol is approved under a number of NDAs (listed in section 2.2 above) which the sponsor has referenced for nonclinical support. The cardiovascular system is the major target organ of albuterol, with findings of hypotension, tachycardia, ECG changes and myocardial necrosis having been observed in nonclinical studies (minipig, rodent and dog). The sponsor is relying on the ProAir HFA approved reference product for labeling.

From the approved product label for ProAir HFA inhalation aerosol (latest version of label approved on 3/7/2012), albuterol is a Pregnancy Category C drug. There are no adequate and well-controlled studies of PROAIR HFA Inhalation Aerosol or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. PROAIR HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a  $\text{mg}/\text{m}^2$  basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control). In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD. In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD.

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 740 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 210 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 100 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 310 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when  $\beta$ -agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

Nonclinical Recommendation: There are no nonclinical safety issues that have been identified with the proposed albuterol MDPI drug product. The proposed drug product is approvable from the nonclinical perspective.

Labeling: The labeling submitted by Teva mirrors the approved labeling for ProAir HFA (NDA 21-457), except for the absence of information on HFA-134a and dose ratios for children. Since the proposed doses of albuterol sulfate in the proposed product are the same as those for ProAir HFA, the dose ratios for adults are unchanged. Proposed changes to labeling include the following: 1) Non-teratogenic reproductive toxicology information was moved from Section 13.2 (Animal Toxicology and/or Pharmacology) to Section 8.1 (Pregnancy); (b) (4)

 <sup>(b) (4)</sup> Section 13.2 (Animal Toxicology and/or Pharmacology). Changes bring labeling into compliance with current Agency practice for nonclinical labeling.

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/s/  
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NIKUNJ S PATEL  
01/27/2015

MARCIE L WOOD  
01/27/2015

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 205636**

**Applicant: Teva Branded  
Pharmaceutical Products, Inc.**

**Stamp Date: 5/5/2014**

**Drug Name: Albuterol sulfate NDA/BLA Type: Standard  
inhalation powder**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable. A pharmacology/toxicology section was not included in this 505(b)(2) submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. Refer to comment under #1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. Refer to comment under #1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable as no toxicology studies were requested or submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. Refer to comment under #4.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable. Refer to comment under #4.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable. Refer to comment under #4.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable. Refer to comment under #4.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed labeling is in the PLR format. Changes in text will be handled in the labeling review.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

No comments.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No issues from the nonclinical perspective.

Nikunj S. Patel, Ph.D.

\_\_\_\_\_  
Reviewing Pharmacologist

\_\_\_\_\_  
Date

Marcie L. Wood, Ph.D.

\_\_\_\_\_  
Team Leader/Supervisor

\_\_\_\_\_  
Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
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/s/  
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NIKUNJ S PATEL  
06/18/2014

MARCIE L WOOD  
06/18/2014