CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Anesthesia and Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Infection Control and Dental Device
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

NDA 201-820 – Regulatory Device Consult

Date: October 11, 2012

To: Mr. Carmen DeBellas, Regulatory Project Manager (OND/OAP/DAIOP)

From: Mr. Sugato De, M.S., Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer

Applicant: Chiesi Pharmaceuticals Inc.

Product Name: Tobramycin 300 mg/4mL Solution (CHF 1538)

Indication: Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged six years and older.

A. Executive Summary

In NDA 201-820, Chiesi Pharmaceuticals has proposed a novel formulation of inhaled tobramycin (Tobramycin 300 mg/4 mL Inhalation Solution, hereafter referred to as CHF 1538). The formulation is composed of tobramycin, sulfuric acid, and sodium chloride in aqueous solution, using water for injection. The preservative-free sterile inhalation solution formulation has been developed for use in the treatment of pseudomonal pulmonary infections.

The oral inhalation of CHF 1538 via nebulizer requires the use of a nebulizer and an air compressor. Clinical studies for the proposed drug-device combination have used exclusively the Pari LC Plus Nebulizer with the either the Pari TurboBOY N Compressor or the Pari TurboBOY S Compressor. Due to differences in product availability between the United States and Europe, the proposed to-be-marketed (TBM) device configuration intended to deliver CHF 1538 is the Pari LC Plus Nebulizer along the Pari Vios compressor. Accordingly, in vitro cascade impaction studies comparing the clinical trial configurations of the device to the proposed market configuration are necessary in order to establish relative equivalence. This data is required to establish the relevance of the findings of the clinical trial.

In formal communications, the sponsor was asked to perform in vitro characterization studies intended to establish relative equivalence in terms of particle size, delivered dose and respirable dose between the clinical trial configurations and the proposed to-be-marketed configuration. The Agency indicated that these studies were expected to utilize a breathing pattern indicative of a representative patient with cystic fibrosis. Using this breathing pattern, the applicant proceeded to provide comparative cascade impaction data using an appropriate number of device samples and test runs to account for potential inter-and intra-sample variability.

RECOMMENDATION: At this stage of review, the sponsor has provided a range of descriptive information and comparative analyses to establish relative equivalence between the two clinical trial configurations and the to-be-marketed configuration of proposed drug-device combination. Collectively, these tests are sufficient to demonstrate that the to-be-marketed device configuration (Pari LC Plus Nebulizer and Pari Vios Compressor) reliably administers a delivered dose of (b) (4) mg with an median particle size of approximately (b) (4) µm. As shown, in Table 1 below, the overall differences in particle specifications between the measured configurations are minimal from a statistical perspective.

Table 1: Summary of Results from *in vitro* Studies with the To-Be-Marketed Configuration and the Clinical Trial Configurations (N=15)

In Vitro Parameter	To-Be-Marketed	Clinical Trial Units		Ratio of Test/Reference (CI)[1]		Figure Reference for Individual Values
	Vios	TB-N	TB-S	Vios/TB-N	Vios/TB-S	
MMAD NGI (µm)	[redacted] (b) (4)			1.05 (1.01-1.08)	0.99 (0.97-1.02)	Figure 8
GSD NGI				1.01 (0.98-1.04)	1.01 (0.99-1.03)	Figure 9
FPD, < 5 µm NGI (mg)				0.93 (0.91-0.96)	0.99 (0.97-1.01)	Figure 10
FPF NGI (%)				0.96 (0.94-0.99)	1.01 (0.98-1.03)	Figure 11
TEM NGI (mg)				0.97 (0.94-0.99)	0.98 (0.96-1.01)	Figure 12
DD (mg)				0.95 (0.91-0.98)	0.97 (0.94-1.01)	Figure 2

[1] Mean Ratio of Individual Test/Reference for compressor units used with the same LC Plus nebulizer unit: not the ratio of the means. CI=Confidence Interval.

The in vitro characterization of the aerosol output from the PARI LC Plus used with different compressors supports consistent total drug and lung-targeted delivery from the different device configurations. As shown above, the variable compressors do not have a significant impact on particle characterization.

In view of the above, it is expected that for the to-be-marketed PARI LC Plus nebulizer with the Vios compressor, a highly comparable amount of drug will be delivered to the lung and this will thus support a comparable clinical efficacy to that observed in clinical trials both in terms of inhibition of bacterial growth and improvements in lung function. In essence, from a device perspective, the labeling of the product with the Vios compressor would directly reflect and be entirely consistent with all the clinical data generated using the TurboBOY S and TurboBOY N compressors.

In conclusion, it is unlikely that the subtle differences in particle characterization and dose delivery observed during *in vitro* studies when CHF 1538 is delivered by the TurboBOY (used in clinical studies) compared to the proposed Vios compressor would impart any clinical impact in terms of decreased efficacy for patients with CF. Accordingly, assuming that CDER determines the clinical study information provided for review to be a sufficient basis for safety and effectiveness, CDRH recommends approval of the proposed drug-device combination.

CDRH strongly believes that relevant measured specifications (e.g. emitted dose, respirable dose, particle size) for the drug-device combination are necessary whenever recommended doses and/or device specifications are listed in labeling. This information is useful to prescribers and physicians to distinguish between a recommended dose specification and the actual measured dose specification. The importance of this information dependent on the observed difference between the recommended and measured values and also on the therapeutic index of the drug under consideration.

B. Device Description

Overview:

The oral inhalation delivery of CHF 1538 via nebulizer requires the use of an air compressor. Clinical studies have used exclusively the PARI TurboBOY and PARI TurboBOY N compressors and the PARI LC Plus nebulizer. Due to changes in the proposed market (EU versus US), an alternate compressor, PARI Vios, in conjunction with the PARI LC Plus nebulizer is proposed for the US commercial market.

The identification of all models, device accessories and the relevant 510(k) status of the FDA-cleared devices referenced in Chiesi's NDA are shown in Table 2 and Table3. The TurboBOY and TurboBOY N compressors used throughout the entire clinical development program, which was conducted in Europe, are not compatible with US standards for voltage and amperage. Therefore, clearance was never sought in the US for either the TurboBOY or the TurboBOY N and references to 510(k) clearances for these devices are not possible.

Table 2: 510(k) Status of Compressor

Compressors	510(k) Application Number	510(k) Status (Decision Date)
PARI Vios	K092918	Substantially Equivalent (04 February 2010)

Table 3: 510(k) Status of Nebulizer

Nebulizers	510(k) Application Number	510(k) Status (Decision Date)
PARI LC Plus	PARI Master Modification K935540[1]	Substantially Equivalent (17 March 1995)

[1] This submission included the LC Plus reusable nebulizer along with other devices.

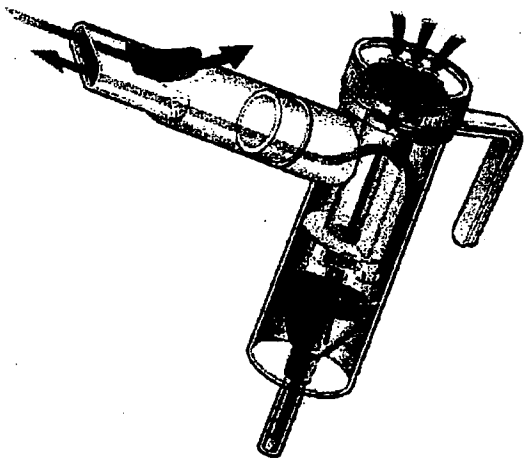


Figure 1: PARI LC Plus Nebulizer

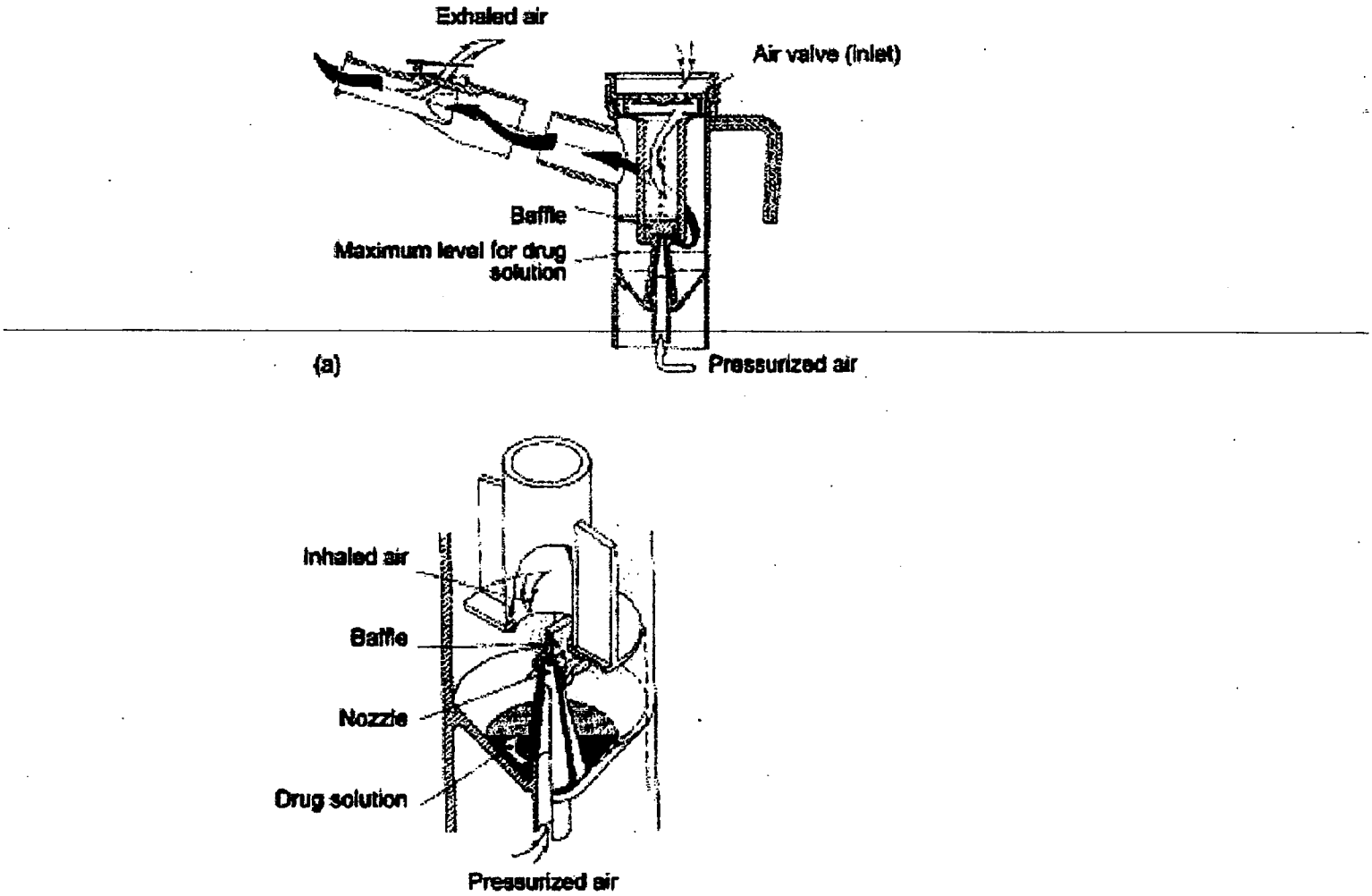


Figure 2: Breathing Gas Path Components of PARI LC Plus Nebulizer

The information provided for review illustrates the gas path of the nebulizer and demonstrates that no adulterations or modifications have been made to the 510(k) approved device design. The Instructions for Use for the device are not affected by the proposed configuration.

In response to a Type A meeting request made by FDA on 14 December 2011, Chiesi provided the technological differences between the proposed PARI Vios compressor, the PARI TurboBOY N and TurboBOY (the compressors used in the clinical study), and the TurboBOY S (which replaced the TurboBOY) in Table 4. The technological information of the DeVilbiss Pulmo-Aide® used for TOBI® Inhalation Solution, 300 mg/5 mL is also listed in Table 4 for comparison purposes.

Compressor Comparison:

While specific information pertaining to the differences between the TurboBOY Compressors and the Vios Compressor were not obtained from PARI, the sponsor provided the following descriptive comparison:

Table 4: Comparative Performance Specifications for Compressors

Compressor	Intended Use	Performance Pressure	Flow Rate	Materials	Filters	Operating Principles	Power Supply	Target Population
PARI Vios	Home, hospital or clinic use. Single flow rate, to be used with jet nebulizer, general purpose	(b) (4)					120 V 60 Hz 1.5 A 80 W	Adult and pediatric patients
PARI TurboBOY N	As Vios						230 V 50 Hz 0.7 A 80 W	Patients ages 4 and older
PARI TurboBOY S	As Vios						230-240 V 50 Hz 0.5 A 65 W	Patients ages 4 and older
PARI TurboBOY[1]	As Vios						230-240 V 50 Hz 0.5 A 65 W	Patients ages 4 and older
DeVilbiss Pulmo-Aide[2]	Home health care use. To be used with a jet (pneumatic nebulizer						115 V 60 Hz 1.3 A 90 W	Adult and pediatric patients

[1] TurboBOY no longer available from PARI and replaced by the TurboBOY S

[2] Information on the Pulmo-Aide compressor taken from http://www.phc-online.com/Pulmo-Aide Nebulizer p/devilbiss-5650.htm, accessed 15 December 2011. The procedure and apparatus used by DeVilbiss to measure operating pressure and flow rate is unknown by Chiesi. The flow and pressure will be dependent on any restriction that the testing method uses at the end of the tubing.

C. Device Performance

Comparative Particle Characterization Analysis (CHF 1538 – CT Configuration vs. TBM Configuration

To compare the TBM configuration with the clinical trial (CT) configurations for CHF 1538, the following device combinations were tested by NGI experiments:

- PARI LC Plus Nebulizer, TurboBoy S (TB-S) Compressor, CHF 1538 (CT Configuration 1);
- PARI LC Plus Nebulizer, TurboBoy N (TB-N) Compressor, CHF 1538 (CT Configuration 2); and
- PARI LC Plus Nebulizer, Vios Compressor, CHF 1538 (TBM Configuration 1).

Note that the (b) (4) is no longer being proposed as part of the to-be-marketed drug device combination.

At the December 16, 2011 Type A meeting, there was general agreement with Chiesi's proposed study to compare the aerodynamic particle size distribution (APSD) of the CT compressors with that of the TBM compressor. Therefore, Chiesi performed APSD experiments with the three configurations listed above according to protocol SP-096-002-012; the APSD was carried out using NGI.

The current version of the validated method for NGI collections, VTM 096-002-01, is provided in Appendix B; the procedure generally follows the methodology of USP <1601>. The drug solutions were (b) (4)

The delivered dose (DD) specification was established using breath simulation a representative breath pattern for a patient with cystic fibrosis:

- (b) (4)
-
-
-

This breathing pattern was selected based on observed patterns in cystic fibrosis patients. The DD collection time of (b) (4) was selected during test method development. (b) (4) is beyond the observed sputter point, which is about 9.5 minutes, and allows the collection of approximately one-third of the total dose.

In the DD method, (b) (4). The "delivered dose" (b) (4) (b) (4)

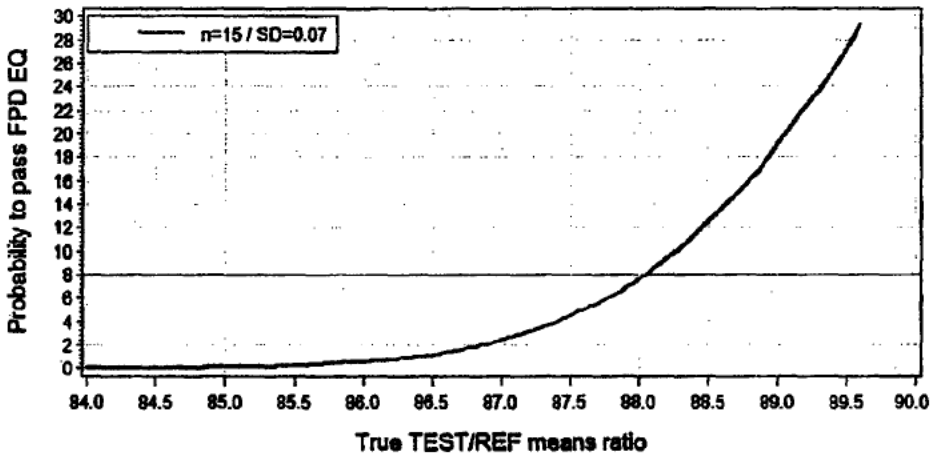
Materials Tested:

- CHF 1538, Tobramycin Inhalation Solution (300 mg/4 mL), Lot 05909E;
- PARI LC Plus nebulizers, Lot 1000007154809, PARI Respiratory Equipment, Inc.;
- PARI Vios compressors, Part Number 310F35-LCS, PARI Respiratory Equipment, Inc.;
- PARI TurboBoy N compressors, Part Number 085G1201, PARI GmbH; and
- PARI TurboBoy S compressors, Part Number 053G1210, PARI GmbH

Sample Size Rationale:

The goal of the study was to perform enough NGI experiments with each configuration to be able to detect less than a (b) (4) difference between any two compressors with a 90% confidence interval. This was achieved by performing 15 collections per configuration (Table 14).

The data in Figure 6 show the power of N=15 with the observed Test/Reference Fine Particle Dose (FPD) standard deviation of 0.07 with N=15 experiments; there is 92% power to detect a 12% difference between any two combinations.



[1]TEST=Vios compressor; REF=TurboBOY S or TurboBOY N compressor; FPD=Fine Particle Dose; EQ=Equivalence

Figure 3: Power Function Anlaysis for NGI Experiments to Determine Sample Size

Fifteen PARI LC Plus nebulizers and fifteen compressor units of each model were randomly selected. Each nebulizer unit was tested with all three types of compressors. The total number of NGI collections was 15 for each of the three compressor types (Vios, TurboBOY S and TurboBOY N). The collections were randomized according to the scheme in Table 5.

Table 5: Collection Schedule for APSD by NGI

Nebulizer Unit	Product-Compressor Combination[1]				
	Run 1	Run 2	Run 3	Run 4	Run 5
1	CHF: TB-N1	TOBI: TB-N1	CHF: V1	TOBI: PA1	CHF: TB-S1
2	TOBI: TB-N2	CHF: V2	TOBI: PA2	CHF: TB-S2	CHF: TB-N2
3	CHF: V3	TOBI: PA3	CHF: TB-S3	CHF: TB-N3	TOBI: TB-N3
4	TOBI: PA4	CHF: TB-S4	CHF: TB-N4	TOBI: TB-N4	CHF: V4
5	CHF: TB-S5	CHF: TB-N5	TOBI: TB-N5	CHF: V5	TOBI: PA5
6	CHF: TB-N6	TOBI: TB-N6	CHF: V6	TOBI: PA6	CHF: TB-S6
7	TOBI: TB-N7	CHF: V7	TOBI: PA7	CHF: TB-S7	CHF: TB-N7
8	CHF: V8	TOBI: PA8	CHF: TB-S8	CHF: TB-N8	TOBI: TB-N8
9	TOBI: PA9	CHF: TB-S9	CHF: TB-N9	TOBI: TB-N9	CHF: V9
10	CHF: TB-S10	CHF: TB-N10	TOBI: TB-N10	CHF: V10	TOBI: PA10
11	CHF: TB-N11	TOBI: TB-N11	CHF: V11	TOBI: PA11	CHF: TB-S11
12	TOBI: TB-N12	CHF: V12	TOBI: PA12	CHF: TB-S12	CHF: TB-N12
13	CHF: V13	TOBI: PA13	CHF: TB-S13	CHF: TB-N13	TOBI: TB-N13
14	TOBI: PA14	CHF: TB-S14	CHF: TB-N14	TOBI: TB-N14	CHF: V14
15	CHF: TB-S15	CHF: TB-N15	TOBI: TB-N15	CHF: V15	TOBI: PA15

[1] CHF=CHF 1538 Tobramycin Inhalation Solution (300 mg/4 mL), TOBI=Tobramycin Inhalation Solution (300 mg/5 mL), PA=DeVilbiss Pulmo-Aide compressor, V=PARI VIOS compressor, TB-S=PARI TurboBoy S compressor, and TB-N=PARI TurboBoy N compressor. Testing was performed "column-wise".

Results:

The mean results of the tobramycin collected on each stage are presented in Table 6 below:

Table 6: NGI Testing of CHF 1538 Using LC Plus, Mean Results per Compressor Type (n=15): Individual Stage Results

Description of Result[1]	Vios		TurboBOY N		TurboBOY S	
	Mean	% RSD	Mean	% RSD	Mean	% RSD
Induction Port (mg)	3.3	11.3	3.0	15.8	3.2	14.7
Stage 1 (mg)	10.2	10.5	9.8	11.0	10.7	11.9
Stage 2 (mg)	22.4	8.5	21.0	9.8	22.9	10.2
Stage 3 (mg)	32.2	6.6	32.8	5.4	32.8	8.4
Stage 4 (mg)	37.8	8.6	40.2	6.0	38.9	10.6
Stage 5 (mg)	31.5	7.6	33.2	6.0	31.9	6.9
Stage 6 (mg)	15.2	17.9	15.7	19.8	14.5	18.1
Stage 7 (mg)	8.3	12.8	9.9	13.4	8.1	10.8
Filter (mg)	7.8	12.3	9.2	14.0	8.4	16.6
Nebulizer-Retained (mg)	128.7	5.8	126.2	4.3	124.7	8.6
Drug in Nebulizer at T_0 (mg)	306.9	1.9	309.5	1.2	306.7	1.3
Total Tobramycin collected (mg)	297.4	2.7	300.9	2.4	296.3	2.2
TEM (mg)	168.7	4.2	174.7	4.3	171.6	4.8
Mass balance (%)	96.9	1.7	97.2	1.8	96.6	1.8
FPD (< 5 µm) (mg)	93.5	4.5	100.8	5.9	94.6	3.6
FPF (< 5 µm) as % TEM	55.5	3.2	57.7	3.8	55.2	3.8
MMAD (µm)	(b) (4)					
GSD	2.3	4.3	2.3	4.1	2.3	3.9
Sputter Point (min)	6.5	8.2	6.3	2.7	6.5	4.7
Compressor Flow Rate (L/min)[2]	(b) (4)					
Compressor Pressure Range (psi)	(b) (4)					

[1] A total of 15 NGI experiments were performed with each configuration in the table; 15 compressor units of each compressor type were tested with a total of 15 nebulizer units in a randomized order. Each nebulizer unit was tested once with a unit of each compressor type. The data are extracted from report RP-096-002-15 (for protocol SP-096-002-012).

[2] The compressor properties of flow rate and pressure were determined independent of the NGI apparatus prior to each NGI collection. These measurements are carried out according to the method VTM-096-002-02.

Figure 4, showing stage-by-stage data of the APSD for the TBM configuration and the CT configurations, indicates the deposition profiles are similar.

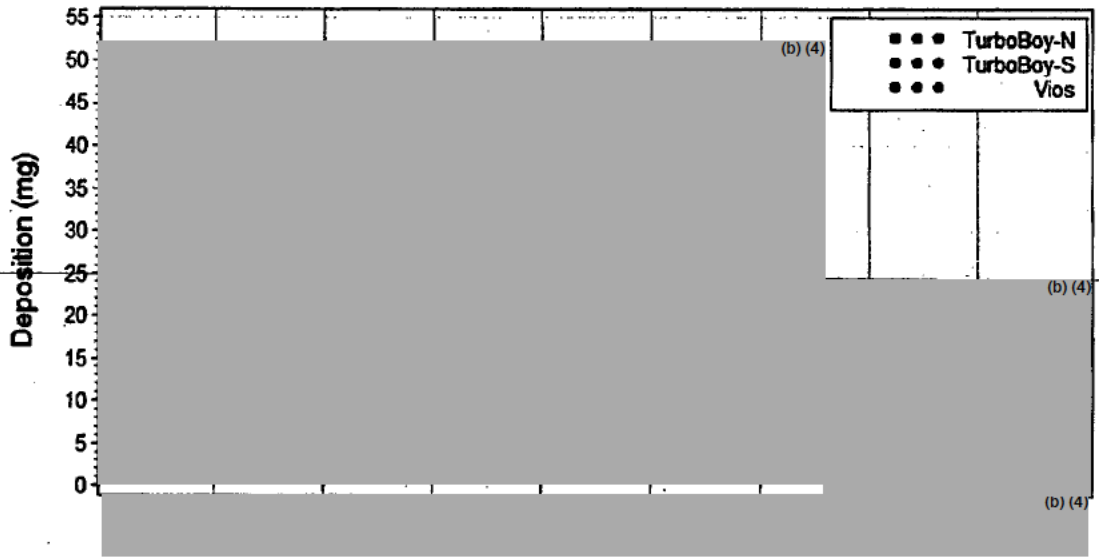


Figure 4: Individual-Stage NGI Deposition for the TBM Configuration and CT Configurations

Statistical Analysis of Equivalence:

To evaluate the equivalence of the TBM and CT device configurations, the *in vitro* data have been subjected to statistical analyses with particular reference to conventional equivalence limits. In addition, the *in vitro* data have been considered in the context of clinical factors and the therapeutic scenario.

A summary of the results with statistical analysis for five APSD parameters is provided in Table 7.

A comparison of the Vios to TurboBOY S and TurboBOY N was performed with a two-sided 90% confidence interval (CI) for the ratio of Test/Reference (Vios/TurboBOY S or Vios/TurboBOY N), using the SAS statistical program (Windows version 9.2). A comparison was performed for each of the key APSD parameters from the data set (N=15 for each configuration). The ratios of the Test/Reference were determined for the different compressor units used with the same LC Plus nebulizer unit: for example, the ratio of the MMAD from Vios unit 1 to MMAD from TB-N unit 1, both using LC Plus unit 1. The means of those MMAD Test/Reference ratios were used for the analysis.

For all six key aerosol performance parameters, the confidence intervals are well within the acceptance criteria of (b) (4) moreover, the largest observed difference is 7% in FPD between Vios and TurboBOY N. Therefore, the compared combinations are concluded to be substantially equivalent.

Table 7: Summary of Results from *in vitro* Studies with the To-Be-Marketed Configuration and the Clinical Trial Configurations (N=15)

In Vitro Parameter	To-Be-Marketed	Clinical Trial Units		Ratio of Test/Reference (CI)[1]		Figure Reference for Individual Values
	Vios	TB-N	TB-S	Vios/TB-N	Vios/TB-S	
MMAD NGI (µm)	(b) (4)			1.05 (1.01-1.08)	0.99 (0.97-1.02)	Figure 8
GSD NGI				1.01 (0.98-1.04)	1.01 (0.99-1.03)	Figure 9
FPD, < 5 µm NGI (mg)				0.93 (0.91-0.96)	0.99 (0.97-1.01)	Figure 10
FPF NGI (%)				0.96 (0.94-0.99)	1.01 (0.98-1.03)	Figure 11
TEM NGI (mg)				0.97 (0.94-0.99)	0.98 (0.96-1.01)	Figure 12
DD (mg)				0.95 (0.91-0.98)	0.97 (0.94-1.01)	Figure 2

[1] Mean Ratio of Individual Test/Reference for compressor units used with the same LC Plus nebulizer unit: not the ratio of the means. CI=Confidence Interval.

Comparative Particle Characterization Analysis (TOBI – DeVilbiss PulmoAide vs. TurboBOY N)

In the Complete Response Letter, FDA requested that Chiesi collect data to show comparability of drug delivery between the to-be-marketed product and the approved reference product, TOBI, establishing a link to the previous findings of safety and efficacy necessary for a 505(b)(2) application. FDA recommended the following device configurations:

- PARI LC Plus Nebulizer, DeVilbiss Pulmo-Aide Compressor, TOBI; and
- PARI LC Plus Nebulizer, TurboBoy N Compressor, TOBI.

At the December 16, 2011 Type A meeting, there was general agreement with Chiesi's proposed study to compare the APSD of TOBI with that of CHF 1538. Therefore, Chiesi performed concurrent (side-by-side) APSD experiments with TOBI and CHF 1538.

Materials:

The TOBI NGIs were run according to the same procedures, and randomized with the NGI runs of CHF 1538 as presented above. The materials used for this study, in addition to those listed previously, were as follows:

- TOBI Tobramycin Inhalation Solution (300 mg/5 mL), Novartis Pharmaceuticals Corp.; and
- DeVilbiss Pulmo-Aide compressors, Part Number 5650D, DeVilbiss Healthcare.

Fifteen NGI experiments were performed: 15 units of each compressor type (TurboBOY N or DeVilbiss Pulmo-Aide) were tested with a total of 15 LC Plus nebulizer units in a randomized order (Table 8). Each nebulizer unit was tested once with a unit of each compressor type.

Results:

Table 8: APSD by NGI: Comparison of CHF 1538 and TOBI as Delivered by LC Plus Nebulizer with Different Compressors

Parameter	CHF 1538 Tobramycin 300 mg/4 mL		TOBI Tobramycin 300 mg/5 mL	
	Vios	TB-N	TB-N	Pulmo-Aide
TEM NGI (mg)	(b) (4)			
FPD NGI (mg)				
FPF NGI (%)				
MMAD NGI (µm)				
GSD NGI				
Sputter Point (min)				

1 Data are presented as mean (% RSD)

The stage-by-stage data of the APSD for TOBI and CHF 1538, with the different compressor-nebulizer configurations demonstrates the comparable deposition profiles:

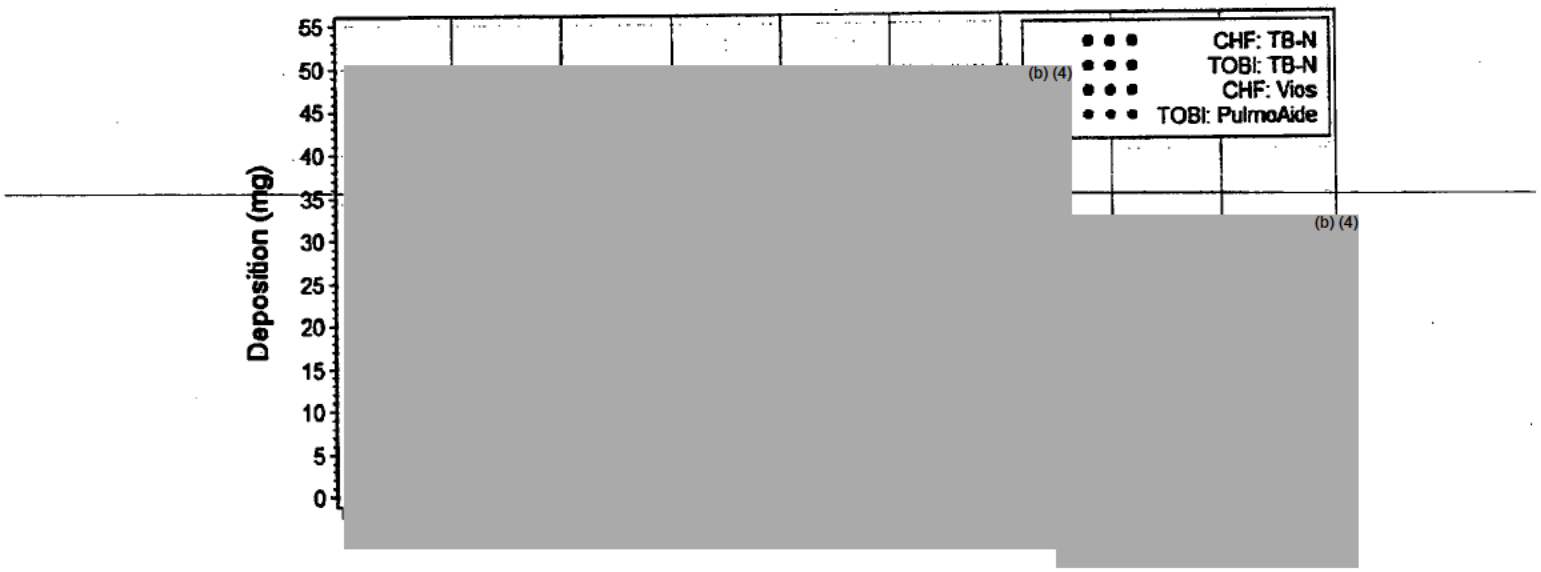


Figure 5: Individual-Stage NGI Deposition for TOBI and CHF 1538 Using Different Compressors with the LC Plus Nebulizer

Discussion of Delivered Dose (DD) vs. Total Emitted Mass (NGI)

In the Type A meeting held between Chiesi and FDA on December 16, 2011, FDA stated that DD would be compared to TEM. Total emitted mass was collected for each configuration. Table 9 provides the comparison of the results from these two different types of *in vitro* measurements. The absolute amounts from DD are expected to be less than the TEM because the DD experiment uses breathing simulation which has an exhalation phase (thus loss of drug to atmosphere). The NGI is performed using a 15 L/min constant, uninterrupted flow of nebulized solution on to the impactor plates within a closed system. Therefore, the NGI experiment collects almost ⅔ of the total drug, whereas the DD experiment collects less than half of the drug because of the breath cycling. Therefore, the observed result (Table 9) of a greater TEM versus DD is consistent with the collection methods. Both TEM and DD share the trend of quantity versus compressor type; although the differences between the types are not significant, there is a trend of TurboBOY N > TurboBOY S > Vios for both TEM and DD. Applying the worst case scenario (or lower boundary of a 95% confidence interval), the differences are 5% and 3% for DD and TEM, respectively. Given the normal variability that is often present within a cystic fibrosis patient and between cystic fibrosis patients in nebulized drug delivery, such differences are considered unlikely to be clinically relevant.

Table 9: Comparison of Delivered Dose with Breathing Simulation to TEM by NGI

In vitro Parameter	To-Be-Marketed	Clinical Trial Units		Ratio of Test/Reference (CI[1])	
	Vios	TB-N	TB-S	Vios/TB-N	Vios/TB-S
TEM (mg)	(b) (4)			0.97 (0.94-0.99)	0.98 (0.96-1.01)
DD (mg)				0.95 (0.91-0.98)	0.97 (0.94-1.01)

[1] Confidence Interval

D. Review Conclusions and Recommendation

At this stage of review, the sponsor has provided a range of descriptive information and comparative analyses to establish relative equivalence between the two clinical trial configurations and the to-be-marketed configuration of proposed drug-device combination. Collectively, these tests are sufficient to demonstrate that the to-be-marketed device configuration (Pari LC Plus Nebulizer and Pari Vios Compressor) reliably administers a delivered dose of (b) (4) mg with an median particle size of approximately (b) (4) µm. As shown, in Table 1 below, the overall differences in particle specifications between the measured configurations are minimal from a statistical perspective.

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The in vitro characterization of the aerosol output from the PARI LC Plus used with different compressors supports consistent total drug and lung-targeted delivery from the different device configurations. As shown above, the variable compressors do not have a significant impact on particle characterization.

In view of the above, it is expected that for the to-be-marketed PARI LC Plus nebulizer with the Vios compressor, a highly comparable amount of drug will be delivered to the lung and this will thus support a comparable clinical efficacy to that observed in clinical trials both in terms of inhibition of bacterial growth and improvements in lung function. In essence, from a device perspective, the labeling of the product with the Vios compressor would directly reflect and be entirely consistent with all the clinical data generated using the TurboBOY S and TurboBOY N compressors.

In conclusion, it is unlikely that the subtle differences in particle characterization and dose delivery observed during *in vitro* studies when CHF 1538 is delivered by the TurboBOY (used in clinical studies) compared to the proposed Vios compressor would impart any clinical impact in terms of decreased efficacy for patients with CF. Accordingly, assuming that CDER determines the clinical study information provided for review to be a sufficient basis for safety and effectiveness, CDRH recommends approval of the proposed drug-device combination.

CDRH strongly believes that relevant measured specifications (e.g. emitted dose, respirable dose, particle size) for the drug-device combination are necessary whenever recommended doses and/or device specifications are listed in labeling. This information is useful to prescribers and physicians to distinguish between a recommended dose specification and the actual measured dose specification. The importance of this information dependent on the observed difference between the recommended and measured values and also on the therapeutic index of the drug under consideration.

It is recommended that the following language be incorporated in parts of the label where dosing information and/or instructions is provided:

"Under standardized in vitro testing at a fixed flow rate of (b) (4) L/min, the to-be-marketed configuration of the proposed device (PARI LC Plus with PARI VIOS Compressor), the measured total emitted mass is (b) (4) mg with a mass median aerosol diameter of (b) (4) µm. The respirable fraction ((b) (4) µm) is (b) (4) %."

Mr. Sugato De, M.S., Lead Reviewer — 10/11/12 Date

Dr. Lex Schultheis, ARDB Branch Chief — 10/11/12 Date

Dr. Tejashri Purohit-Sheth, Clinical Deputy Director — 10/11/12 Date

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/s/

CARMEN L DEBELLAS
10/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Anesthesia and Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Infection Control and Dental Device
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

NDA 201-820 – Regulatory Device Consult

Date: October 11, 2012

To: Mr. Carmen DeBellas, Regulatory Project Manager (OND/OAP/DAIOP)

From: Mr. Sugato De, M.S., Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer

Applicant: Chiesi Pharmaceuticals Inc.

Product Name: Tobramycin 300 mg/4mL Solution (CHF 1538)

Indication: Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged six years and older.

A. Executive Summary

In NDA 201-820, Chiesi Pharmaceuticals has proposed a novel formulation of inhaled tobramycin (Tobramycin 300 mg/4 mL Inhalation Solution, hereafter referred to as CHF 1538). The formulation is composed of tobramycin, sulfuric acid, and sodium chloride in aqueous solution, using water for injection. The preservative-free sterile inhalation solution formulation has been developed for use in the treatment of pseudomonal pulmonary infections.

The oral inhalation of CHF 1538 via nebulizer requires the use of a nebulizer and an air compressor. Clinical studies for the proposed drug-device combination have used exclusively the Pari LC Plus Nebulizer with the either the Pari TurboBOY N Compressor or the Pari TurboBOY S Compressor. Due to differences in product availability between the United States and Europe, the proposed to-be-marketed (TBM) device configuration intended to deliver CHF 1538 is the Pari LC Plus Nebulizer along the Pari Vios compressor. Accordingly, in vitro cascade impaction studies comparing the clinical trial configurations of the device to the proposed market configuration are necessary in order to establish relative equivalence. This data is required to establish the relevance of the findings of the clinical trial.

In formal communications, the sponsor was asked to perform in vitro characterization studies intended to establish relative equivalence in terms of particle size, delivered dose and respirable dose between the clinical trial configurations and the proposed to-be-marketed configuration. The Agency indicated that these studies were expected to utilize a breathing pattern indicative of a representative patient with cystic fibrosis. Using this breathing pattern, the applicant proceeded to provide comparative cascade impaction data using an appropriate number of device samples and test runs to account for potential inter-and intra-sample variability.

RECOMMENDATION: At this stage of review, the sponsor has provided a range of descriptive information and comparative analyses to establish relative equivalence between the two clinical trial configurations and the to-be-marketed configuration of proposed drug-device combination. Collectively, these tests are sufficient to demonstrate that the to-be-marketed device configuration (Pari LC Plus Nebulizer and Pari Vios Compressor) reliably administers a delivered dose of (b) (4) mg with an median particle size of approximately (b) (4) µm. As shown, in Table 1 below, the overall differences in particle specifications between the measured configurations are minimal from a statistical perspective.

Table 1: Summary of Results from *in vitro* Studies with the To-Be-Marketed Configuration and the Clinical Trial Configurations (N=15)

In Vitro Parameter	To-Be-Marketed	Clinical Trial Units		Ratio of Test/Reference (CI)[1]		Figure Reference for Individual Values
	Vios	TB-N	TB-S	Vios/TB-N	Vios/TB-S	
MMAD NGI (µm)	[redacted] (b) (4)			1.05 (1.01-1.08)	0.99 (0.97-1.02)	Figure 8
GSD NGI				1.01 (0.98-1.04)	1.01 (0.99-1.03)	Figure 9
FPD, < 5 µm NGI (mg)				0.93 (0.91-0.96)	0.99 (0.97-1.01)	Figure 10
FPF NGI (%)				0.96 (0.94-0.99)	1.01 (0.98-1.03)	Figure 11
TEM NGI (mg)				0.97 (0.94-0.99)	0.98 (0.96-1.01)	Figure 12
DD (mg)				0.95 (0.91-0.98)	0.97 (0.94-1.01)	Figure 2

[1] Mean Ratio of Individual Test/Reference for compressor units used with the same LC Plus nebulizer unit: not the ratio of the means. CI=Confidence Interval.

The in vitro characterization of the aerosol output from the PARI LC Plus used with different compressors supports consistent total drug and lung-targeted delivery from the different device configurations. As shown above, the variable compressors do not have a significant impact on particle characterization.

In view of the above, it is expected that for the to-be-marketed PARI LC Plus nebulizer with the Vios compressor, a highly comparable amount of drug will be delivered to the lung and this will thus support a comparable clinical efficacy to that observed in clinical trials both in terms of inhibition of bacterial growth and improvements in lung function. In essence, from a device perspective, the labeling of the product with the Vios compressor would directly reflect and be entirely consistent with all the clinical data generated using the TurboBOY S and TurboBOY N compressors.

In conclusion, it is unlikely that the subtle differences in particle characterization and dose delivery observed during *in vitro* studies when CHF 1538 is delivered by the TurboBOY (used in clinical studies) compared to the proposed Vios compressor would impart any clinical impact in terms of decreased efficacy for patients with CF. Accordingly, assuming that CDER determines the clinical study information provided for review to be a sufficient basis for safety and effectiveness, CDRH recommends approval of the proposed drug-device combination.

CDRH strongly believes that relevant measured specifications (e.g. emitted dose, respirable dose, particle size) for the drug-device combination are necessary whenever recommended doses and/or device specifications are listed in labeling. This information is useful to prescribers and physicians to distinguish between a recommended dose specification and the actual measured dose specification. The importance of this information dependent on the observed difference between the recommended and measured values and also on the therapeutic index of the drug under consideration.

B. Device Description

Overview:

The oral inhalation delivery of CHF 1538 via nebulizer requires the use of an air compressor. Clinical studies have used exclusively the PARI TurboBOY and PARI TurboBOY N compressors and the PARI LC Plus nebulizer. Due to changes in the proposed market (EU versus US), an alternate compressor, PARI Vios, in conjunction with the PARI LC Plus nebulizer is proposed for the US commercial market.

The identification of all models, device accessories and the relevant 510(k) status of the FDA-cleared devices referenced in Chiesi's NDA are shown in Table 2 and Table3. The TurboBOY and TurboBOY N compressors used throughout the entire clinical development program, which was conducted in Europe, are not compatible with US standards for voltage and amperage. Therefore, clearance was never sought in the US for either the TurboBOY or the TurboBOY N and references to 510(k) clearances for these devices are not possible.

Table 2: 510(k) Status of Compressor

Compressors	510(k) Application Number	510(k) Status (Decision Date)
PARI Vios	K092918	Substantially Equivalent (04 February 2010)

Table 3: 510(k) Status of Nebulizer

Nebulizers	510(k) Application Number	510(k) Status (Decision Date)
PARI LC Plus	PARI Master Modification K935540[1]	Substantially Equivalent (17 March 1995)

[1] This submission included the LC Plus reusable nebulizer along with other devices.

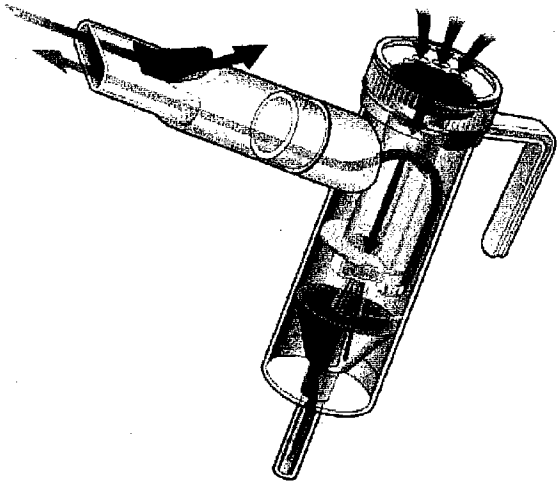


Figure 1: PARI LC Plus Nebulizer

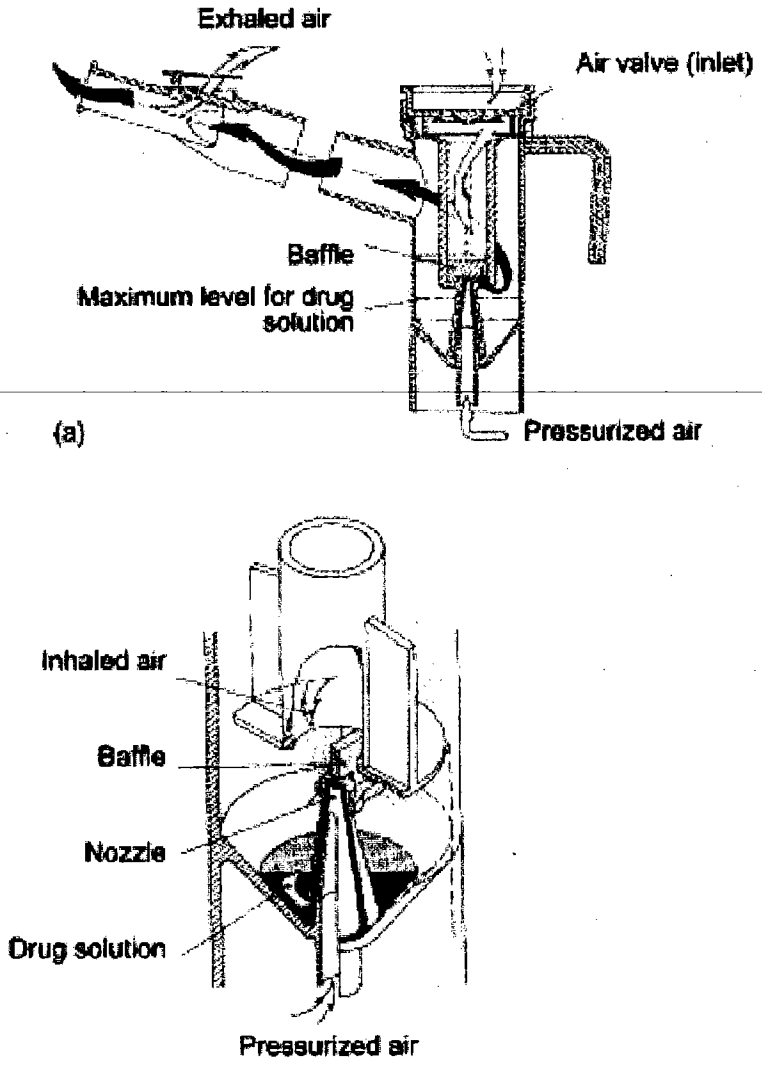


Figure 2: Breathing Gas Path Components of PARI LC Plus Nebulizer

The information provided for review illustrates the gas path of the nebulizer and demonstrates that no adulterations or modifications have been made to the 510(k) approved device design. The Instructions for Use for the device are not affected by the proposed configuration.

In response to a Type A meeting request made by FDA on 14 December 2011, Chiesi provided the technological differences between the proposed PARI Vios compressor, the PARI TurboBOY N and TurboBOY (the compressors used in the clinical study), and the TurboBOY S (which replaced the TurboBOY) in Table 4. The technological information of the DeVilbiss Pulmo-Aide® used for TOBI® Inhalation Solution, 300 mg/5 mL is also listed in Table 4 for comparison purposes.

Compressor Comparison:

While specific information pertaining to the differences between the TurboBOY Compressors and the Vios Compressor were not obtained from PARI, the sponsor provided the following descriptive comparison:

Table 4: Comparative Performance Specifications for Compressors

Compressor	Intended Use	Performance Pressure	Flow Rate	Materials	Filters	Operating Principles	Power Supply	Target Population
PARI Vios	Home, hospital or clinic use. Single flow rate, to be used with jet nebulizer, general purpose	(b) (4)					120 V 60 Hz 1.5 A 80 W	Adult and pediatric patients
PARI TurboBOY N	As Vios						230 V 50 Hz 0.7 A 80 W	Patients ages 4 and older
PARI TurboBOY S	As Vios						230-240 V 50 Hz 0.5 A 65 W	Patients ages 4 and older
PARI TurboBOY[1]	As Vios						230-240 V 50 Hz 0.5 A 65 W	Patients ages 4 and older
DeVilbiss Pulmo-Aide[2]	Home health care use. To be used with a jet (pneumatic nebulizer						115 V 60 Hz 1.3 A 90 W	Adult and pediatric patients

[1] TurboBOY no longer available from PARI and replaced by the TurboBOY S

[2] Information on the Pulmo-Aide compressor taken from http://www.phc-online.com/Pulmo-Aide Nebulizer p/devilbiss-5650.htm, accessed 15 December 2011. The procedure and apparatus used by DeVilbiss to measure operating pressure and flow rate is unknown by Chiesi. The flow and pressure will be dependent on any restriction that the testing method uses at the end of the tubing.

C. Device Performance

Comparative Particle Characterization Analysis (CHF 1538 – CT Configuration vs. TBM Configuration

To compare the TBM configuration with the clinical trial (CT) configurations for CHF 1538, the following device combinations were tested by NGI experiments:

- PARI LC Plus Nebulizer, TurboBoy S (TB-S) Compressor, CHF 1538 (CT Configuration 1);
- PARI LC Plus Nebulizer, TurboBoy N (TB-N) Compressor, CHF 1538 (CT Configuration 2); and
- PARI LC Plus Nebulizer, Vios Compressor, CHF 1538 (TBM Configuration 1).

Note that the (b) (4) is no longer being proposed as part of the to-be-marketed drug device combination.

At the December 16, 2011 Type A meeting, there was general agreement with Chiesi's proposed study to compare the aerodynamic particle size distribution (APSD) of the CT compressors with that of the TBM compressor. Therefore, Chiesi performed APSD experiments with the three configurations listed above according to protocol SP-096-002-012; the APSD was carried out using NGI.

The current version of the validated method for NGI collections, VTM 096-002-01, is provided in Appendix B; the procedure generally follows the methodology of USP <1601>. The drug solutions were (b) (4)

The delivered dose (DD) specification was established using breath simulation a representative breath pattern for a patient with cystic fibrosis:

- (b) (4)

This breathing pattern was selected based on observed patterns in cystic fibrosis patients. The DD collection time of (b) (4) was selected during test method development. (b) (4) is beyond the observed sputter point, which is about 9.5 minutes, and allows the collection of approximately one-third of the total dose.

In the DD method, (b) (4) The "delivered dose" (b) (4) (b) (4)

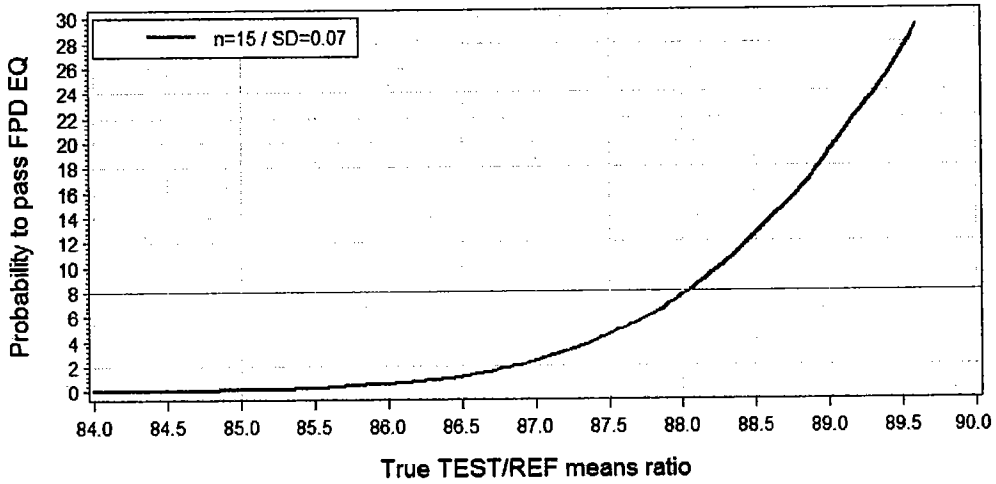
Materials Tested:

- CHF 1538, Tobramycin Inhalation Solution (300 mg/4 mL), Lot 05909E;
- PARI LC Plus nebulizers, Lot 1000007154809, PARI Respiratory Equipment, Inc.;
- PARI Vios compressors, Part Number 310F35-LCS, PARI Respiratory Equipment, Inc.;
- PARI TurboBoy N compressors, Part Number 085G1201, PARI GmbH; and
- PARI TurboBoy S compressors, Part Number 053G1210, PARI GmbH

Sample Size Rationale:

The goal of the study was to perform enough NGI experiments with each configuration to be able to detect less than a 15% difference between any two compressors with a 90% confidence interval. This was achieved by performing 15 collections per configuration (Table 14).

The data in Figure 6 show the power of N=15 with the observed Test/Reference Fine Particle Dose (FPD) standard deviation of 0.07 with N=15 experiments; there is 92% power to detect a 12% difference between any two combinations.



[1]TEST=Vios compressor; REF=TurboBOY S or TurboBOY N compressor; FPD=Fine Particle Dose; EQ=Equivalence

Figure 3: Power Function Anlaysis for NGI Experiments to Determine Sample Size

Fifteen PARI LC Plus nebulizers and fifteen compressor units of each model were randomly selected. Each nebulizer unit was tested with all three types of compressors. The total number of NGI collections was 15 for each of the three compressor types (Vios, TurboBOY S and TurboBOY N). The collections were randomized according to the scheme in Table 5.

Table 5: Collection Schedule for APSD by NGI

Nebulizer Unit	Product-Compressor Combination[1]				
	Run 1	Run 2	Run 3	Run 4	Run 5
1	CHF: TB-N1	TOBI: TB-N1	CHF: V1	TOBI: PA1	CHF: TB-S1
2	TOBI: TB-N2	CHF: V2	TOBI: PA2	CHF: TB-S2	CHF: TB-N2
3	CHF: V3	TOBI: PA3	CHF: TB-S3	CHF: TB-N3	TOBI: TB-N3
4	TOBI: PA4	CHF: TB-S4	CHF: TB-N4	TOBI: TB-N4	CHF: V4
5	CHF: TB-S5	CHF: TB-N5	TOBI: TB-N5	CHF: V5	TOBI: PA5
6	CHF: TB-N6	TOBI: TB-N6	CHF: V6	TOBI: PA6	CHF: TB-S6
7	TOBI: TB-N7	CHF: V7	TOBI: PA7	CHF: TB-S7	CHF: TB-N7
8	CHF: V8	TOBI: PA8	CHF: TB-S8	CHF: TB-N8	TOBI: TB-N8
9	TOBI: PA9	CHF: TB-S9	CHF: TB-N9	TOBI: TB-N9	CHF: V9
10	CHF: TB-S10	CHF: TB-N10	TOBI: TB-N10	CHF: V10	TOBI: PA10
11	CHF: TB-N11	TOBI: TB-N11	CHF: V11	TOBI: PA11	CHF: TB-S11
12	TOBI: TB-N12	CHF: V12	TOBI: PA12	CHF: TB-S12	CHF: TB-N12
13	CHF: V13	TOBI: PA13	CHF: TB-S13	CHF: TB-N13	TOBI: TB-N13
14	TOBI: PA14	CHF: TB-S14	CHF: TB-N14	TOBI: TB-N14	CHF: V14
15	CHF: TB-S15	CHF: TB-N15	TOBI: TB-N15	CHF: V15	TOBI: PA15

[1] CHF=CHF 1538 Tobramycin Inhalation Solution (300 mg/4 mL), TOBI=Tobramycin Inhalation Solution (300 mg/5 mL), PA=DeVilbiss Pulmo-Aide compressor, V=PARI VIOS compressor, TB-S=PARI TurboBoy S compressor, and TB-N=PARI TurboBoy N compressor. Testing was performed "column-wise".

Results:

The mean results of the tobramycin collected on each stage are presented in Table 6 below:

Table 6: NGI Testing of CHF 1538 Using LC Plus, Mean Results per Compressor Type (n=15): Individual Stage Results

Description of Result[1]	Vios		TurboBOY N		TurboBOY S	
	Mean	% RSD	Mean	% RSD	Mean	% RSD
Induction Port (mg)	3.3	11.3	3.0	15.8	3.2	14.7
Stage 1 (mg)	10.2	10.5	9.8	11.0	10.7	11.9
Stage 2 (mg)	22.4	8.5	21.0	9.8	22.9	10.2
Stage 3 (mg)	32.2	6.6	32.8	5.4	32.8	8.4
Stage 4 (mg)	37.8	8.6	40.2	6.0	38.9	10.6
Stage 5 (mg)	31.5	7.6	33.2	6.0	31.9	6.9
Stage 6 (mg)	15.2	17.9	15.7	19.8	14.5	18.1
Stage 7 (mg)	8.3	12.8	9.9	13.4	8.1	10.8
Filter (mg)	7.8	12.3	9.2	14.0	8.4	16.6
Nebulizer-Retained (mg)	128.7	5.8	126.2	4.3	124.7	8.6
Drug in Nebulizer at T_0 (mg)	306.9	1.9	309.5	1.2	306.7	1.3
Total Tobramycin collected (mg)	297.4	2.7	300.9	2.4	296.3	2.2
TEM (mg)	168.7	4.2	174.7	4.3	171.6	4.8
Mass balance (%)	96.9	1.7	97.2	1.8	96.6	1.8
FPD (< 5 μm) (mg)	93.5	4.5	100.8	5.9	94.6	3.6
FPF (< 5 μm) as % TEM	55.5	3.2	57.7	3.8	55.2	3.8
MMAD (μm)	4.3	4.1	4.1	5.0	4.3	4.7
GSD	2.3	4.3	2.3	4.1	2.3	3.9
Sputter Point (min)	6.5	8.2	6.3	2.7	6.5	4.7
Compressor Flow Rate (L/min)[2]	4.3	1.2	5.1	0.6	4.3	1.3
Compressor Pressure Range (psi)	18.2-20.3		24.3-26.5		18.6-20.5	

[1] A total of 15 NGI experiments were performed with each configuration in the table; 15 compressor units of each compressor type were tested with a total of 15 nebulizer units in a randomized order. Each nebulizer unit was tested once with a unit of each compressor type. The data are extracted from report RP-096-002-15 (for protocol SP-096-002-012).

[2] The compressor properties of flow rate and pressure were determined independent of the NGI apparatus prior to each NGI collection. These measurements are carried out according to the method VTM-096-002-02.

Figure 4, showing stage-by-stage data of the APSD for the TBM configuration and the CT configurations, indicates the deposition profiles are similar.

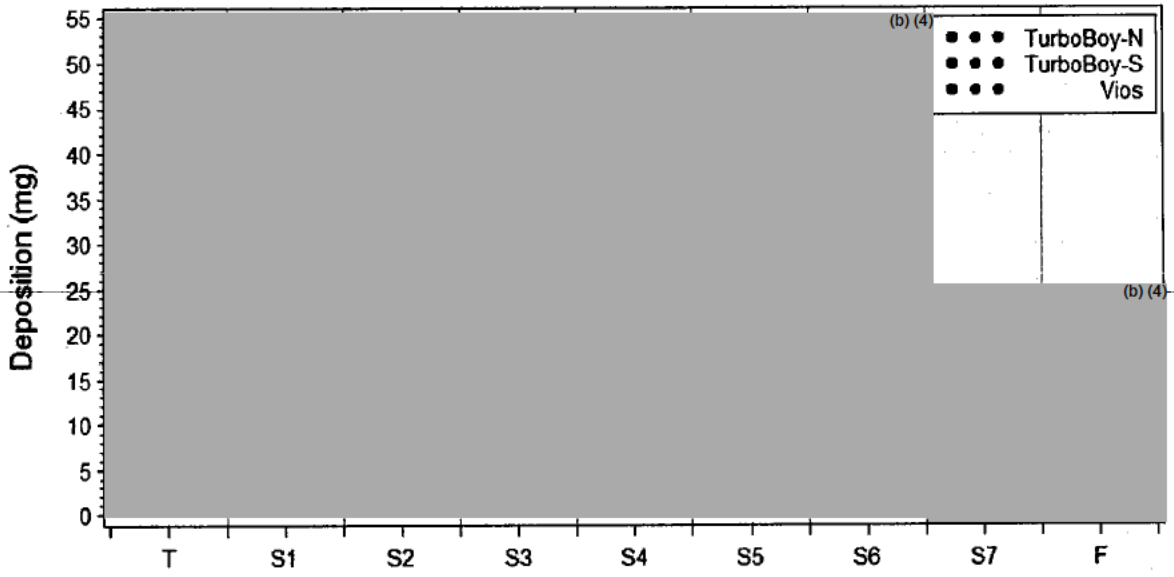


Figure 4: Individual-Stage NGI Deposition for the TBM Configuration and CT Configurations

Statistical Analysis of Equivalence:

To evaluate the equivalence of the TBM and CT device configurations, the *in vitro* data have been subjected to statistical analyses with particular reference to conventional equivalence limits. In addition, the *in vitro* data have been considered in the context of clinical factors and the therapeutic scenario.

A summary of the results with statistical analysis for five APSD parameters is provided in Table 7.

A comparison of the Vios to TurboBOY S and TurboBOY N was performed with a two-sided 90% confidence interval (CI) for the ratio of Test/Reference (Vios/TurboBOY S or Vios/TurboBOY N), using the SAS statistical program (Windows version 9.2). A comparison was performed for each of the key APSD parameters from the data set (N=15 for each configuration). The ratios of the Test/Reference were determined for the different compressor units used with the same LC Plus nebulizer unit: for example, the ratio of the MMAD from Vios unit 1 to MMAD from TB-N unit 1, both using LC Plus unit 1. The means of those MMAD Test/Reference ratios were used for the analysis.

For all six key aerosol performance parameters, the confidence intervals are well within the acceptance criteria of (b) (4) moreover, the largest observed difference is 7% in FPD between Vios and TurboBOY N. Therefore, the compared combinations are concluded to be substantially equivalent.

Table 7: Summary of Results from *in vitro* Studies with the To-Be-Marketed Configuration and the Clinical Trial Configurations (N=15)

In Vitro Parameter	To-Be-Marketed	Clinical Trial Units		Ratio of Test/Reference (CI)[1]		Figure Reference for Individual Values
	Vios	TB-N	TB-S	Vios/TB-N	Vios/TB-S	
MMAD NGI (µm)	(b) (4)					Figure 8
GSD NGI						Figure 9
FPD, < 5 µm NGI (mg)						Figure 10
FPF NGI (%)						Figure 11
TEM NGI (mg)						Figure 12
DD (mg)						Figure 2

[1] Mean Ratio of Individual Test/Reference for compressor units used with the same LC Plus nebulizer unit: not the ratio of the means. CI=Confidence Interval.

Comparative Particle Characterization Analysis (TOBI – DeVilbiss PulmoAide vs. TurboBOY N)

In the Complete Response Letter, FDA requested that Chiesi collect data to show comparability of drug delivery between the to-be-marketed product and the approved reference product, TOBI, establishing a link to the previous findings of safety and efficacy necessary for a 505(b)(2) application. FDA recommended the following device configurations:

- PARI LC Plus Nebulizer, DeVilbiss Pulmo-Aide Compressor, TOBI; and
- PARI LC Plus Nebulizer, TurboBoy N Compressor, TOBI.

At the December 16, 2011 Type A meeting, there was general agreement with Chiesi's proposed study to compare the APSD of TOBI with that of CHF 1538. Therefore, Chiesi performed concurrent (side-by-side) APSD experiments with TOBI and CHF 1538.

Materials:

The TOBI NGIs were run according to the same procedures, and randomized with the NGI runs of CHF 1538 as presented above. The materials used for this study, in addition to those listed previously, were as follows:

- TOBI Tobramycin Inhalation Solution (300 mg/5 mL), Novartis Pharmaceuticals Corp.; and
- DeVilbiss Pulmo-Aide compressors, Part Number 5650D, DeVilbiss Healthcare.

Fifteen NGI experiments were performed: 15 units of each compressor type (TurboBOY N or DeVilbiss Pulmo-Aide) were tested with a total of 15 LC Plus nebulizer units in a randomized order (Table 8). Each nebulizer unit was tested once with a unit of each compressor type.

Results:

Table 8: APSD by NGI: Comparison of CHF 1538 and TOBI as Delivered by LC Plus Nebulizer with Different Compressors

Parameter	CHF 1538 Tobramycin 300 mg/4 mL		TOBI Tobramycin 300 mg/5 mL	
	Vios	TB-N	TB-N	Pulmo-Aide
TEM NGI (mg)	(b) (4)			
FPD NGI (mg)				
FPF NGI (%)				
MMAD NGI (µm)				
GSD NGI				
Sputter Point (min)				

1 Data are presented as mean (% RSD)

The stage-by-stage data of the APSD for TOBI and CHF 1538, with the different compressor-nebulizer configurations demonstrates the comparable deposition profiles:

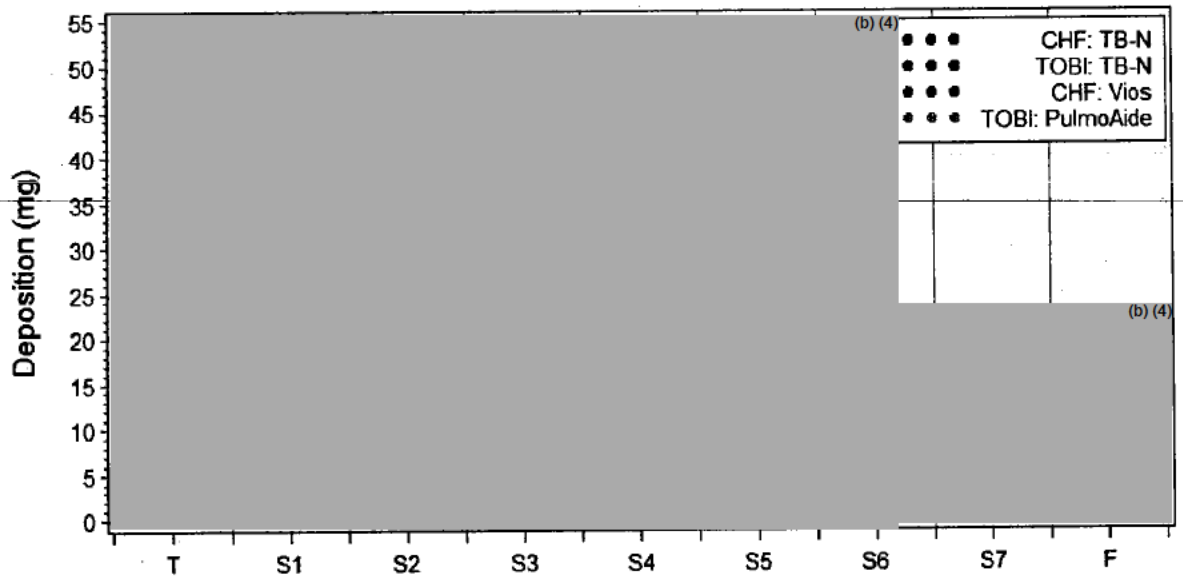


Figure 5: Individual-Stage NGI Deposition for TOBI and CHF 1538 Using Different Compressors with the LC Plus Nebulizer

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Discussion of Delivered Dose (DD) vs. Total Emitted Mass (NGI)

In the Type A meeting held between Chiesi and FDA on December 16, 2011, FDA stated that DD would be compared to TEM. Total emitted mass was collected for each configuration. Table 9 provides the comparison of the results from these two different types of *in vitro* measurements. The absolute amounts from DD are expected to be less than the TEM because the DD experiment uses breathing simulation which has an exhalation phase (thus loss of drug to atmosphere). The NGI is performed using a 15 L/min constant, uninterrupted flow of nebulized solution on to the impactor plates within a closed system. Therefore, the NGI experiment collects almost ⅔ of the total drug, whereas the DD experiment collects less than half of the drug because of the breath cycling. Therefore, the observed result (Table 9) of a greater TEM versus DD is consistent with the collection methods. Both TEM and DD share the trend of quantity versus compressor type; although the differences between the types are not significant, there is a trend of TurboBOY N > TurboBOY S > Vios for both TEM and DD. Applying the worst case scenario (or lower boundary of a 95% confidence interval), the differences are 5% and 3% for DD and TEM, respectively. Given the normal variability that is often present within a cystic fibrosis patient and between cystic fibrosis patients in nebulized drug delivery, such differences are considered unlikely to be clinically relevant.

Table 9: Comparison of Delivered Dose with Breathing Simulation to TEM by NGI

***In vitro* Parameter**	**To-Be-Marketed**	**Clinical Trial Units**		**Ratio of Test/Reference (CI[1])**	
	Vios	**TB-N**	**TB-S**	**Vios/TB-N**	**Vios/TB-S**
TEM (mg)	(b) (4)				
DD (mg)					

[1] Confidence Interval

D. Review Conclusions and Recommendation

At this stage of review, the sponsor has provided a range of descriptive information and comparative analyses to establish relative equivalence between the two clinical trial configurations and the to-be-marketed configuration of proposed drug-device combination. Collectively, these tests are sufficient to demonstrate that the to-be-marketed device configuration (Pari LC Plus Nebulizer and Pari Vios Compressor) reliably administers a delivered dose of (b) (4) mg with an median particle size of approximately (b) (4) µm. As shown, in Table 1 below, the overall differences in particle specifications between the measured configurations are minimal from a statistical perspective.

Table 1: Summary of Results from *in vitro* Studies with the To-Be-Marketed Configuration and the Clinical Trial Configurations (N=15)

In Vitro Parameter	To-Be-Marketed	Clinical Trial Units		Ratio of Test/Reference (CI)[1]		Figure Reference for Individual Values
	Vios	TB-N	TB-S	Vios/TB-N	Vios/TB-S	
MMAD NGI (µm)	(b) (4)					Figure 8
GSD NGI						Figure 9
FPD, < 5 µm NGI (mg)						Figure 10
FPF NGI (%)						Figure 11
TEM NGI (mg)						Figure 12
DD (mg)						Figure 2

[1] Mean Ratio of Individual Test/Reference for compressor units used with the same LC Plus nebulizer unit: not the ratio of the means. CI=Confidence Interval.

The in vitro characterization of the aerosol output from the PARI LC Plus used with different compressors supports consistent total drug and lung-targeted delivery from the different device configurations. As shown above, the variable compressors do not have a significant impact on particle characterization.

In view of the above, it is expected that for the to-be-marketed PARI LC Plus nebulizer with the Vios compressor, a highly comparable amount of drug will be delivered to the lung and this will thus support a comparable clinical efficacy to that observed in clinical trials both in terms of inhibition of bacterial growth and improvements in lung function. In essence, from a device perspective, the labeling of the product with the Vios compressor would directly reflect and be entirely consistent with all the clinical data generated using the TurboBOY S and TurboBOY N compressors.

In conclusion, it is unlikely that the subtle differences in particle characterization and dose delivery observed during *in vitro* studies when CHF 1538 is delivered by the TurboBOY (used in clinical studies) compared to the proposed Vios compressor would impart any clinical impact in terms of decreased efficacy for patients with CF. Accordingly, assuming that CDER determines the clinical study information provided for review to be a sufficient basis for safety and effectiveness, CDRH recommends approval of the proposed drug-device combination.

CDRH strongly believes that relevant measured specifications (e.g. emitted dose, respirable dose, particle size) for the drug-device combination are necessary whenever recommended doses and/or device specifications are listed in labeling. This information is useful to prescribers and physicians to distinguish between a recommended dose specification and the actual measured dose specification. The importance of this information dependent on the observed difference between the recommended and measured values and also on the therapeutic index of the drug under consideration.

It is recommended that the following language be incorporated in parts of the label where dosing information and/or instructions is provided:

(b) (4)

Mr. Sugato De, M.S., Lead Reviewer — Date: 10/11/12

Dr. Lex Schultheis, ARDB Branch Chief — Date: 10/11/12

Dr. Tejashri Purohit-Sheth, Clinical Deputy Director — Date: 10/11/12

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/s/

CARMEN L DEBELLAS
10/11/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**October 01, 2012**
To:	John Farley, MD Director **Division of Anti-Infective Products (DAIP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	Tobramycin Inhalation Solution
Dosage Form and Route:	Solution for Oral Inhalation
Application Type/Number:	NDA 201-820
Applicant:	Chiesi Pharmaceuticals

1 INTRODUCTION

On April 12, 2012, Chiesi Pharmaceuticals re-submitted for the Agency's review a New Drug Application (NDA 201-820) for Tobramycin Inhalation Solution, an aminoglycoside antibacterial indicated for the management of cystic fibrosis patients with *pseudomonas aeruginosa*. NDA 201-820 was originally submitted on October 22, 2010, and received a Complete Response (CR) letter on August 25, 2011, citing Chemistry, Manufacturing, and Control (CMC) deficiencies.

On May 17, 2012, the Division of Anti-Infective Products (DAIP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Tobramycin Inhalation Solution. This review is written in response to a request by DAIP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Tobramycin Inhalation Solution.

2 MATERIAL REVIEWED

- Draft Tobramycin Inhalation Solution PPI and IFU received on June 18, 2012 and received by DMPP on September 24, 2012
- Draft Tobramycin Inhalation Solution Prescribing Information (PI) received on June 18, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on September 24, 2012
- DMPP review of TOBI Podhaler (tobramycin inhalation powder) Patient Information (PPI) and Instructions for Use (IFU) dated August 28, 2012

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the Package Insert (PI) to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
10/01/2012

LASHAWN M GRIFFITHS
10/01/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

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

Memorandum

Date: September 26, 2012

To: Carmen DeBellas, Pharm.D., RPh, Regulatory Project Manager
Division of Anti-Infective Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion

Subject: NDA #201820
Tobramycin Inhalation Solution

As requested in your consult dated May 10, 2012, the Division of Professional Drug Promotion (DPDP) has reviewed the draft labeling for Tobramycin Inhalation Solution.

DPDP's, PI comments are based on the clean version of the labeling titled, "201820 #2 label.doc" which was sent via email from Carmen DeBellas on September 24, 2012.

DPDP's comments are provided in the attached, clean version of the labeling. If you have any questions about DPDP's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on this label.

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/s/

CHRISTINE G CORSER
09/26/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 201820	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Bethkis Established/Proper Name: tobramycin 300mg/ 4mL Solution		
Applicant: Chiesi Pharmaceuticals		
Date of Receipt: Original 10/25/12 Class 2 Resubmission Date 4/13/12		
PDUFA Goal Date: 10/13/12	Action Goal Date (if different): 10/12/12	
Proposed Indication(s): Management of Cystic Fibrosis Patients with *P aeruginosa*		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 50-753 TOBI (tobramycin) Inhalation Solution USP	

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Phase 1 bioavailability study and pharmacokinetic study.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES X NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES X NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES X NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES X NO

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
TOBI	50753	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A X YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO X

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

☐ NO ☐ YES

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The applicant is request a new concentration 300 mg/4mL Tobramycin Solution. The approved TOBI is 300 mg/5mL.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO x

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES X NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES X NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES X NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Tobrex Oint (NDA 50-555); Tobrex Opth Solution (NDA 50-541) + generics; Tobramycin Sulfate Injection (NDA 50-789) + generics

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): TOBI (tobramycin) 300 mg/5mL Solution Patent number 5508269

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES X NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

CARMEN L DEBELLAS
09/20/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Review

Date:	September 11, 2012
Reviewer:	Aleksander Winiarski, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Bethkis (Tobramycin) Inhalation Solution, 300 mg/4 mL
Application Type/Number:	NDA 201820
Applicant:	Chiesi Pharmaceutical, Inc.
OSE RCM #:	2012-1655

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed labels and labeling for Bethkis (Tobramycin) Inhalation Solution, 300 mg/4 mL LDPE ampules, NDA 201820, for areas of vulnerability that could lead to medication errors.

2 BACKGROUND AND REGULATORY HISTORY

Tobramycin Inhalation Solution, 300 mg/4 mL, is a 505 (b)(2) application that was submitted to the FDA on October 22, 2010. The application references Tobi (Tobramycin) Inhalation Solution, 300 mg/5 mL (NDA 050753). The OSE label and labeling review #2010-2309, dated June 30, 2011 made several recommendations, however these recommendations were not initially sent to the Applicant. The recommendations were sent to the Applicant on June 22, 2012 and the Applicant submitted revised label and labeling for their product on July 20, 2012.

3 MATERIALS REVIEWED

DMEPA reviewed the revised labels and labeling submitted by the Applicant on July 23, 2012. See Appendix for samples. We also reviewed OSE review #2010-2309 to ensure our recommendations were incorporated into the revised labels and labeling.

4 DISCUSSION

The Applicant followed most but not all of the recommendations made in our prior review. One of the recommendations that the Applicant did not implement was DMEPA's request that the Applicant follow the FDA/CDER Guidance for Industry (dated July 2002) titled "Inhalation Drug Products Packaged in Semipermeable Container Closure Systems", which recommends to overwrap each semipermeable container individually within the protective secondary packaging. However, the referenced listed drug (RLD) for this application, Tobi uses similar packaging (4 ampules per pouch) and the AERS search for our prior label and labeling review for this application (OSE review 2010-2309) did not identify errors related to the Tobi packaging. Therefore, we find the Applicant's proposed packaging acceptable. However, on September 6, 2012 an information request was sent to the Applicant inquiring why the Applicant decided not to follow the recommendations as requested by DMEPA. We await the Applicant's reply.

Additionally, the Applicant made changes beyond our recommendations such as changing the appearance of the proprietary and established names by changing the letter case from title to all capitals. These changes result in decreased readability of the established and proprietary names on the pouch foil and carton labeling.

5 CONCLUSION

DMEPA concludes that the proposed labels and labeling can be improved by increasing the readability of important information and by improving the instructions for use by adding illustrations and including lay-person terms.

6 RECOMMENDATIONS

Because the Applicant made additional changes beyond our recommendations, we recommend that our outstanding concerns be forwarded to the Applicant for further revisions of the labeling. Our outstanding recommendations include:

6.1 COMMENTS TO THE DIVISION

A. Full Prescribing Information - Instructions for Use

1. Revise the instructions for use to include illustrations, such as diagrams of the product and steps in the use process, to aid consumers understanding of the product. Refer to the Tobi instructions for use as an example.

6.2 COMMENTS TO THE APPLICANT

A. Foil Pouch Labeling

Principal Display Panel

1. We acknowledge that you followed our recommendation to ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10(g)(2). However you also changed the letter case from title to all capitals, which decreases readability. Change the established name statements from all capital letters to title case letters.
2. Incorporate the proprietary name “Bethkis” in title case.
3. Add the NDC number to the top portion of the labeling.

B. Carton Labeling

All Panels

1. See A1 and A2 above.
2. Revise the appearance of the NDC number from xxxxx-xxx-xx to the actual number you plan on using in the marketplace.
3. Revise the appearance of the telephone number from 1-800-xxx-xxxx to the actual number you plan on using in the marketplace.
4. The numbers expressing the strength are in different font size, specifically the 3 as compared to the zeros in 300 mg. Revise the appearance of the strength “300 mg / 4 mL” so that the zeros are the same font size as the number 3. Additionally, increase the prominence of the product strength statement.
5. Remove the bolding from the statements “For Oral Inhalation Only by Nebulizer” and “Single-Use Only, Discard Each Ampule After One Use”, because they compete for prominence with the storage statement.

C. Ampule Label

1. See A2 above.

If you have questions or need clarification, please contact OSE Regulatory Project Manager, Karen Townsend, at 301-796-5413.

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/s/

ALEKSANDER P WINIARSKI
09/11/2012

TODD D BRIDGES
09/11/2012

M E M O R A N D U M

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

DATE: November 7, 2011

TO: John Alexander, M.D., Team Leader, DAIP
Shrimant Mishra, M.D., Medical Officer, DAIP
Division of Anti-Infective Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D,
Team Leader (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Division Director (Acting)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 201820

APPLICANT: Chiesi Farmaceutici S.p.A. (Chiesi)
Via Palermo 26/A, 43122 Parma, Italy
E-mail: info@chiesigroup.com
Sponsor's Responsible Officer: Helen G. Cicirello, M.D.

DRUG: Proposed [redacted]® (CHF 1538)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Management of cystic fibrosis patients with *Pseudomonas aeruginosa*

CONSULTATION REQUEST DATE: December 13, 2010

I. BACKGROUND:

This CIS Addendum is submitted to addend the CIS for CHF 1538 entered into DARRTS on July 14, 2011 to provide supplemental information regarding the inspection of Chiesi Farmaceutici.

NDA 201820 for CHF 1538 was submitted by Chiesi Pharmaceuticals Inc. on October 22, 2010 to support a labeling claim for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. In support of the application, the sponsor submitted data from two double-blind, randomized, placebo-controlled efficacy and safety studies (CT01 and CT02) and one open-label, active-control (TOBI versus CHF 1538) comparator study (CT03). A consult from DAIOP (now DAIP) was received on December 13, 2010 for inspection of the clinical sites enrolling in the pivotal trials CT01 and CT03 in order to verify the quality of conduct of these studies for this NDA. The PDUFA date for this NDA was August 25, 2011. DSI requested foreign inspections of four sites (including Chiesi Pharmaceuticals Inc). This CIS Addendum will provide information which has become available since finalization of the CIS on July 14, 2011. There is no change in the previous conclusion regarding data integrity for the three clinical investigator sites. This findings and recommendation in this addendum pertain to the sponsor/monitor Chiesi Farmaceutici S.p.A. (Chiesi). Please see the original CIS for further background, including outlines of the protocols audited and a brief summary of study results.

II. RESULTS (by Site):

Name of CI or Sponsor Location	**Protocol #/ Site #/ # of Subjects:**	**Inspection Date**	**Preliminary Classification**	**Final Classification**
Dr. Henryk Mazurek Klinika Bronchologii I Mukowiscydozy Oddzial Terenowy Instytutu Gruzlicy I Chorob Pluc Ul. Marii Sklodowskiej – Curie 2 34-700 Rabka-Zdroj, Poland	Study CT02 Site #21 N=33 Study CT03 Site #301 N=50	March 28, 2011- April 05, 2011	NAI	NAI
Dr. Maria Trawinska Bartnicka Cystic Fibrosis Centre Specialistic Mother And Child Care Centre Polanki St. 119 80-308 Gdansk, Poland	Study CT02 Site #26 N=29 Study CT03 Site #308	April 7, 2011- April 15, 2011	VAI	VAI

Name of CI or Sponsor Location	Protocol #/ Site #/ # of Subjects:	Inspection Date	Preliminary Classification	Final Classification
	N=16			
Dr. Nikolai Kapranov The Cystic Fibrosis Department, Research Centre Of Medical Genetics Rams Matweewskaya St. 10-4-293 Moscow, Russia	Study CT02 Site #32 N=24	April 11, 2011- April 15, 2011	VAI	VAI
Chiesi Farmaceutici S.p.A. (Chiesi) Via Palermo 26/A, 43122 Parma, Italy	**Study CT02** With focus on oversight of Drs. Mazurek, Bartnicka, and Kapranov, Iwona Stelmach, Ferenc Gonczi and Maciej Kaczmarski **Study CT03** With focus on oversight of Drs. Mazurek and Bartnicka	June 27, 2011- July 8, 2011	VAI	VAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

PLEASE SEE FULL SUMMARY IN THE CIS COMPLETED JULY 14, 2011 UPDATED INFORMATION IS PROVIDED BELOW.

1. **Dr. Maria Trawinska Bartnicka**
   Cystic Fibrosis Centre
   Specialistic Mother & Child Care Centre
   Polanki St. 119
   80-308 Gdansk, Poland

   There is no change in the previous conclusion regarding data integrity. Please see full summary in the CIS finalized July 14, 2011.

2. **Dr. Henryk Mazurek**
   Klinika Bronchologii I Mukowiscydozy
   Oddzial Terenowy Instytutu Gruzlicy I Chorob Pluc
   Ul. Marii Sklodowskiej – Curie 2
   34-700 Rabka-Zdroj, Poland

   There is no change in the previous conclusion regarding data integrity. Please see full summary in the CIS finalized July 14, 2011.

3. **Dr. Nikolai Kapranov**
   Filatov Children's City Clinical Hospital #13 (current location)
   Outpatient Department
   15 Zoologicheskaya Str.
   Moscow, Russia 123242

   There is no change in the previous conclusion regarding data integrity. Please see full summary in the CIS finalized July 14, 2011.

4. **Chiesi Farmaceutici S.p.A. (Chiesi)**
   Via Palermo 26/A, 43122 Parma, Italy
   E-mail:info@chiesigroup.com
   Sponsor's Responsible Officer: Helen G. Cicirello, M.D.

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.810 between June 27, 2011 and July 8, 2011. This was a directed inspection that was concentrated on sponsor/monitor obligations as related to the conduct of Protocol DM/PR/10000/002/01 (Study CT02) and Protocol CMA-0631-PR-0010 CT03, to support a labeling claim for CHF 1538 for the management of cystic fibrosis patients with *P. aeruginosa.* The inspection covered the sponsor/monitoring responsibilities for CT02 and CT03.

During the inspection the following items were reviewed in detail: sponsor selection of monitors, monitoring plans and contracts with monitors used, and test article accountability. In addition, monitoring files for three CIs previously

inspected for conduct of these studies (Dr. Henryk Mazurek, Dr. Nikolai Ivanovich Kapranov Dr. Maria Trawinska Bartnicka) and 3 additional CIs (Dr. Kalman Gyurokovits, Dr. Alexander Chuchalin and Dr. Yarema Voznetsya) for the adequacy of sponsor/CRO oversight. There were no limitations to the inspection.

b. General observations/commentary:

There were 210 subjects enrolled into the study at the inspected clinical sites. An audit of 44 subjects' records, out of a total of 210 subjects enrolled, was conducted. Specifically, the inspection of the sponsor's site revealed that there was inadequate monitoring of the study. A Form FDA 483, Inspectional Observations, was issued to the sponsor for:

1) Failure to monitor studies; inadequate monitoring of studies [21CFR50]. For example:

   a. Respiratory function measurement input variables (i.e. age and height) entered into the spirometry software were not retained and the predicted values were inconsistent despite changes in subjects' input variables such as age and height, during Study CT02 at Site 26 (Dr. Maria Trawinska Bartnicka, Poland, n=29), Site 23 (Dr. Iwona Stelmach, Poland, n=12), Site 13 (Dr Ferenc Gonczi, Hungary, n=14) and Site 29 (Dr. Maciej Kaczmarski, Poland, n=11) This should have been identified during monitoring. At Site 26 (Dr. Maria Trawinska Bartnicka), there were duplicate height measurements, one which was recorded in the source documents during the physical examination and some data which was entered directly into the spirometer by the technician, but was not documented in the source document. For example, for Subject 26001 the height was documented to be 146 cm on 12/10/02 at Visit 1 during the physical examination. The FEV_1 % predicted normal value was recorded as 72.0%. At Visit 2, the predicted normal value was documented as 68% on 12/16/02 and 88% on 12/30/02. The same height should have been used for each visit, but there is no record of height which would have been entered in the spirometer to account for the different values.

   b. At Site 26 (Dr. Maria Trawinska Bartnicka), the input data on the CRF was height, birth date, and gender; however the FEV_1 % of Predicted Normal did not change when the input data was changed. Alternatively, in some patients, if the input did not change the output changed.

   OSI Reviewer Comments: *The CI/Sponsor submitted documentation containing the corrected FEV_1 predicted normal values and FEV_1 % of predicted normal values using the subject heights as recorded in the CRF*

from Site # 26 (Dr. Maria Trawinska Bartnicka) to the NDA. The original analysis found that in the ITT population, the changes in FEV_1 % predicted normal from baseline were significantly greater in the CHF 1538 group than in the Placebo group at all visits except Visit 5, the end of the first "OFF" cycle. The mean change from baseline to primary endpoint in FEV_1 % of predicted normal was higher in the CHF 1538 group (6.97%) than in the Placebo group (0.59%) ($p < 0.001$). The efficacy in the CHF 1538 arm on FEV_1 % of predicted normal was significantly superior compared to that of the placebo in all visits, except at Visit 5 (end of the first "OFF" cycle). The results from the reanalysis using the recalculated FEV_1 % from this site did not alter the overall conclusions of the study. Specifically for the primary endpoint, the mean change from baseline in FEV_1 % predicted at the end of the 3rd treatment cycle (Visit 8, Week 20) continued to be higher in the CHF 1538 group (7.03%) than in the Placebo group (0.58%) ($p < 0.001$). This issue was discussed with the review division Medical Officer and Team Leader. Given that recalculation of FEV_1 % from this site did not alter the overall conclusions of the study, the changes observed may not impact the review division's analysis.

The sponsor acknowledged in a letter dated July 21, 2011 that it has requested verification of the source data from two additional sties, Site #13 (Dr Ferenc Gonczi) and Site #29 (Dr. Maciej Kaczmarski) and that they plan to verify the source data against the CRFs of those sites. The sponsor also recovered the spirometer source input data for Site # 23 from Dr. Iwona Stelmach and they plan to compare the source data against the CRFs.

2) Failure to submit a protocol amendment [21CFR312.30]. There are no protocol amendments or exemptions requested for approval by the Ethics Committee to allow various sites not to perform respiratory function measurements per protocol for Study CT02. Whole body plethysmograph equipment was not available at 16 investigational sites in order to perform respiratory function measurements for Residual Volume (RV) and Total Lung Capacity (TLC) during Visits 1-9 per Section 7.105 of the protocol

OSI Reviewer Comments: *Since the wording in the study protocol, section 7.105 allows the use of a spirometer instead of whole body plethysmograph, OSI does not consider the failure to collect Residual Volume and Total Lung Capacity to be a regulatory violation. In addition, since spirometry adequately characterizes the key changes in lung function that are of interest in CF trials, the absence of whole-body plethysmograph at this site does not appear to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

c. Assessment of data integrity:

Although regulatory violations were noted, it is unlikely that they significantly impact

overall data reliability. Based on the provided Establishment Inspection Report (EIR), overall the study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

The review division may wish to consider excluding data from the sites of Drs. Stelmach, Gonczi, and Kaczmarski from the efficacy analysis for this application if the sponsor fails to submit the recalculated FEV_1 % predicted normal.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites and the sponsor/monitor were inspected in support of this application. While regulatory violations occurred at two of the three CI sites and at the sponsor Chiesi Farmaceutici S.p.A., the primary efficacy and safety data from each site appears to be reliable (with updates as noted below) to support a regulatory approval decision based upon submission of corrected information with respect to spirometry data. Please see full summary in the CIS finalized July 14, 2011 for the inspectional findings for the three clinical investigator sites. There is no change in the previous conclusion regarding data integrity for the three CI sites. The overall assessment of findings and OSI recommendations in this addendum pertain to the sponsor/monitor Chiesi Farmaceutici S.p.A..

Regulatory violations documented at Chiesi Farmaceutici S.p.A.'s site were failure to ensure proper monitoring of the study. Monitors failed to identify that respiratory function input variables (i.e. age and height) were not properly retained at the site. In addition, the predicted values were inconsistent despite changes in subjects' input variables such as age and height, during Study CT02 at Site 26 (Dr. Maria Trawinska Bartnicka), Site 23 (Dr. Iwona Stelmach), Site 13 (Dr. Ferenc Gonczi), and Site 29 (Dr. Maciej Kaczmarski).

Although Chiesi Farmaceutici S.p.A. did not adequately monitor the respiratory function input variables and predicted values at the two sites, the sponsor provided results from the reanalysis using the recalculated FEV_1 % from Dr. Maria Trawinska Bartnicka's site (Site #26). The recalculations did not alter the overall conclusions of the study. The results of the recalculation was submitted to the NDA. In addition, in a letter dated July 21, 2011, the Applicant stated that improvements to Chiesi's oversight of Clinical Research Organizations (CROs) have been implemented since the time of study CT02 including the oversight of study monitors. In addition, the sponsor's letter indicates that it has requested verification of the source data from two additional sites, Site #13 (Dr Ferenc Gonczi) and Site #29 (Dr. Maciej Kaczmarski), and they plan to verify the source data against the CRFs for those sites. The sponsor also recovered the spirometer source input data for site # 23 from Dr. Iwona Stelmach and plan to compare the source data against the CRFs. The letter from Chiesi also shows that the sponsor plans to address the above observations in an SOP on Clinical Research Organization.

In order to assess the potential impact of the data from Site #s 13, 29 and 23, on the study outcome, the review division should consider requesting that the sponsor recalculate the FEV_1 % predicted at the sites of Drs. Stelmach, Gonczi and Kaczmarski. The review division may wish to consider excluding data from Site #s 13, 29, and 23 from the efficacy analysis if the sponsor fails to submit recalculated FEV_1 % predicted normal.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

KASSA AYALEW
11/08/2011

SUSAN D THOMPSON
11/08/2011

TEJASHRI S PUROHIT-SHETH
11/08/2011

M E M O R A N D U M

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

DATE: July 7, 2011

TO: John Alexander, M.D., Team Leader, DAIP
Shrimant Mishra, M.D., Medical Officer, DAIP
Division of Anti-Infective Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D,
Team Leader (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Branch Chief (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 201820

APPLICANT: Chiesi Farmaceutici S.p.A. (Chiesi)
Via Palermo 26/A, 43122 Parma, Italy
E-mail: info@chiesigroup.com
Sponsor's Responsible Officer: Helen G. Cicirello, M.D.

DRUG: Proposed [redacted]® (CHF 1538)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Management of cystic fibrosis patients with *Pseudomonas aeruginosa*

CONSULTATION REQUEST DATE: December 13, 2010

DIVISION ACTION GOAL DATE: July 15, 2011

PDUFA DATE: August 25, 2011

I. BACKGROUND:

Chiesi Pharmaceuticals Inc. submitted a new drug application NDA 201820 for CHF 1538, on October 22, 2010 to support a labeling claim for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. In support of the application, the sponsor submitted data from two double-blind, randomized, placebo-controlled efficacy and safety studies (CT01 and CT02) and one open-label, active-control (TOBI versus CHF 1538) comparator study (CT03).

A consult from DAIOP (now DAIP) was received on December 13, 2011 for inspection of the clinical sites enrolling in the pivotal trials CT01 and CT03 in order to verify the quality of conduct of these studies for this NDA.

Study CT02: Double-blind, multinational, multicenter, randomized, placebo-controlled, parallel groups clinical trial of intermittent CHF 1538 (Tobramycin 300 mg/4 mL Inhalation Solution) or placebo in three 4-week cycles treatment, given in addition to other anti-pseudomonal treatments, in patients with cystic fibrosis (CF) and a positive culture for *P. aeruginosa*

Study CT02 is a double blind, multinational, multicenter, randomized, placebo-controlled study. There were 247 subjects enrolled in Study CT02 (161 CHF 1538, 86 placebo) with cystic fibrosis and *P. aeruginosa* infection. The objective of the study was to compare the efficacy and tolerability of inhaled aerosolized tobramycin and placebo, given in addition to other anti-pseudomonal therapies and administered via a nebulizer ("Pari Turbo Boy"', Pari, Germany), over a 24-week study period (three 4-week "on" cycles, each followed by a 4-week "off' cycle) in a b.i.d. regimen.

This study was performed at eight study centers located in Hungary, nine study centers in Poland and four study centers in Russia. At each center, the Investigator was responsible for ensuring that the investigation was conducted according to the signed Investigator Agreement, the protocol, the study procedures manuals, and Good Clinical Practice (GCP) Guidelines. The Principal Investigator at each site was to be responsible for management of the study, including maintenance of the study file and subject records, correspondence with the IRB or IEC, and completion of case report forms (CRFs).

Monitoring of Clinical Investigator (CI) sites was conducted by (b) (4)
local regional offices in Poland and Hungary and by (b) (4)

[redacted]. Chiesi Pharmaceuticals Inc. conducted three audits related to this study; two CI site audits (Dr. Mazurek and Dr. Sands in Poland) and an audit of "ITALICA study documentation", which took place at [redacted]. This audit evaluated data management functions, which according to the study report were contracted to [redacted].

Clinical Study Report CT03: A multicentre, multinational, open-label, randomized, parallel group clinical trial of Tobrineb®/Actitob®/Bramitob® (tobramycin solution for nebulization, 300 mg twice daily in 4 mL unit dose vials) compared to TOBI in the treatment of patients with cystic fibrosis and chronic infection with *Pseudomonas aeruginosa*.

Study CT03 is an open-label, multinational, multicentre, randomized, reference product controlled, parallel-group study in 320 patients with cystic fibrosis and *P. aeruginosa* chronic infection, to compare the efficacy and tolerability of 300 mg nebulized Tobrineb/Actitob®/ Bramitob® and 300 mg TOBI®, both administered via a nebulizer (Pari Turbo Boy®, Pari, Germany), over a 4-week treatment in a twice-daily regimen. During the subsequent 48-week period subjects who had a positive culture for *P. aeruginosa* at Visit 4 of the first 8-week study period and/or if deemed appropriate by the Investigators were treated with Bramitob®/Tobrineb®/Actitob® (tobramycin nebulizer solution, 300 mg twice daily in 4 ml unit dose vials), in addition to other antipseudomonal and/or standard treatments. The "on/off" phases were repeated 6 times for a total duration of 48 weeks.

This study was performed at two study centers in Hungary, eight study centers in Poland, ten study centers in Russia, nine study centers in Ukraine, two study centers in Germany, one study center in the Czech Republic, eight study centers in Spain, and three study centers in France. At each center, the Investigator was to be responsible for ensuring that the investigation was conducted according to the signed Investigator Agreement, the protocol, the study procedures manuals, and Good Clinical Practice (GCP) Guidelines. The Principal Investigator at each site was to be responsible for management of the study, including maintenance of the study file and subject records, correspondence with the IRB or IEC, and completion of case report forms (CRFs).

Monitoring of CI sites in Russia, Ukraine, Poland, Hungary, Germany, Czech Republic, and France was conducted by [redacted]). Monitoring of CI sites in Spain was conducted by [redacted] Chiesi Pharmaceuticals Inc. and [redacted] conducted audits related to this study. Chiesi conducted two audits, one of the Hungarian Trial Master File and one of a CI site (Dr. Holics, Hungary). [redacted] conducted 3 CI site audits (Dr Chuchalin in Russia and two unidentified sites in Poland).

II. RESULTS (by Site):

Name of CI or Sponsor Location	Protocol #/ Site #/ # of Subjects:	Inspection Date	Preliminary Classification	Final Classification
Dr. Henryk Mazurek Klinika Bronchologii I Mukowiscydozy Oddzial Terenowy Instytutu Gruzlicy I Chorob Pluc Ul. Marii Sklodowskiej – Curie 2 34-700 Rabka-Zdroj, Poland	Study CT02 Site #21 N=33 Study CT03 Site #301 N=50	March 28, 2011- April 05, 2011	NAI	Pending
Dr. Maria Trawinska Bartnicka Cystic Fibrosis Centre Specialistic Mother And Child Care Centre Polanki St. 119 80-308 Gdansk, Poland	Study CT02 Site #26 N=29 Study CT03 Site #308 N=16	April 7, 2011- April 15, 2011	VAI	Pending
Dr. Nikolai Kapranov The Cystic Fibrosis Department, Research Centre Of Medical Genetics Rams Matweewskaya St. 10-4-293 Moscow, Russia	Study CT02 Site #32 N=24	April 11, 2011- April 15, 2011.	VAI	Pending
Chiesi Farmaceutici S.p.A. (Chiesi) Via Palermo 26/A, 43122 Parma, Italy	**Study CT02** With focus on oversight of Drs. Mazurek, Bartnicka, and Kapranov **Study CT03** With focus on oversight of Drs. Mazurek and Bartnicka	Pending	Pending	Pending

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary

communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Dr. Maria Trawinska Bartnicka
Cystic Fibrosis Centre
Specialistic Mother & Child Care Centre
Polanki St. 119
80-308 Gdansk, Poland

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between April 7, 2011 and April 15, 2011.

This inspection covered subjects enrolled in Study CT02 (protocol DM/PR/10000/002/01) and Study CT03 (Protocol CMA-0631-PR-OO10). Subjects were enrolled in the CT02 study at this site from December 10, 2002 to November 25, 2003. There were 31 subjects screened, 29 subjects were randomized to treatment, and 29 subjects completed the CT02 study. Nineteen of the 29 randomized subject's files were reviewed for completeness and accuracy. All 29 subjects' files were reviewed for the presence of signed ICF's and to verify the primary and secondary efficacy and safety endpoints.

Subjects were enrolled in the CT03 study at this site from May 12, 2009 to March 29, 2010. There were 17 subjects screened for entry into the study, and 16 subjects were randomized to treatment. All 16 subjects that were randomized completed the initial 8 week phase of Study CT03. Eight of the 16 randomized subject's files were reviewed for completeness and accuracy. All 16 subjects' files were reviewed for the presence of signed ICF's and to verify the primary and secondary efficacy and safety endpoints.

Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

The observations noted are based on the Form FDA 483 and the EIR.

b. General observations/commentary:

There was no evidence of under reporting of adverse events or protocol deviations. The primary efficacy endpoint was verifiable for all subject records reviewed. The inspection of Dr. Maria Trawinska Bartnicka's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. For example:

i. Study CT02: The primary efficacy variable, FEV_1 expressed as percentage of predicted normal could not be verified for several instances of the lung function measurements in 21 of the 29 subjects because the predicted values remained constant despite changes in subjects' input variables, i.e. age and height, throughout the length of the study. The MES Lung Test 1000 Spirometer generates predicted results based on the input values of sex, age and height. When changes in height and age occurred, the resulting predicted values failed to change. Therefore, the predicted values were not always consistent with documented changes. Examples of inconsistencies include: Subjects #26011, #26012, #26014, and #26031.

OSI Reviewer Comments: *The CI failed to maintain adequate and accurate case histories with respect to the primary efficacy variable, FEV_1 expressed as percentage of predicted normal. The CI should have properly utilized the correct input variables (age and height) to calculate the primary efficacy variable.*

In response to the Form FDA 483 observation, the CI presented documentation (received May 4, 2011) that shows the input variables (i.e. age and height) entered into the spirometry software were not retained during Study CT02. Height measurements were taken twice; once during physical examination and once by site staff performing spirometry. The height measurement taken during the physical examination is the height recorded in the source data. The height measurement taken for the spirometry measurement was the one entered directly into the spirometer. The spirometry software used at the time did not retain and record the height measurement on the spirometry printout during the spirometry evaluation. This resulted in the discrepancy of the input variables.

The CI presented documentation containing the corrected FEV_1 predicted normal values and FEV_1 % of predicted normal values using the subject heights as recorded in the CRF. With the help of the study sponsor, Chiesi Farmaceutici, SpA., the CI presented recalculated FEV_1 % predicted values used in the reanalysis of FEV_1 % mean change from Baseline at each study visit, i.e., replacing all FEV_1 % predicted values in the original study database originating from this site while maintaining all other values of FEV_1% predicted from the other sites involved in the study. The original analysis found that in the ITT population, the changes in FEV_1 % predicted normal from baseline were significantly greater in the CHF 1538 group than in the Placebo group at all visits except Visit 5, the end of the first "OFF" cycle. The mean change from baseline to primary endpoint in FEV_1 % of predicted normal was higher in the CHF 1538 group (6.97%) than in the Placebo group (0.59%) ($p < 0.001$). The efficacy in the CHF 1538 arm on FEV_1 % of predicted normal was significantly superior compared to that of the placebo in all visits, except at Visit 5 (end of the first "OFF" cycle).

The results from the reanalysis using the recalculated FEV_1 % from this site did not alter the overall conclusions of the study. Specifically for the primary

endpoint, the mean change from baseline in FEV_1 % predicted at the end of the 3rd treatment cycle (Visit 8, Week 20) continued to be higher in the CHF 1538 group (7.03%) than in the Placebo group (0.58%) ($p< 0.001$). This issue was discussed with the review division Medical Officer and Team Leader. Given that recalculation of FEV1 % from this site did not alter the overall conclusions of the study, the changes observed may not impact the review division's analysis.

Dr. Maria Trawinska Bartnicka's response (received May 4, 2011) to the Form FDA 483 acknowledges the above observation and provided documentation containing the corrected FEV_1 predicted normal values and FEV_1 % predicted normal values using the subject heights and age as recorded in the CRF.

The EIR of the inspectional findings from Dr. Bartnicka's site indicates that the FEV_1 values for Study CT02 entered into the spirometry software were not retained. OSI made an Information Request (IR) to the applicant requesting an assessment be provided of how pervasive this type of software data retention error was across study sites that enrolled subjects in Study CT02. In addition, the applicant was asked to address how the procedure for correcting the FEV_1 predicted values and FEV_1% predicted values was validated and to provide assurance that the revised submitted values are accurate. This information will be presented and discussed in Part III below.

ii. The tabulated pulmonary function tests Study CT02, i.e., FEV_1, FVC, and FEF expressed as a percentage of predicted normal were incorrectly rounded to whole numbers while the protocol defined case report forms provided for the FEV_1, FVC, and FEF (% of predicted normal) values to be recorded to the tenth digit or one number to the right of the decimal point. Specifically:

1) The FEV_1, FVC, and FEF (% of predicted) for Subject #26012 were reported as 85, 81, and 95% respectively at Visit 8. The actual % of predicted values were 85.4, 80.7, and 94.9%.

2) The FEV_1, FVC, and FEF (% of predicted) for Subject #26014 were reported as 77, 87, and 52 respectively at Visit 8. The actual % of predicted values were tabulated as 76.9, 86.7, and 52.3%.

OSI Reviewer Comments: *The CI failed to maintain adequate and accurate case histories with respect to the results of the pulmonary function tests (FEV_1, FVC, and FEF) expressed as percentage of predicted normal values. The CI incorrectly rounded the values to whole numbers while the protocol defined case report forms provided for the FEV_1, FVC, and FEF (% predicted normal) values to be recorded to the tenth digit or one number to the right of the decimal point.*

Dr. Maria Trawinska Bartnicka's response (received May 4, 2011) to the Form

FDA 483 acknowledges the above observation and describes a plan to implement corrective actions to prevent incorrect rounding of values to whole numbers in future studies. Rounding to the whole number for FEV_1 is unlikely to significantly impact the data.

There were no Form FDA 483 observations made related to CT03.

c. Assessment of data integrity:

Regulatory violations were observed at this site, including failure to retain source data in the spirometry software during Study CT02. Availability of the same information (subject height and age) in the case report form allowed recalculation of the FEV_1 % predicted which do not appear to have significantly altered the efficacy conclusions from this study. In the Applicant's response dated June 28, 2011, to OSI's Information Request, the Applicant submitted a revised recalculation of the efficacy outcome, which still showed no significant effect. The methodology used by Chiesi appears to be valid. The data are considered reliable in support of the application.

2. Dr. Henryk Mazurek
Klinika Bronchologii I Mukowiscydozy
Oddzial Terenowy Instytutu Gruzlicy I Chorob Pluc
Ul. Marii Sklodowskiej – Curie 2
34-700 Rabka-Zdroj, Poland

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between March 28, 2011 and April 05, 2011. This inspection covered Study CT02 (Protocol DM/PR/10000/002/01) and Study CT03 (Protocol CMA-0631-PR-OO10).

Subjects were enrolled in Study CT02 study at this site from November 29, 2002 to July 21, 2004. There were 41 subjects screened for entry into the study, and 33 subjects were randomized to treatment. All 33 subjects that were randomized completed the CT02 study. Seventeen of the 33 randomized subject's files were reviewed for completeness and accuracy. All 33 subjects' files were reviewed for the presence of signed ICF's and to verify the primary and secondary efficacy and safety endpoints.

Subjects were enrolled in Study CT03 at this site from April 20, 2009 to February 22, 2011. There were 62 subjects screened for entry into the study, and 50 subjects were randomized to treatment. Forty-nine of the 50 randomized subjects completed the initial phase of Study CT03. Twenty-five of the 50 randomized subject's files were reviewed for completeness and accuracy. All 50 subjects' files were reviewed for the presence of signed ICF's and to verify the primary and secondary efficacy and safety endpoints.

Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

There was no evidence of under reporting of adverse events or protocol deviations. The primary efficacy endpoint was verifiable for all subject records reviewed.

b. General observations/commentary:

The inspection of Dr. Henryk Mazurek's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. Assessment of data integrity:

Based on inspectional findings and the observations noted, efficacy and safety data obtained from this site are considered reliable.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. Dr. Nikolai Kapranov
Filatov Children's City Clinical Hospital #13 (current location)
Outpatient Department
15 Zoologicheskaya Str.
Moscow, Russia 123242

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between April 11, 2011 and April 15, 2011. This inspection covered Study CT02 (Protocol DM/PR/10000/002/01).

At this site, a total of 31 subjects were screened, 24 subjects were enrolled, and 21 subjects completed the study. Subject #3206 was withdrawn due to SAEs (a reaction to the drug both during and after administration). Two other subjects withdrew: Subject #32004 was a minor whose parents withdrew consent and Subject #32025 withdrew because his parents thought he was in the placebo group due to poor response and wanted him to get the actual drug. During the inspection primary efficacy endpoint data (FEV_1 values) and informed consent forms for all study subjects were evaluated. The primary efficacy endpoint data were verifiable.

Comprehensive subject file reviews were performed for a total of 12 study subjects. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target

disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

There was no evidence of under reporting of adverse events or protocol deviations. The primary efficacy endpoint was verifiable for all subject records reviewed.

b. General observations/commentary:

The inspection of Dr. Nikolai Kapranov's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

1. Failure to prepare and maintain adequate and accurate records. For example :

i. In nearly all cases reviewed, the "Treatment No." of the study drug or placebo kits dispensed was not recorded at the time of dispensing. Records completed at the time of dispensing, including physician notes (visit notes) and subsequently, line entries in the subject specific Drug-Dispensing Logs, failed to include the "Treatment No." of the boxes or bags dispensed. Thus, study records do not allow confirmation that the correct treatments (drug or placebo) were dispensed to subjects. Protocol Section 6.301 states that the external box (70 vials per box), and each 5-vial interior bag, contain labeling that includes a "Treatment No." (1 to 360) and a "Cycle" (1, 2 or 3). By study design, the "Treatment No" on the boxes and bags corresponded to the randomization numbers of the subjects for whom the treatments were intended. The "Cycle" numbers (1-3) corresponded to the start of the treatment cycle at which the boxes were to be dispensed. In most records reviewed, dispensing records (physician visit notes) state that 70 vials of study drug were dispensed, but fail to specify the "Treatment No."or cycle number that appeared on the boxes and bags that contained the vials.

***OSI Reviewer Comments**: In response to the Form FDA 483 observation, the CI submitted pages from the drug dispensing log provided by (b) (4) which contain the randomization number (which is identical to the "Treatment No") that indicates medication was dispensed to subjects in Study CT02.*

The CI also provided an example of the Drug Dispensing Log, which shows the randomization number (that is also the "Treatment No."*) and the cycle in which the treatment was dispensed. The EIR also includes a tear-off label from each patient kit (containing the randomization/*"Treatment No."*), which was affixed to the first page of the subject's CRF.*

The data presented by Dr. Kapranov in his response letter contains adequate documentation to confirm that study drug correctly dispensed to subjects, as identified in the data listings. Therefore, this observation does not impact data reliability.

ii. For Subject #32006, study records and source documents fail to include source documents, including physician visit notes, lab test results (hematology, chemistry, sputum analysis), and pulmonary function test results including spirometry readings were missing. The original study file for this subject was given to the subject five years after the study was completed, and it was reportedly lost in a fire.

OSI Reviewer Comments: *The CI's response (dated April 5, 2011) to the Form FDA 483 acknowledges the above observation. To prevent this from happening in the future, the CI has instituted a Clinical Study Conducting Policy to ensure that original documents will never be out of the control of the Principal Investigator in the future.*

Corrective actions to prevent similar occurrences in future studies appear to be adequate, and this isolated finding is unlikely to impact overall data reliability.

iii. Dr. Kapranov failed to retain control of source records. Two additional study subjects (#32012 and #32018) were given their original medical files, including source documentation, which were retained outside of the control of the Principal Investigator. Subjects #32012 and #32018 were given their medical files, containing source documentation, in March 2008. These files were not returned to the Principal Investigator until February, 2011 in anticipation of this FDA inspection.

OSI Reviewer Comments: *The CI response (dated April 5, 2011) to the Form FDA 483 acknowledges the above observation. Although the records were out of the control of the Principal Investigator for a period of time, the records were later retrieved for Subjects #32012 and #32018. According to the CI, the retrieved records were unaltered and complete.*

While it is common practice for patients to maintain their own medical records in some regions, given their participation in this clinical study, the clinical investigator should have retained at least copies of relevant source documents with the study records for all subjects. While the above finding is a regulatory violation, as records were recovered, the finding is unlikely to impact overall data reliability. Corrective actions to prevent similar occurrence in future studies proposed by the CI appear to be adequate. No significant deficiencies were noted with the returned source records and data listings.

iv. Study records fail to identify who collected the required blood samples throughout the study, and source document visit records (including physician notes) do not indicate that blood samples were collected.

OSI Reviewer Comments: *The CI response (dated April 5, 2011) to the Form FDA 483 acknowledges the above observation.*

The study delegation log does not list the nurse who collected blood samples for the

study. However, exhibits contained in the EIR demonstrate that laboratory results from the hospital laboratory exist, which demonstrates that blood samples were collected. In his response letter dated April 5, 2011, the CI states that he has instituted a Clinical Study Conducting Policy to ensure all study staff and their responsibilities are identified in the study delegation log.

While the above finding is a regulatory violation, the observation does not significantly impact overall data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

v. There is no record of any study-specific training provided to nurses who collected blood samples, although this was the first study at Dr. Kapranov's site that required use of vacutainer tubes for the collection of blood samples.

OSI Reviewer Comments: *The CI response (dated April 5, 2011) to the Form FDA 483 indicates that the study nurse had prior training regarding the use of vacutainers. Therefore, the observation does not appear to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

vi. Review of source data values for the primary efficacy parameter FEV_1 against values recorded in the CRF and NDA data listings revealed four data discrepancies as follows:

(1) Subject #32028, Visit 7: The source data for FEV_1 shows value of 1.12; CRF & CSR listing shows value of 1.09;
(2) Subject #32027, Visit 5: The source data for FEV_1 shows value of 1.08; CRF & CSR listing show values of 1.07;
(3) Subject #32031, Visit 7: The source data for FEV_1 shows value of 3.27; CRF & CSR listing show values of 2.82;
(4) Subject #32031, Visit 2: The source data for FEV_1 shows value of 2.60; CRF & CSR listing show values of 2.58

OSI Reviewer Comments: *Source data and CRF values should have been recorded accurately. An investigator is required to ensure the accuracy of the data in the CRF and all required reports.*

Although the clinical investigator failed to adequately document the FEV_1 values according to the investigational plan, which is a regulatory violation, this observation had impact on a small percentage of the values from this site making it unlikely that the observed discrepancies significantly impacted analyses or overall data reliability. This issue was discussed with the review division Medical Officer and Team Leader and they concurred with this assessment.

2. Failure to ensure the study was conducted in accordance with the general investigational plan and protocol.

For all study subjects, the CI did not measure and report Residual Volume and Total Lung Capacity values as required by Section 7.105 of the protocol. It was known at the start of the study that the laboratory used by the site to perform lung function testing did not have the equipment necessary (whole-body plethysmograph) for the measurement of Residual Volume or Total Lung Capacity. There is no record of an exemption from the protocol requirement for this test being requested by the site or provided by the sponsor. Although this deviation from the protocol was documented in the CRA's initiation visit report, there is no record of notification to the Ethics Committee or notification to the FDA prior to submission of the clinical study report regarding this protocol deviation.

OSI Reviewer Comments: *Study CT02 protocol, section 7.105, states "A self-calibrated spirometer* ***and/or*** *a whole body plethysmograph will be used for all respiratory function measurements at the clinic visits." The CI response (dated April 5, 2011) indicates that the CI interpreted the* ***"and/or"*** *statement to mean that Residual Volume and Total Lung Capacity were optional. Since the wording in the study protocol, section 7.105 allows the use of a spirometer instead of whole body plethysmograph, OSI does not consider the failure to collect Residual Volume and Total Lung Capacity to be a regulatory violation. In addition, since spirometry adequately characterizes the key changes in lung function that are of interest in CF trials, the absence of whole-body plethysmograph at this site does not appear to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

c. Assessment of data integrity:

Although regulatory violations were observed at this site, it is unlikely based on the nature of the violations and the availability of alternative source documentation to confirm subject dosing, that they significantly affect the overall reliability of safety and efficacy data from the site. The data are considered reliable in support of the application.

4. Chiesi Farmaceutici S.p.A. (Chiesi)
Via Palermo 26/A, 43122 Parma, Italy
E-mail:info@chiesigroup.com
Sponsor's Responsible Officer: Helen G. Cicirello, M.D.

a. What was inspected?

This inspection is pending.

b. General observations/commentary:

This inspection is pending.

c. Assessment of data integrity:

This inspection is pending.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. While regulatory violations occurred at two of the three sites, primary efficacy and safety data from each site appears adequately reliable (with updates as noted below) to support a regulatory approval decision.

The inspections documented regulatory violations at Dr. Bartnicka's site involving inadequate recordkeeping. FEV_1 expressed as a percentage of predicted normal was calculated incorrectly because the required input variables (age and height) were not appropriately changed in at least one instance during the study in 21 of the 29 subjects. Dr. Bartnicka responded with a recalculation of FEV_1 using appropriate input data. The resultant recalculated FEV_1s did not result in alteration in the conclusions of the study. The sponsor also provided an adequate response to queries regarding validation methods for recalculation of FEV_1 % predicted. Although, several regulatory violations were observed at Dr. Maria Trawinska Bartnicka's site, the data from Dr. Bartnicka's site appear generally reliable. The preliminary classification for this inspection is Voluntary Action Indicated (VAI).

Regulatory violations documented at Dr. Kapranov's site include inadequate recordkeeping and failure to follow the protocol. Although the Treatment No. of the study drug was not recorded at the time of dispensing, the Clinical Investigator provided pages obtained from (b) (4) which contained the randomization number (identical to the Treatment No.) which documents that subjects actually received study drug. The remainder of the valid observations at Dr. Kapranov's site do not appear to significantly impact data integrity or subject protection. The preliminary classification for the this inspection is VAI.

The inspection of Dr. Mazurekis' site did not reveal regulatory violations and preliminary classification for this inspection is No Action Indicated (NAI).

OSI submitted an Information Request (IR) to the Applicant requesting that they provide an assessment of how pervasive this type of software error (failure to retain source data) identified at Dr. Bartnicka's site was across Study CT02 study sites. In a letter dated June 28, 2011, the Applicant provided a response to the IR. The software error identified during the inspection of Dr, Bartnicka's site was an issue at only one additional site of the 21 sites enrolling in Study CT02. Dr. Iwona Stelmach's site (Site #23) in Poland also had software which did not retain the source date (subject height and age). Dr. Stelmach screened 12 subjects and enrolled 11 for CT02 study. Although the number of subjects enrolled at this site is small, the review division may wish to consider requesting that the sponsor recalculate the FEV_1 % predicted at Dr. Stelmach's site based on case report form source data (subject height and age) in order to assess the potential impact on study outcome.

Follow-Up Actions: The inspection of the sponsor, Chiesi Farmaceutici S.p.A. (Chiesi), is pending. The observations for Dr. Mazurek are based on preliminary communications with the FDA Field investigators. A CIS addendum will be generated after receipt of the EIR from the sponsor inspection and Dr. Mazurek.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

KASSA AYALEW
07/11/2011

SUSAN D THOMPSON
07/14/2011

TEJASHRI S PUROHIT-SHETH
07/14/2011
On behalf of

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Anesthesia and Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Infection Control and Dental Device
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

NDA 201-820 – Regulatory Device Consult

Date: June 10, 2004

To: Mr. Carmen DeBellas, Regulatory Project Manager (OND/OAP/DAIOP)

From: Mr. Sugato De, M.S., Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer

Applicant: Chiesi Pharmaceuticals Inc.

Product Name: Tobramycin 300 mg/4mL Solution (CHF 1538)

Indication: Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged six years and older.

Executive Summary

In NDA 201-820, Chiesi Pharmaceuticals has proposed a novel formulation of inhaled tobramycin (Tobramycin 300 mg/4 mL Inhalation Solution, hereafter referred to as CHF 1538). The formulation is composed of tobramycin, sulfuric acid, and sodium chloride in aqueous solution, using water for injection. The preservative-free sterile inhalation solution formulation has been developed for use in the treatment of pseudomonal pulmonary infections.

In this regulatory consult, the sponsor has provided a summary of a variety of studies intended to validate the in vitro performance of tobramycin inhalation solution. From the information provided for review, it appears that the intended to-be-marketed combination product is the proposed tobramycin solution, along with the either the Pari LC Plus Nebulizer or the (b) (4). The proposed compressor for both nebulizers is the Vios Compressor. However, the clinical studies for the combination product were done using the new solely the Pari LC Plus Nebulizer and the TurboBoy N and S compressors.

The reviewing team in the Center for Drug Evaluation and Research (CDER) has requested feedback regarding the sponsor's proposal for a bridging study between the to-be-marketed combination product and the product tested in clinical studies.

RECCOMENDATION: At this stage of review, it is unclear whether in vitro bridging data between the to-be-marketed combination product and the product tested in clinical study will be sufficient to justify not providing additional clinical data for the to-be-marketed version. Depending on such factors as disease progression, patient age and weight, targeted patients may have a range of breathing patterns. Individualized breathing patterns influence particle motion in the airways, affecting deposition of the drug product irrespective of particle size, nebulization time, flow rate etc. Accordingly, in vitro tests can only mimic a limited number of representative conditions, and does not account for variability between patients or device usability. Apart from this, the in vitro study data provided for review at this stage of review are not sufficient and require several clarifications.

Recommended CDRH Clinical Hold Issues:

1. In the original NDA submission, it appears that a variety of in vitro tests have been performed to create a bridge between the to-be-marketed version of the combination product and the product tested in the clinical trial for Tobramycin 300 mg/4 mL Inhalation Solution (CHF1538). Please note that in vitro data alone may be insufficient to provide a reasonable assurance of safety and efficacy. Specifically, the results of the studies cannot be adequately defined across the range of patients with chronic pulmonary infection due to *Pseudomanas aeruginosa.* Depending on such factors as disease progression, patient age and weight, targeted patients may have a range of breathing patterns. Individualized breathing patterns influence particle motion in the airways, affecting deposition of the drug product irrespective of particle size, nebulization time, flow rate etc. Accordingly, in vitro tests can only mimic a limited number of representative conditions, and does not account for variability between patients or device usability. For example, a delay between device actuation and inhalation may significantly reduce delivered dose. Please provide a scientific analysis of (1) the effect of variable breathing patterns on drug deposition in the patient airway and (2) the effect or a mistimed inhalation in regards to device actuation.

2. An adequate description of the proposed devices has not been provided for review. Please provide a separate device module for the proposed NDA incorporating all descriptive information for all referenced nebulizers and compressors, and all relevant performance data. In addition, please identify all models, device accessories and relevant 510(k) application numbers for each device. Please include the following descriptive information in the device module:

    a. Provide a tabular summary of all design and specification differences between (1) the Pari LC Plus Nebulizer and (b) (4) and (2) the TurboBoy S Compressor, Turbo Boy N Compressor and the Vios Compressor. Please provide a summary analysis of the effect of each noted design difference on the output specifications for the device.
    b. Please provide engineering drawings for each proposed device, including depictions of each device component. Please specifically cite the inner dimension of the primary actuator orifice and describe the orientation of the actuator in relation to the patient delivery port.
    c. Identify all patient interface accessories (i.e., tee adapter, mouthpiece, mask) and provide engineering drawings which show any breathing holes and/or valves.
    d. Illustrate and explain the breathing gas path, including all valves and orifices, during inhalation and exhalation.
    e. Please provide a list of all device components. Indicate whether each is intended for a single-use (disposable), single-patient reuse or multiple-patient reuse, and ensure that this information appears in the labeling for your device.
    f. Please provide a shelf-life specification for each of the proposed devices and either cite or provide the corresponding test reports.
    g. Provide a summary document detailing the use of the proposed devices with Tobramycin 300 mg/4mL solution (CHF1538). Specifically, please describe how the drug is loaded into the device, and provide drug-specific instructions for use in terms of device actuation. In addition, please summarize the dosage cycles for the drug (delivered dose per actuation, actuations per treatment, treatments per day etc.).

3. At the current stage of review, adequate comparative particle characterization data has not been provided for review for the proposed to-be-marketed (TBM) combination product and he product tested in clinical trial (CT). While some relevant data is referenced, the overall methodology, procedures used and statistical analyses applied require further clarification. Please note that in order to create an in vitro bridge between these two device configurations, comparative data must be comprehensive and have a sufficient level of statistical significance. The Center for Devices and

Radiological Health (CDRH) recommends that you perform a side-by-side particle characterization assessment for the to-be-marketed device and the device configuration used in the clinical trial incorporating the following:

a. Pari LC Plus Nebulizer, TurboBoy S Compressor, CHF 1538 (CT Configuration 1)
b. Pari LC Plus Nebulizer, TurboBoy N Compressor, CHF 1538 (CT Configuration 2)
c. Pari LC Plus Nebulizer, Vios Compressor, CHF 1538 (TBM Configuration 1)
d. [redacted] (b) (4)

Please note that if the particle characterization data for TBM Configuration 2 is not substantially equivalent to the two clinical configurations, additional in vitro data (e.g. [redacted] (b) (4) [redacted] (b) (4)) may be required to assess the source of the differences. Also, please note that CDRH does not consider data collected for the [redacted] (b) (4) compressor critical information for the bridge between the to-be-marketed device and the devices used in the clinical trials.

CDRH evaluates the equivalent performance of nebulizers via comparative particle characterization data with a cascade impactor consisting of at least six stages (i.e. Next Generation Cascade Impactor). Laser diffraction is currently not accepted as a standalone method of particle characterization due to concerns regarding reproducibility, specificity, and resolution. Please provide particle characterization data for each of the four device configurations cited above with the proposed formulation of tobramycin (CHF 1538) using the drug's labeled concentration, dose volume and salt content. Note that each run should continue until the nebulizer is empty, as indicated by sputtering (i.e., erratic aerosolization). In addition, if the specified nebulizers operate over a range of flow rates, it is recommended that data be collected at the minimum and maximum flow rates allowable. Test reports should include the following:

a. The original nebulizer dose volume in milliliters of drug.
b. The amount of drug in micrograms recovered on each impactor plate, throat, and outlet filter.
c. The dead volume in micrograms (the amount of drug remaining in the medication cup when sputtering begins and treatment ends).
d. The drug mass recovered in the cascade impactor in the respirable size range (i.e., [redacted] (b) (4) or [redacted] (b) (4) microns, depending on the type of impactor used) expressed as a percent of the total drug mass in the nebulizer cup.
e. The mass median aerodynamic diameter (MMAD- the diameter above and below which lies 50% of the mass of the particles) of the particles recovered in the impactor.
f. The geometric standard deviation of the MMAD.

4. In order to adequately evaluate substantial equivalence, sufficient data must be provided to assess potential sources of variability in terms of particle size, total emitted mass and respirable mass that may be attributable to the device. Please note that an adequate number of device samples should be tested in order to assess potential sources of inter-sample variability (drug batch, nebulizer and compressor batches, and manufacturing site etc.). Also, in order to assess intra-sample variability, please provide data demonstrating that single sample of each of the two to-be-marked configurations can deliver the prescribed dose of the proposed drug in a repeatable manner over the intended number of actuations. For each of the two to-be-marketed device configurations, please provide sufficient data to demonstrate that each is able to deliver the prescribed dose in a repeatable manner irrespective of potential sources of inter-sample variability. These data are required to demonstrate that the dosing specifications in your labeling are validated to a specified level of statistical confidence. CDRH recommends that you consider the following recommendations in regards to evaluating potential sources of variability for the proposed combination product:

a. Please provide data demonstrating that an individual sample of each of the two proposed device configurations will consistently deliver a specified dose for each medication tested. In doing so, please validate dose specifications in terms of particle size, total emitted mass, and respirable mass. These data are intended to demonstrate dose repeatability. In your test report, please note the number of runs that were used for each individual device sample-drug combination, and provide a statistical justification explaining why this number is sufficient to validate the dose specifications in your labeling.

b. Please provide data characterizing the potential affect of inter-sample variability on the dose specifications in your labeling. Please specify the number of device samples that were used in your performance tests, and provide a statistical analysis explaining why this number of samples is sufficient to demonstrate with an appropriate level of confidence that (1) variability in individual device samples do not noticeably affect the dosing specifications of the proposed device and that (2) develop confidence for particle specifications overall, irrespective of inter-sample variability.

c. In analyzing the results of the tests cited above, please provide a justification of why the levels of variability shown are appropriate for the use of the devices in delivering the proposed drug formulation.

5. CDRH believes that your device labeling is an essential component in communicating the aerosolized therapy dosing specifications of your proposed device. Accordingly, please include the following information in your labeling and provide copies of all updated documentation. It may be appropriate to include a separate device package insert describing drug-specific instructions for use, relevant warnings and cautions, and the summary of measured particle specifications. Please note that each specification listed in the labeling should have an appropriate level of confidence as demonstrated by your performance testing.

a. For each individual drug in your performance testing, please update your proposed labeling with mass-median aerosol diameter (MMAD), total delivered dose, total respirable dose, respirable fraction and geometric standard deviation (GSD).

b. For each specification identified above, please a specify range of values at specified confidence interval based on statistical analysis of the observed data in your performance testing. For each range of values, please specify the total number of masks, nebulizers, and sample data points used to determine the specified confidence interval.

c. We recommend that you characterize particle size using three categories: course particles, fine particles, and extra-fine particles. As a function of the total dose delivered, please include specifications for the total mass and the fraction of each of these size ranges.

Additional Comments:

Please note that if the clinical study performed is sufficient for a complete evaluation of safety and efficacy, additional comparisons between the approved tobramycin formulation (TOBI® Tobramycin Inhalation Solution) and the proposed formulation (CHF 1538) may not be essential. If an in vitro bridge to the originally approved TOBI® formulation is required for review from a clinical perspective, it is unclear how this may be accomplished using the proposed devices. The proposed device configuration is not intended to deliver the original TOBI® formulation, and the currently approved device configuration for TOBI® (Pari LC Plus w/ Devilbiss Compressor) was never intended to deliver the new formulation. While output from the two device configurations may be equivalent, it may not be possible to predict efficacy because in vitro testing may not adequately predict the distribution of the drug within the airways.

DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date	04/05/11
To	Shrimant Mishra, MD, Medical Officer Division of Anti-Infective and Ophthalmology Products
From	Robert Lim, MD, Medical Officer Division of Pulmonary and Allergy Products, HFD-570
Through	Anthony G. Durmowicz, MD, Medical Team Leader Division of Pulmonary and Allergy Products, HFD-570
Through	Badrul Chowdhury, M.D. Ph.D., Director Division of Pulmonary, Allergy, and Rheumatology Products, HFD-570
Subject	Medical Officer Consultation: DPARP review and comment on the necessity of further clinical/in vitro testing to support the use of a different nebulizer/compressor system to deliver CHF 1538, an inhaled tobramycin product for patients with Cystic Fibrosis.

General Information

NDA #	NDA 201820
Sponsor	Chiesi Pharmaceuticals
Drug Product	Tobramycin (inhaled, 300mg/4mL)
Requested from	Shrimant Mishra, MD, Medical Officer Division of Anti-Infective and Ophthalmology Products
Date of Request	January 25, 2011
Materials Reviewed	Consultation Request; clinical study reports for protocols CT01, CT02, and CT03; quality studies from 12/14/2010

1. Background

The Division of Anti-Infective and Ophthalmology Products (DAIOP) has requested that the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) comment on NDA 201820 submitted by Chiesi Pharmaceuticals for CHF 1538, an inhaled tobramycin product for use on an alternating month basis in Cystic Fibrosis (CF) patients. In the submitted application, the sponsor has included 2 randomized, placebo controlled, double-blind, trials, CT01 (28 day duration) and CT02, (6 month duration) and one open label active controlled trial, CT03 (28 day duration). Both CT01 and CT02 delivered the medication using the PARI TurboBOY compressor and LC Plus nebulizer. Trial CT03 used a PARI Boy N compressor and LC Plus nebulizer. Trials CT01 and CT02 showed improvement in percent predicted FEV-1 from baseline, as compared to placebo controls. Trial CT03 demonstrated that the test drug was non-inferior to TOBI, an FDA approved inhaled preparation of tobramycin, based on a noninferiority margin of 4.5% in change from baseline in FEV-1. A problem with the program is that the compressors used in these studies are not available in the U.S. and have not been used in any of the CHF 1538 clinical trials. In addition, the nebulizer manufacturer PARI, may also be phasing out the LC Plus nebulizer. As a result, for the U.S. product, the sponsor is planning to market the CHF 1538 for use with a compressor/nebulizer system that was not used in any of the CHF 1538 clinical studies (the PARI Vios compressor and either the LC Plus or (b) (4) (b) (4)). In order to justify the change in the device, the sponsor has conducted some *in vitro* testing to assess how the compressors and nebulizers perform in combination with each other.

In addition to changing the delivery system, the sponsor has also changed the osmolality of the test product late in the course of the CHF 1538 development program. The osmolality of the drug used in pivotal trials CT01 and CT02 ((b) (4) mOsmoles/kg) differs from that used in CT03 ((b) (4) mOsmoles/kg). The formulation in the CT03 trial is closer to the planned TBM product ((b) (4) mOsmoles/kg). Due to these issues, DAIOP has asked DPARP the following specific questions:

1. Are the *in vitro* studies alone enough to assess the performance/comparability of these devices/device combinations? Do further clinical or further in-vitro studies need to be conducted?
2. To what extent do such osmolality changes affect the interpretation of the submitted *in vitro* data?

DAIOP would also welcome input regarding 3 specific aspects of the clinical trials. These are as follows:

3. Assessing the use and timing of concomitant CF specific medications and their potential impact on interpreting the study results.
4. Evaluating how to best establish baseline pulmonary function testing when multiple baseline measurements are taken.
5. Evaluating how the timing of PFT measurements can affect interpretation of results.

Below are DPARP's responses to the above questions and input regarding the clinical trials:

2. Response to Questions/Comments:

Question 1: Are the *in vitro* studies alone enough to assess the performance/comparability of these devices/device combinations? Do further clinical or further in-vitro studies need to be conducted?

DPARP response to question 1:
No, in our opinion *in vitro* studies alone are not an acceptable means to bridge clinical safety and efficacy findings from one drug-device combination product to another. Changing the compressor/jet nebulizer system for an inhaled drug/device combination can significantly affect the dosing, delivery, and absorption of the drug and these differences cannot be predicted by *in vitro* testing alone. This is especially true in patients with chronic lung disease, who may have abnormal breathing patterns, ventilation, and/or flow rates. As such, DPARP stresses to IND Sponsors that pivotal studies be performed using the to-be-marketed (TBM) drug/device combination.

Question 2: To what extent do such osmolality changes affect the interpretation of the submitted *in vitro* data?

DPARP response to question 2:
Changes in osmolality of an inhaled drug may affect the interpretation of the submitted *in vitro* data, depending on the magnitude of the changes. Ideally, any *in vitro* testing should be performed using the same formulation as the TBM product. Significant changes in osmolality may also affect the clinical safety/tolerability/efficacy profile. This further underscores the need for further clinical testing.

DAIOP comment 3: Assessing the use and timing of concomitant CF specific medications and their potential impact on interpreting the study results.

DPARP response to comment 3:
Usage and timing of concomitant CF medications could potentially impact the study results. In general, as a serious disease with no treatments that directly address the chloride transport defect that causes the clinical manifestations of CF, new investigational therapies are given in addition to what is considered "standard of care." These "standard of care" therapies may differ based on when and where the studies were conducted. For example, the low rate of DNase (a drug considered as standard of care for CF patients in the United States) usage patients in study CT01 may be responsible for the greater improvement in FEV1 observed in that trial compared to studies CT02 and CT03. With regard to concomitant medications allowed in the studies, all used as CF therapies had to be started 4 weeks prior to study entry, and kept at a constant dose during the study period. While it is possible that 4 weeks may not be enough time for some concomitant medications to reach maximal therapeutic effect, the inclusion of a placebo/active

comparator arm for comparison should minimize the impact of concomitant medications on interpretation of the study results.

With regard to the timing of administration of concomitant CF medications, there is no evidence strongly supporting any specific order of medication administration (Flume PA, *et al* 2007). Despite this, the CF community has published guidelines on the ordering of inhaled therapies (antibiotics, mucolytics such as hypertonic saline and DNAse, ICS, etc.) and other therapies, such as chest physiotherapy, based on the theoretical benefit. As ordering of therapies could theoretically impact study results, the clinical trials should specify not only which concomitant therapies are allowed but the order in which they are to be administered.

DAIOP comment 4: Evaluating how to best establish baseline pulmonary function testing when multiple baseline measurements are taken.

DPARP response to comment 4:
In general, when "change from baseline" in a pulmonary function parameter is used as a clinical efficacy endpoint in a clinical trial, the definition of how the baseline measurement is defined must be pre-specified in the protocol and statistical analysis plan. In the majority of trials, the baseline parameter is the pulmonary function measurement taken closest to the actual first dose of the study drug. If there is adequate justification that pulmonary function measurements could vary significantly over a relatively short period of time, then one could consider the averaging of several determinations taken over a brief period of time as the baseline. However, this determination should be justified and prespecified and not arrived at based on post hoc analyses of the study results.

DAIOP comment 5: Evaluating how the timing of PFT measurements can affect interpretation of results.

DPARP response to comment 5:
Timing of PFT measurements can affect interpretation of results. In general, pulmonary function, as determined by spirometry is at its nadir early in the morning and improves through the day. When used as a major efficacy endpoint, pulmonary function should be assessed at about the same time of the day.

Additional Comments:

To ensure consistency, in general, *in vitro* determinations conducted for comparative purposes should be conducted at the same time, on the same machinery using the same formulation as that used in clinical trials.

References:

Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines Chronic Medications for Maintaenance of Lung Health. Am J Respir Crit Care Med 2007; 176:957–969.

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

/s/

ROBERT H LIM
04/05/2011

ANTHONY G DURMOWICZ
04/05/2011

BADRUL A CHOWDHURY
04/05/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 201820 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Tobramycin 300 mg/4mL Inhalation Solution		
Applicant: Chiesi Pharmaceutical, Inc. Agent for Applicant (if applicable):		
Date of Application: 10/22/10 Date of Receipt: 10/25/10 Date clock started after UN:		
PDUFA Goal Date: 8/25/11	Action Goal Date (if different):	
Filing Date: 12/24/10	Date of Filing Meeting: 12/10/10	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): management of cystic fibrosis patients with *P. aeruginosa*		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) X 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): 72,068	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	x			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
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 is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		x		
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)]?** ***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).*		x		
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*** **If yes**, please list below:		x		

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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		x		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		x		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	x			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, 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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**x**			
Index: Does the submission contain an accurate comprehensive index?	**x**			
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:	**x**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

x legible x English (or translated into English) x pagination x navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	x			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	x			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&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…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	x			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**x**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	x			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	x			
If a request for full waiver/partial waiver/deferral is included, 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) ***If no, request in 74-day letter***	x			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		x		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	x			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		x		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	x			
Is the PI submitted in PLR format?[4]	x			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	x			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	x			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	x			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	x			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	x			CDRH
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		x		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10/19/05	x			

If yes, distribute minutes before filing meeting				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		x		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/5/11

BLA/NDA/Supp #: 201820

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME : tobramycin

DOSAGE FORM/STRENGTH: 300 mg/ 4mL Inhalation Solution

APPLICANT: Chiesi Pharmaceuticals, Inc.

PROPOSED INDICATION: Management of Cystic Fibrosis patients with *P. aeruginosa*

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Carmen DeBellas	Y
	CPMS/TL:	John Alexander	Y
Cross-Discipline Team Leader (CDTL)	John Alexander		Y
Clinical	Reviewer:	Shrimant Mishra	Y
	TL:	John Alexander	Y
Clinical Microbiology (*for antimicrobial products*)			
	Reviewer And TL:	Frederic Marsik	Y

Clinical Pharmacology	Reviewer:	Yongheng Zhang	Y
	TL:	Charles Bonapace	Y
Biostatistics	Reviewer:	Thamban Valappil	Y
	TL:	Mark Gamalo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wendelyn Schmidt	Y
	TL:	Amy Ellis	Y
Product Quality (CMC)	Reviewer:	Shrikant Pagay	Y
	TL:	Rapti Madurawe	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Robert Mello	Y
	TL:	John Metcalfe	Y
Facility Review/Inspection	Reviewer:	Kassa Ayalew	Y
	TL:	Jean Mulinde	Y
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:	Brantley Dorch	Y

Other reviewers		
Other attendees	Wiley Chambers, Acting Division Director Katherine Laessig, Deputy Director	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES X NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	X Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: X NO ☐ To be determined Reason:

• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: Comments for 74 day letter	☐ Not Applicable X YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Katherine Laessig

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:
Pre-NDA Meeting 10/19/2005
Submission Date 10/22/2010
Receipt Date 10/25/2010
Filing Date 12/24/2010
74 Day Letter 1/7/2011
Proprietary Name Review 1/25/2011
Midcycle Review 3/ 28/ 2011
Labeling to Sponsor 8/15/ 2011
Wrap-up Meeting 8 /22/ 2011
PDUFA Date 8/25/2011

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): Chemistry, Manufacturing and Controls: 1. There are significant changes between the clinically tested and to-be-marketed drug substance, drug product and the device combination. At this stage of review, it is unclear if the in vitro information provided is sufficient to bridge these multiple changes. We are providing the above comment to give you preliminary notice of a potential review issue. We also request that you submit the following information: Chemistry, Manufacturing and Controls: 1. Provide in a tabular format a side-by-side comparison of the Tobramycin for Inhalation Solution manufacturing process used by (b) (4) and Catalent, USA. The manufacturing process should also include the (b) (4). The comparison should include

	information on the process scale, process steps, in-process parameters and in-process tests (such as temperature control in preparation of tobramycin solution, pH, etc.). These processes should be of a minimum pilot scale. 2. Provide in a tabular format a side-by-side comparison of the [redacted] (b) (4) tobramycin solution) sourced from the two vendors in [redacted] (b) (4) and the third vendor in [redacted] (b) (4) ([redacted] (b) (4)). Provide a Letter of Authorization from each of the three [redacted] (b) (4) vendors to access their respective DMF for the [redacted] (b) (4). 3. The 12-month long-term stability update for the primary drug product batches should be provided by February 28, 2011. 4. Does the leachable study provided in the NDA include an evaluation of the label adhesive on the primary container? If not, provide information on leachables from the label adhesive. 5. Clarify if the osmolality values provided for the clinical and primary stability drug product batches (given in the Quality Overall Summary, Section 2.3.P-Table 3) are based on the USP test method. Chemistry, Manufacturing and Controls (Microbiology Issues): 1. Please specify whether the biological indicator, [redacted] (b) (4) 4. Please provide the microbiological product quality results of drug product hold time studies performed using the commercial processing equipment. <u>Review Classification:</u> X Standard Review ☐ Priority Review
ACTIONS ITEMS	
	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74

X	Conduct labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

APPEARS THIS WAY ON ORIGINAL

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

/s/

CARMEN L DEBELLAS
01/20/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 201820	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Tobramycin 300 mg/4 mL Solution		
Applicant: Chiesi Pharmaceuticals		
Date of Receipt: 10/25/10		
PDUFA Goal Date: 8/25/11	Action Goal Date (if different):	
Proposed Indication(s): management of cystic fibrosis patients with P aeruginosa		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 50-753 TOBI (tobramycin Inhalation Solution USP	Clinical

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

(b) (4) 300 mg/4mL Solution is basically the same product as TOBIO 300 mg/5mL except for the amount of tobramycin solution in the vial, the nebulizer and the compressor used to deliver the dose.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO X

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO X

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES X NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO x

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES X NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): TOBI (tobramyin) 300mg/5mL Solution
Patent number 5508269

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES X NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5,508,269

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES X NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO X

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES x NO Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

CARMEN L DEBELLAS
01/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Anesthesia and Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Infection Control and Dental Device
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

NDA 201-820 – Regulatory Device Consult

Date: June 10, 2009

To: Mr. Carmen DeBellas, Regulatory Project Manager (OND/OAP/DAIOP)

From: Mr. Sugato De, M.S., Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer

Applicant: Chiesi Pharmaceuticals Inc.

Product Name: Tobramycin 300 mg/4mL Solution (CHF 1538)

Indication: Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged six years and older.

Executive Summary

In NDA 201-820, Chiesi Pharmaceuticals has proposed a novel formulation of inhaled tobramycin (Tobramycin 300 mg/4 mL Inhalation Solution, hereafter referred to as CHF 1538). The formulation is composed of tobramycin, sulfuric acid, and sodium chloride in aqueous solution, using water for injection. The preservative-free sterile inhalation solution formulation has been developed for use in the treatment of pseudomonal pulmonary infections.

In this regulatory consult, the sponsor has provided a summary of a variety of studies intended to validate the in vitro performance of tobramycin inhalation solution. From the information provided for review, it appears that the intended to-be-marketed combination product is the proposed tobramycin solution, along with the either the Pari LC Plus Nebulizer or the (b) (4) Nebulizer. The proposed compressor for both nebulizers is the Vios Compressor. However, the clinical studies for the combination product were done using the new solely the Pari LC Plus Nebulizer and the TurboBoy N and S compressors.

The reviewing team in the Center for Drug Evaluation and Research (CDER) has requested feedback regarding the sponsor's proposal for a bridging study between the to-be-marketed combination product and the product tested in clinical studies.

RECCOMENDATION: At this stage of review, it is unclear whether in vitro bridging data between the to-be-marketed combination product and the product tested in clinical study will be sufficient to justify not providing additional clinical data for the to-be-marketed version. Depending on such factors as disease progression, patient age and weight, targeted patients may have a range of breathing patterns. Individualized breathing patterns influence particle motion in the airways, affecting deposition of the drug product irrespective of particle size, nebulization time, flow rate etc. Accordingly, in vitro tests can only mimic a limited number of representative conditions, and does not account for variability between patients or device usability. Apart from this, the in vitro study data provided for review at this stage of review are not sufficient and require several clarifications.

Recommended CDRH Clinical Hold Issues:

1. In the original NDA submission, it appears that a variety of in vitro tests have been performed to create a bridge between the to-be-marketed version of the combination product and the product tested in the clinical trial for Tobramycin 300 mg/4 mL Inhalation Solution (CHF1538). Please note that in vitro data alone may be insufficient to provide a reasonable assurance of safety and efficacy. Specifically, the results of the studies cannot be adequately defined across the range of patients with chronic pulmonary infection due to *Pseudomanas aeruginosa.* Depending on such factors as disease progression, patient age and weight, targeted patients may have a range of breathing patterns. Individualized breathing patterns influence particle motion in the airways, affecting deposition of the drug product irrespective of particle size, nebulization time, flow rate etc. Accordingly, in vitro tests can only mimic a limited number of representative conditions, and does not account for variability between patients or device usability. For example, a delay between device actuation and inhalation may significantly reduce delivered dose. Please provide a scientific analysis of (1) the effect of variable breathing patterns on drug deposition in the patient airway and (2) the effect or a mistimed inhalation in regards to device actuation.

2. An adequate description of the proposed devices has not been provided for review. Please provide a separate device module for the proposed NDA incorporating all descriptive information for all referenced nebulizers and compressors, and all relevant performance data. In addition, please identify all models, device accessories and relevant 510(k) application numbers for each device. Please include the following descriptive information in the device module:

    a. Provide a tabular summary of all design and specification differences between (1) the Pari LC Plus Nebulizer and (b) (4) Nebulizer and (2) the (b) (4) and the Vios Compressor. Please provide a summary analysis of the effect of each noted design difference on the output specifications for the device.
    b. Please provide engineering drawings for each proposed device, including depictions of each device component. Please specifically cite the inner dimension of the primary actuator orifice and describe the orientation of the actuator in relation to the patient delivery port.
    c. Identify all patient interface accessories (i.e., tee adapter, mouthpiece, mask) and provide engineering drawings which show any breathing holes and/or valves.
    d. Illustrate and explain the breathing gas path, including all valves and orifices, during inhalation and exhalation.
    e. Please provide a list of all device components. Indicate whether each is intended for a single-use (disposable), single-patient reuse or multiple-patient reuse, and ensure that this information appears in the labeling for your device.
    f. Please provide a shelf-life specification for each of the proposed devices and either cite or provide the corresponding test reports.
    g. Provide a summary document detailing the use of the proposed devices with Tobramycin 300 mg/4mL solution (CHF1538). Specifically, please describe how the drug is loaded into the device, and provide drug-specific instructions for use in terms of device actuation. In addition, please summarize the dosage cycles for the drug (delivered dose per actuation, actuations per treatment, treatments per day etc.).

3. At the current stage of review, adequate comparative particle characterization data has not been provided for review for the proposed to-be-marketed (TBM) combination product and he product tested in clinical trial (CT). While some relevant data is referenced, the overall methodology, procedures used and statistical analyses applied require further clarification. Please note that in order to create an in vitro bridge between these two device configurations, comparative data must be comprehensive and have a sufficient level of statistical significance. The Center for Devices and

Radiological Health (CDRH) recommends that you perform a side-by-side particle characterization assessment for the to-be-marketed device and the device configuration used in the clinical trial incorporating the following:

a. Pari LC Plus Nebulizer, TurboBoy S Compressor, CHF 1538 (CT Configuration 1)
b. Pari LC Plus Nebulizer, TurboBoy N Compressor, CHF 1538 (CT Configuration 2)
c. Pari LC Plus Nebulizer, Vios Compressor, CHF 1538 (TBM Configuration 1)
d. [redacted] (b) (4)

Please note that if the particle characterization data for TBM Configuration 2 is not substantially equivalent to the two clinical configurations, additional in vitro data (e.g. [redacted] (b) (4) Nebulizer w/ [redacted] (b) (4) Compressors) may be required to assess the source of the differences. Also, please note that CDRH does not consider data collected for the [redacted] (b) (4) compressor critical information for the bridge between the to-be-marketed device and the devices used in the clinical trials.

CDRH evaluates the equivalent performance of nebulizers via comparative particle characterization data with a cascade impactor consisting of at least six stages (i.e. Next Generation Cascade Impactor). Laser diffraction is currently not accepted as a standalone method of particle characterization due to concerns regarding reproducibility, specificity, and resolution. Please provide particle characterization data for each of the four device configurations cited above with the proposed formulation of tobramycin (CHF 1538) using the drug's labeled concentration, dose volume and salt content. Note that each run should continue until the nebulizer is empty, as indicated by sputtering (i.e., erratic aerosolization). In addition, if the specified nebulizers operate over a range of flow rates, it is recommended that data be collected at the minimum and maximum flow rates allowable. Test reports should include the following:

a. The original nebulizer dose volume in milliliters of drug.
b. The amount of drug in micrograms recovered on each impactor plate, throat, and outlet filter.
c. The dead volume in micrograms (the amount of drug remaining in the medication cup when sputtering begins and treatment ends).
d. The drug mass recovered in the cascade impactor in the respirable size range (i.e. [redacted] (b) (4) or [redacted] (b) (4) microns, depending on the type of impactor used) expressed as a percent of the total drug mass in the nebulizer cup.
e. The mass median aerodynamic diameter (MMAD- the diameter above and below which lies 50% of the mass of the particles) of the particles recovered in the impactor.
f. The geometric standard deviation of the MMAD.

4. In order to adequately evaluate substantial equivalence, sufficient data must be provided to assess potential sources of variability in terms of particle size, total emitted mass and respirable mass that may be attributable to the device. Please note that an adequate number of device samples should be tested in order to assess potential sources of inter-sample variability (drug batch, nebulizer and compressor batches, and manufacturing site etc.). Also, in order to assess intra-sample variability, please provide data demonstrating that single sample of each of the two to-be-marked configurations can deliver the prescribed dose of the proposed drug in a repeatable manner over the intended number of actuations. For each of the two to-be-marketed device configurations, please provide sufficient data to demonstrate that each is able to deliver the prescribed dose in a repeatable manner irrespective of potential sources of inter-sample variability. These data are required to demonstrate that the dosing specifications in your labeling are validated to a specified level of statistical confidence. CDRH recommends that you consider the following recommendations in regards to evaluating potential sources of variability for the proposed combination product:

a. Please provide data demonstrating that an individual sample of each of the two proposed device configurations will consistently deliver a specified dose for each medication tested. In doing so, please validate dose specifications in terms of particle size, total emitted mass, and respirable mass. These data are intended to demonstrate dose repeatability. In your test report, please note the number of runs that were used for each individual device sample-drug combination, and provide a statistical justification explaining why this number is sufficient to validate the dose specifications in your labeling.

b. Please provide data characterizing the potential affect of inter-sample variability on the dose specifications in your labeling. Please specify the number of device samples that were used in your performance tests, and provide a statistical analysis explaining why this number of samples is sufficient to demonstrate with an appropriate level of confidence that (1) variability in individual device samples do not noticeably affect the dosing specifications of the proposed device and that (2) develop confidence for particle specifications overall, irrespective of inter-sample variability.

c. In analyzing the results of the tests cited above, please provide a justification of why the levels of variability shown are appropriate for the use of the devices in delivering the proposed drug formulation.

5. CDRH believes that your device labeling is an essential component in communicating the aerosolized therapy dosing specifications of your proposed device. Accordingly, please include the following information in your labeling and provide copies of all updated documentation. It may be appropriate to include a separate device package insert describing drug-specific instructions for use, relevant warnings and cautions, and the summary of measured particle specifications. Please note that each specification listed in the labeling should have an appropriate level of confidence as demonstrated by your performance testing.

   a. For each individual drug in your performance testing, please update your proposed labeling with mass-median aerosol diameter (MMAD), total delivered dose, total respirable dose, respirable fraction and geometric standard deviation (GSD).

   b. For each specification identified above, please a specify range of values at specified confidence interval based on statistical analysis of the observed data in your performance testing. For each range of values, please specify the total number of masks, nebulizers, and sample data points used to determine the specified confidence interval.

   c. We recommend that you characterize particle size using three categories: course particles, fine particles, and extra-fine particles. As a function of the total dose delivered, please include specifications for the total mass and the fraction of each of these size ranges.

Additional Comments:

Please note that if the clinical study performed is sufficient for a complete evaluation of safety and efficacy, additional comparisons between the approved tobramycin formulation (TOBI® Tobramycin Inhalation Solution) and the proposed formulation (CHF 1538) may not be essential. If an in vitro bridge to the originally approved TOBI® formulation is required for review from a clinical perspective, it is unclear how this may be accomplished using the proposed devices. The proposed device configuration is not intended to deliver the original TOBI® formulation, and the currently approved device configuration for TOBI® (Pari LC Plus w/ Devilbiss Compressor) was never intended to deliver the new formulation. While output from the two device configurations may be equivalent, it may not be possible to predict efficacy because in vitro testing may not adequately predict the distribution of the drug within the airways.

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/s/

CARMEN L DEBELLAS
06/14/2011