

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205433Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

### CLINICAL PHARMACOLOGY REVIEW

<b>NDA: 205-433</b>	Submission Date(s): 10/02/2013
<b>Drug</b>	Tobramycin
<b>Trade Name</b>	KITABIS
<b>OCP Reviewers</b>	Ryan P. Owen, Ph.D.
<b>OCP Team Leader</b>	Kimberly L. Bergman, Pharm.D.
<b>OCP Division</b>	DCP4
<b>OND division</b>	DAIP
<b>Sponsor</b>	PulmoFlow, Inc.
<b>Relevant IND(s)</b>	None
<b>Submission Type; Code</b>	505(b)(2)
<b>Formulation; Strength(s)</b>	5 mL single-dose ampule (carton of 56)
<b>Indication</b>	Management of cystic fibrosis patients with <i>P. aeruginosa</i>
<b>Dosage and Administration</b>	The recommended dosage for both adults and pediatric patients 6 years of age and older is 1 single-use ampule (containing 300 mg tobramycin) administered BID for 28 days.

#### Background

PulmoFlow, Inc. submitted a 505(b)(2) New Drug Application (NDA) dated 10/02/2013 for Tobramycin for Inhalation, USP, which is currently approved for the management of Cystic Fibrosis patients with *P. aeruginosa* in patients 6 years of age and older. The proposed inhalation drug product is qualitatively and quantitatively equivalent to the reference listed drug (RLD), TOBI® (tobramycin) for Inhalation (NDA 50-753; approved in 1997, manufactured by Novartis Pharmaceuticals). In addition, the proposed drug will be co-packaged with one PARI LC® Plus Reusable Nebulizer in the Convenience Kit Carton (b) (4). The formulation of the proposed product is provided below in Table 1.

**Table 1: Composition of the Drug Product (in mg/mL and mg/vial)**

Components of the drug product	mg/ mL	mg/ vial	Role in formulation	Quality reference
Tobramycin	60.0	300	Active substance	USP
Sodium Chloride	2.25	11.25	(b) (4)	USP
(b) (4) Sodium Hydroxide	*	*	pH Adjuster (qs)	NF
(b) (4) Sulfuric Acid	*	*	pH Adjuster (qs)	NF
Water for Injection	(b) (4)		(b) (4)	USP
Nitrogen**	**	**	(b) (4)	NF

\* QS as needed to adjust pH

\*\*used as (b) (4)

The Sponsor is seeking approval of a NDA for tobramycin under 505(b)(2) pathway. The (b) (4) proposed product and the RLD is that the proposed product is co-packaged with the PARI LC<sup>®</sup> Plus Reusable Nebulizer whereas the RLD is not. The Sponsor intends to rely upon the Agency's findings for safety and efficacy and information provided in the approved labeling for TOBI (tobramycin for inhalation). However, the TOBI label is still in the old format, so the Sponsor has submitted a version of their label in the PLR format using the information from the TOBI label. The clinical pharmacology review will consist of proposed labeling edits to the PLR version of the Sponsor's proposed label.

No new clinical pharmacology information was submitted in this application, and the applicant has submitted a request for waiver of the regulatory requirement for bioavailability as outlined in 21 CFR 320.21. The Sponsor has conducted an in vitro bioequivalence study which will serve as the basis for comparison. Please refer to the Office of New Drug Quality Assessment (ONDQA) Biopharmaceutics review for further evaluation of the request for waiver of bioavailability requirements.

### Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application, and no new clinical pharmacology information was submitted. Therefore, this application is acceptable from a clinical pharmacology standpoint.

**Labeling Edits**

The Sponsor's proposed label is pasted in below. Recommended changes from the Reviewer are shown in track changes.

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

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/s/  
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RYAN P OWEN  
08/15/2014

KIMBERLY L BERGMAN  
08/15/2014

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 205-433	<b>Reviewer:</b> Sandra Suarez Sharp, Ph.D	
<b>Division:</b>	DAI		
<b>Sponsor:</b>	PulmoFlow Inc.	<b>Team Leader:</b> Angelica Dorantes, Ph.D	
<b>Trade Name:</b>	KITABIS PAK	<b>Supervisor (acting):</b> Richard Lostritto, Ph.D	
<b>Generic Name:</b>	Tobramycin Inhalation Solution, USP and PARI LC® Plus Reusable Nebulizer	<b>Date Assigned:</b>	Oct 23, 2013
<b>Indication:</b>	The management of cystic fibrosis patients with <i>P. aeruginosa</i> .	<b>Date of Review:</b>	Jul 14, 2014
<b>Formulation/strength</b>	Inhalation solution (300 mg /vial (300 mg/ 5 mL)		
<b>Route of Administration</b>	Nasal		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission dates		Date of informal/Formal Consult	PRIMARY REVIEW DUE DATE
Oct 2, 2013 March 25, 2014		Oct 23, 2013	July 18, 2014
<b>Type of Submission:</b>	505(b)(2)		
<b>Type of Consult:</b>	<ul style="list-style-type: none"> <li>In vitro BE characterization supporting the waiver of in vivo BE studies</li> </ul>		
SUMMARY OF BIOPHARMACEUTICS FINDINGS			
<p><b>Background:</b>  PulmoFlow, Inc. is seeking approval of Kitabis PAK (tobramycin inhalation solution, USP, 300 mg/5 mL and PARI LC® Plus Reusable Nebulizer) for the management of cystic fibrosis patients (aged 6 years and older) with <i>P. aeruginosa</i>. This NDA submission for Kitabis PAK follows the 505 (b)(2) path and makes reference to NDA 50753 for TOBI (Novartis) as the Listed Drug Product (LDP).</p> <p><b>The Drug Product</b>  Kitabis Pak is a co-packaging of tobramycin inhalation solution with a reusable PARI LC® PLUS nebulizer. The proposed inhalation drug product is qualitatively and quantitatively equivalent to TOBI. According to the Applicant, it has the same physicochemical characteristics as the LDP (TOBI). The pH ( (b)(4) ), content of sodium chloride, and osmolarity (135-200 mOsmol) were established in accordance with the USP monograph "Tobramycin Inhalation Solution USP". In addition, the proposed drug product will be co-packaged with one (1) PARI LC® Plus Reusable Nebulizer in the Convenience Kit Carton.</p>			

### ***The Submission***

This application is based primarily on quality and non-clinical data. This 505(b)(2) NDA is supported by in vitro comparisons between Kitabis™ and TOBI in addition to characterization of Kitabis™, including stability for three lots (see CMC section).

An in-vitro characterization of Kitabis™ was performed for the purpose of confirming bioequivalence to the reference product TOBI. Three lots from each product were assessed for Unit Dose Content, Delivered Dose by breathing simulation, and Particle Size Distribution using the new generation impactor (NGI) at a constant flow of 15 L/min. The approved nebulizer (PARI LC PLUS® Reusable Nebulizer) and compressor (DeVilbiss® PulmoAide® air compressor) were used for all data collection. Results for 10 units per lot were collected for each of the three tests, and the key end-points were compared between the two drug products using population bioequivalence.

### ***The Review***

The Biopharmaceutics review is focused on the acceptability of the biowaiver request supported by the following data:

1. Comparative in vitro characterization (In vitro Population BE analysis) for the following attributes:
  - Unit Dose Content
  - Delivered Dose
  - Particle Size Distribution
2. Qualitative and quantitative formulation comparison between the proposed drug product and the Listed Drug Product (NDA 050753, TOBI®, Novartis)).
3. Comparative physicochemical properties (e.g. pH, osmolarity).

### ***Reviewer's Assessment:***

#### **1. In Vitro Characterization Study Supporting the Waiver Request**

For all end-points studied (weight of contents, concentration of tobramycin, content of tobramycin, delivered dose, nebulization time, delivered dose, impactor size mass, fine particle dose, mass median aerodynamic diameter, and geometric standard deviation) the proposed product met the population BE requirements when compared to the listed drug product, TOBI.

#### **2. Qualitative and Quantitative Formulation Comparison Between the Proposed Drug Product and the Listed Drug**

Data were provided to demonstrate that the conditions of use, route of administration, dosage form, strength and the components and composition of the proposed drug product (b) (4) as those of the listed drug, TOBI.

#### **3. Comparative Physicochemical Properties**

The proposed pH 6 (b) (4) is in line with the Listed Drug TOBI® and the pH specification of the USP "Tobramycin Inhalation Solution" monograph. In addition, the same content of sodium chloride (0.225 g/100 mL) as that in TOBI exhibits an osmolality of approx. 0.160-0.185

Osmol/kg being within the range specified in the USP monograph “Tobramycin Inhalation Solution” of 0.135 to 0.200 Osmol per kg.

**RECOMMENDATION:**

ONDQA/Biopharmaceutics has reviewed NDA 205-433 and its amendments submitted on Oct 02, 2013 and March 25, 2014. Data were provided to demonstrate that the conditions of use, route of administration, dosage form, strength, the components and composition, physicochemical properties and in vitro characterization of the proposed drug product [REDACTED] <sup>(b) (4)</sup> of the listed drug product, TOBI.

From the Biopharmaceutics perspective, KITABIS PAK (co-packaging of tobramycin inhalation solution, USP and PARI LC® Plus Reusable Nebulizer) under NDA 205433 is recommended for **APPROVAL**.

**Sandra Suarez Sharp, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Angelica Dorantes, Ph. D.**  
Biopharmaceutics Team Leader  
Office of New Drugs Quality Assessment

cc : Rlostritto

# BIOPHARMACEUTICS ASSESSMENT

## BACKGROUND

### Introduction

Pulmoflow, Inc. is seeking approval of Kitabis™ (Tobramycin Inhalation Solution, USP, 300 mg/5 mL and PARI LC® Plus Reusable Nebulizer) for the management of cystic fibrosis patients (aged 6 years and older) with *P. aeruginosa*. This NDA submission for Kitabis™ follows the 505 (b)(2) path and makes reference to NDA 50753 for TOBI (Novartis). This 505(b)(2) NDA is supported by in vitro comparisons between Kitabis™ and TOBI, in addition to characterization of Kitabis™, including stability for three lots (see CMC section).

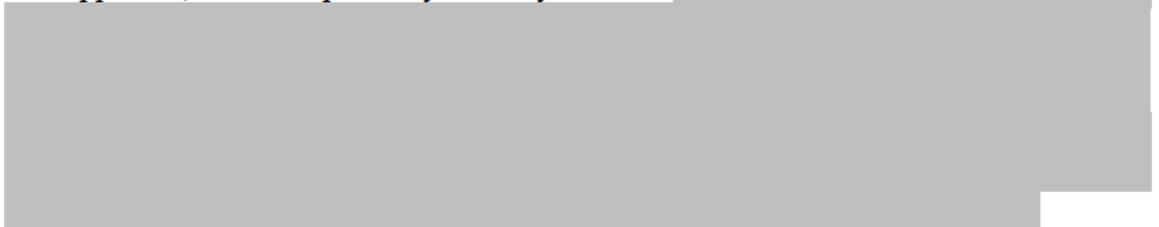
The Biopharmaceutics review is focused on the acceptability of the biowaiver request supported by the following data:

1. Qualitative and quantitative formulation comparison between the proposed drug product and the Listed Drug Product (NDA 050753 for TOBI® manufactured by Novartis).
2. Comparative physicochemical properties (e.g. pH, osmolarity).
3. Comparative in vitro characterization (In vitro Population BE analysis) for the following attributes:
  1. Unit Dose Content
  2. Delivered Dose
  3. Particle Size Distribution

## CHEMISTRY

### Drug Substance

Tobramycin is soluble in (b)(4) water. A target concentration of (b)(4) Tobramycin for KITABIS™ is far from the saturation concentration thus, according to the Applicant, does not pose any stability concern (b)(4)



### Drug Product

The proposed inhalation drug product's components and composition are summarized in Table 1. According to the Applicant, it has the same physicochemical characteristics as the RLD product (TOBI). The pH ((b)(4)), content of sodium chloride, and osmolarity (135-200 mOsmol) were established in accordance with the USP monograph "Tobramycin Inhalation Solution USP". In addition, the proposed drug product will be

co-packaged with one (1) PARI LC® Plus Reusable Nebulizer. The product is contained in a 5mL Low Density Polyethylene (LDPE) vial with twist off cap. Four (4) vials are heat sealed into a foil pouch to protect the LDPE vials.

**Table 1.** Composition of the Drug Product (in mg/ mL and mg/ vial)

Components of the drug product	mg/ mL	mg/ vial	Role in formulation	Quality reference
Tobramycin	60.0	300	Active substance	USP
Sodium Chloride	2.25	11.25	(b) (4)	USP
(b) (4) Sodium Hydroxide	*	*	pH Adjuster (qs)	NF
(b) (4) Sulfuric Acid	*	*	pH Adjuster (qs)	NF
Water for Injection	(b) (4)		(b) (4)	USP
Nitrogen**	**	**		NF

\* QS as needed to adjust pH

\*\*used as (b) (4)

## DATA SUPPORTING THE BIOWAIVER REQUEST

In accordance with 21 CFR 320.22 (b)(3), the Applicant requested a waiver of evidence of in vivo bioequivalence studies. In support of the biowaiver, the following information was submitted:

1. Qualitative and quantitative formulation comparison between the proposed drug product and the Reference Listed Drug (NDA 050753 TOBI® (Novartis)).
2. Comparative physicochemical properties (e.g. pH, osmolarity).
3. Comparative in vitro characterization (In vitro Population BE analysis) for the following attributes:
  4. Unit Dose Content
  5. Delivered Dose
  6. Particle Size Distribution

### 1. Comparison between the proposed drug product and the Listed Drug Product

The following information/data were provided to demonstrate that the conditions of use, active ingredient, route of administration, dosage form and strength of the proposed drug are related to those of the listed drug.

	Listed Drug Product	Proposed Drug Product
	TOBI <sup>®</sup> Solution	Tobramycin Inhalation Solution
<i>Conditions of Use</i>	TOBI is indicated for the management of cystic fibrosis patients with <i>P. aeruginosa</i> .	Kitabis is indicated for the management of cystic fibrosis patients with <i>P. aeruginosa</i> .
<i>Active Ingredient</i>	Tobramycin	Tobramycin
Inactive Ingredients	Each 5mL contains 300 mg tobramycin in 11.25 mg Sodium Chloride, Water for Injection, and Sulfuric Acid and/or Sodium Hydroxide for pH adjustment.	Each 5mL contains 300 mg tobramycin in 11.25 mg Sodium Chloride, Water for Injection, and Sulfuric Acid and/or Sodium Hydroxide for pH adjustment.
<i>Route of Administration</i>	Inhalation	Inhalation
<i>Dosage Form</i>	Solution	Solution
Strength(s)	300 mg/5 mL	300 mg/5 mL
Labeling Comparison <sup>a</sup>	See Module 1, Subsection 1.14	See Module 1, Subsection 1.14

<sup>a</sup> The labeling of the proposed drug and reference listed drug are the same, with the exception of those differences annotated and explained in the side-by-side labeling comparison contained in Module 1, Subsection 1.14.

Components of the drug product	TOBI <sup>®</sup> RLD	PulmoFlow Proposed Product
Tobramycin	300mg/5mL	300mg/5mL
Sodium Chloride	11.25 mg	11.25 mg
Sulfuric Acid*	---	---
Sodium Hydroxide*	---	---
Water for Injection	(b) (4)	(b) (4)
Nitrogen**	---	---

\*to adjust pH

\*\*used for sparging

## 2. Comparative physicochemical properties (e.g. , pH, osmolality)

Aqueous Tobramycin solution is strongly basic (pH 9-11 for a 1 in 10 solution) according to the USP monograph “Tobramycin”. In order to obtain physiological pH values in the solution for inhalation the pH value had to be adjusted to physiological levels. According to the Applicant, as the use of sulfuric acid is described in the USP monograph “Tobramycin Inhalation Solution”, sulfuric acid was chosen to adjust the pH to physiological acceptable values of pH 6 (b) (4) in line with the Listed Drug TOBI® and the pH specification of the USP “Tobramycin Inhalation Solution” monograph.

The concentration of the excipient sodium chloride used for (b) (4) was set at 0.225 g/100 mL. TOBI® having the same Tobramycin concentration of (b) (4) and the same content of sodium chloride (0.225 g/100 mL) exhibits an osmolality of approx. 0.160-0.185 Osmol/kg being within the range specified in the USP monograph “Tobramycin Inhalation Solution” of 0.135 to 0.200 Osmol per kg. The Applicant stated that in order to reach osmolality values in the same range, sodium chloride was selected as excipient that is commonly used in inhalation products and can be regarded as safe. The analogous amount of sodium chloride in KITABIS™ (0.225 g/100 mL) revealed an osmolality value of (b) (4) Osmol/kg.

## 3. Comparative in vitro characterization (In vitro Population BE analysis) for the following attributes:

- Unit Dose Content
- Delivered Dose
- Particle Size Distribution

Three lots of drug product for both KITABIS (TEST) and TOBI (REF) were studied (Table 2). For each lot and test item, a total of 10 units were assessed. The total sample size for both TEST and REF products was thus be 30 (refer to <\\cdsesub1\evsprod\NDA205433\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\5-3-1-3-1> for more details). The key end-points were compared between the two drug products using population bioequivalence with regulatory constants and acceptance criteria as recommended by FDA guidance for industry<sup>1</sup>.

The approved nebulizer (PARI LC PLUS® Reusable Nebulizer) and compressor (DeVilbiss® PulmoAide® air compressor) were used for all data collection.

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<sup>1</sup> Draft Guidance on Budesonide, FDA September 2012. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

**Table 2.** Details of studied drug product lots

<i>Product</i>	<i>KITABIS</i>			<i>TOBI</i>		
Lot No.	1	2	3	1	2	3
Lot ID.	03312 A	03312 B	03312 C	F5038	F5040	F5042
Manufacturing Date	11/13/12	11/14/12	11/15/12	N/K	N/K	N/K
Expiry date	N/A	N/A	N/A	09/2015	10/2015	11/2015

**Reviewer’s Comments**

*Under the PBE method, for each comparative in vitro test described in the guidance for (b)(4), FDA recommends the calculation of a 95 percent confidence interval as a measure of equivalence between the test and reference products that includes the ratio of the geometric means of the two products and the difference in variability between test and reference products. The confidence interval is compared to an acceptance limit that is based on fixed statistical parameters (i.e., the regulatory constants, (b)(4) (b)(4) and takes into consideration the observed within-study variability of the test and reference products. Inherent in the PBE method is the principle that the acceptance limits for the confidence interval depend on the relative variability of the test and reference products observed in the study. In the case of low variability data for the reference product, the acceptance limits narrow, toward the (b)(4) percent criteria used in the geometric mean method, enabling only test products with comparable variability to meet the criteria. Conversely, in the case of high variability data for the reference product, the acceptance limits might be slightly wider. This permits approval of generic products that are comparably or less variable than the reference product (even if the ratio of the geometric means falls slightly outside of the (b)(4) criteria) and, guards against approval of generic products that are more variable than the reference product (even if the ratio of the geometric means falls within the (b)(4) percent criteria).*

*In summary, to test for population bioequivalence, 95% upper confidence bound of either the reference-scaled or constant-scaled linearized criterion<sup>1</sup> are computed. For linearized  $\theta_p$ , if this upper bound is negative, conclude population bioequivalence. If the upper bound is positive, do not conclude population bioequivalence.*

*Linearized tests are based on regulatory limit (b)(4) (b)(4)*

**Unit Dose Content (UDC)**

For each of the 6 lots, 10 vials were assessed. Weight of content (g), concentration of tobramycin (mg/mL) and tobramycin content (mg) were determined by each. Testing was performed in a balanced manner using two analysts, following the in-house test method PVA TOB 02.

UDC was compared between KITABIS and TOBI for the end-points:

- Weight of contents (WoC; g)
- Concentration of tobramycin (Assay; mg/mL)
- Content of tobramycin (Content; mg).

Table 3 summarizes the results of the PBE evaluation. The standard deviation of log-transformed data for the reference product is  $< 0.1 = \sigma_{T0}$  for all three end-point. The latter means that the constant-scaled procedure should be used to determine PBE.

**Table 3.** Summary of PBE analysis for Unit Dose Content, by end-point

End-point	Geometric Mean		Geometric Mean Ratio	Standard Deviation		sT/sR Ratio	95% Upper Confidence Bound	PBE Outcome	Scaling Method
	KITABIS	TOBI		KITABIS	TOBI				
WoC	5.33	5.30	100.6	0.0080	0.0101	0.79	-0.0210	Pass	Constant
Assay	59.09	61.11	96.7	0.0218	0.0194	1.12	-0.0191	Pass	Constant
Content	302.43	310.17	97.5	0.0240	0.0192	1.25	-0.0196	Pass	Constant

**Reviewer’s Comments**

*The 95% upper confidence bound is  $\leq 0$  for all three end-points indicating that KITABIS is bioequivalent to TOBI with respect to Unit Dose Content.*

**Delivered Dose**

The dose delivered from the nebulizer was collected on an inspiratory filter during a breath simulation experiment (using a standard adult breathing pattern of 500 mL tidal volume, I:E 1:1, 15 bmp), following in-house test method PVA BSE 01. Delivered dose collected on the inspiratory filter during breathing simulation is compared between KITABIS and TOBI for the end-points

- Delivered dose (DD; mg)
- Nebulization time (NebTime; min)

Table 4 summarizes the results of the PBE evaluation. The standard deviation of log-transformed data for the reference product is  $< 0.1 = \sigma_{T0}$  for the two end-point. The latter means that the constant-scaled procedure should be used to determine PBE.

**Table 4.** Summary of PBE analysis for Delivered Dose, by end-point

End-point	Geometric Mean		Geometric Mean Ratio	Standard Deviation		sT/sR Ratio	95% Upper Confidence Bound	PBE Outcome	Scaling Method
	KITABIS	TOBI		KITABIS	TOBI				
DD	93.02	96.09	96.8	0.1028	0.0854	1.20	-0.0085	Pass	Constant
NebTime	13.69	13.80	99.2	0.0687	0.0568	1.21	-0.0162	Pass	Constant

**Reviewer's Comments**

The 95% upper confidence bound is  $\leq 0$  for all three end-points indicating that KITABIS is bioequivalent to TOBI with respect to delivered dose.

**Particle size distribution**

For each of the 6 lots, 10 runs were performed following in-house test method PVA NGI 01 using the next generation impactor (NGI) operated at a flow rate of (b) (4) using standard environmental conditions.

The individual results collected for each stage and component of the impactor system is displayed for an initial comparison of KITABIS and TOBI in Figure 1.



**Figure 1.** Individual results (mg), by deposition site and product

Aerodynamic particle size distribution was compared between KITABIS and TOBI for the 6 end-points:

- Delivered dose [DD]
- Impactor sized mass [ISM]

- Fine particle dose  $\frac{(b)(4)}{(b)(4)}$  the mass of particles with aerodynamic size  $(b)(4)$
- Mass median aerodynamic diameter [MMAD; the diameter such that 50% of particles have aerodynamic size < this ( $\mu\text{m}$ )]
- Geometric standard deviation (GSD; no unit)
- Nebulization time [NebTime (min)].

Table 5 summarizes the results of the PBE evaluation. The standard deviation of log-transformed data for the reference product is  $< 0.1 = \sigma_{T0}$  for all the end-points except the Nebulization time. Therefore, the constant-scaled procedure was used to determine PBE for all endpoint except for the nebulization time where the reference scale approach was used.

**Table 5. Summary of PBE analysis for Particle Size Distribution, by end-point**

End-point	Geometric Mean		Geometric Mean	Standard Deviation		sT/sR Ratio	95% CI bound	PBE Outcome	Scaling Method
	KITABI	TOBI	Ratio	KITABI	TOBI				
DD	$(b)(4)$						Pass	Constant	
ISM							Pass	Constant	
$(b)(4)$							Pass	Constant	
MMAD							Pass	Constant	
GSD							Pass	Constant	
NebTime							Pass	Reference	

**Reviewer’s Comments**

The 95% upper confidence bound is  $(b)(4)$  for all three end-points indicating that KITABIS is bioequivalent to TOBI with respect to particle size distribution.

**Reviewer’s Conclusion**

Data were provided to demonstrate that the conditions of use, route of administration, dosage form, strength and the components and composition of the proposed drug product  $(b)(4)$  of the listed drug product, TOBI.

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SANDRA SUAREZ  
07/28/2014

ANGELICA DORANTES  
07/28/2014