

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207356Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 207356

Addendum #1 to the Integrated Quality Assessment (IQA)

Product: ARIKAYCE (amikacin liposome inhalation suspension) 590 mg/8.4 mL

Addendum #1 to Integrated Quality Assessment (IQA) dated 8/22/2018

From: Yushi Feng, ATL, Branch 3, ONDPI

Date: Sep-25-2018

The original Integrated Quality Assessment (IQA) dated 8/22/2018 recommended Approval from the Product Quality perspective. This Addendum documents updates to the drug product long-term storage (2°C to 8°C, before dispensing) shelf life and the in-use storage statements.

Drug product long-term storage (2°C to 8°C, before dispensing) shelf life

Immediately prior to the finalization of the IQA, a teleconference between FDA and the Applicant took place on 8/22/2018 followed by an Amendment (SDN 41, 8/22/2018 - Response to 8/22/2018 teleconference), where the Applicant accepted the acceptance ranges proposed by FDA during the teleconference for the drug product In-Vitro Release (IVR) method (Table 1).

Table 1. Drug Product Specifications In-Vitro Release (IVR) Method Acceptance Ranges (SDN 41, 8/22/2018)

Time (hours)	Amikacin Released
0.5	NMT (b) (4) %
1.5	(b) (4) %
3.0	NLT (b) (4) %

Subsequently, an Information Request was sent to inform the Applicant that the drug product is assigned a shelf life of 9 months when stored at 2°C to 8°C (before dispensing) so the product will meet the release rate of (b) (4) % limit at 1.5 hours. This is based on the stability data on the three process validation batches manufactured at the Therapure Biopharma site (Table 2).

Table 2. In-Vitro Release (IVR) Long Term Storage Stability Data at the 1.5-hour Sampling Time Point

Batch #	% Amikacin Released at Month in Stability Storage							
	0	3	6	9	12	18	24	36
17027	(b) (4)				Scheduled	Scheduled	Scheduled	Scheduled
17030					Scheduled	Scheduled	Scheduled	Scheduled
17035					Scheduled	Scheduled	Scheduled	Scheduled

The IVR data showed that all three batches have downward trending IVR results during stability data points (Figure 1), and all three batches reached (b) (4) % (the lower end of the spec limits) at month 9 time point. If the downward trend holds (extrapolation of data trending suggests so), the next time point data at 12-month for all three batches would go below (b) (4) % resulting in out of specification.

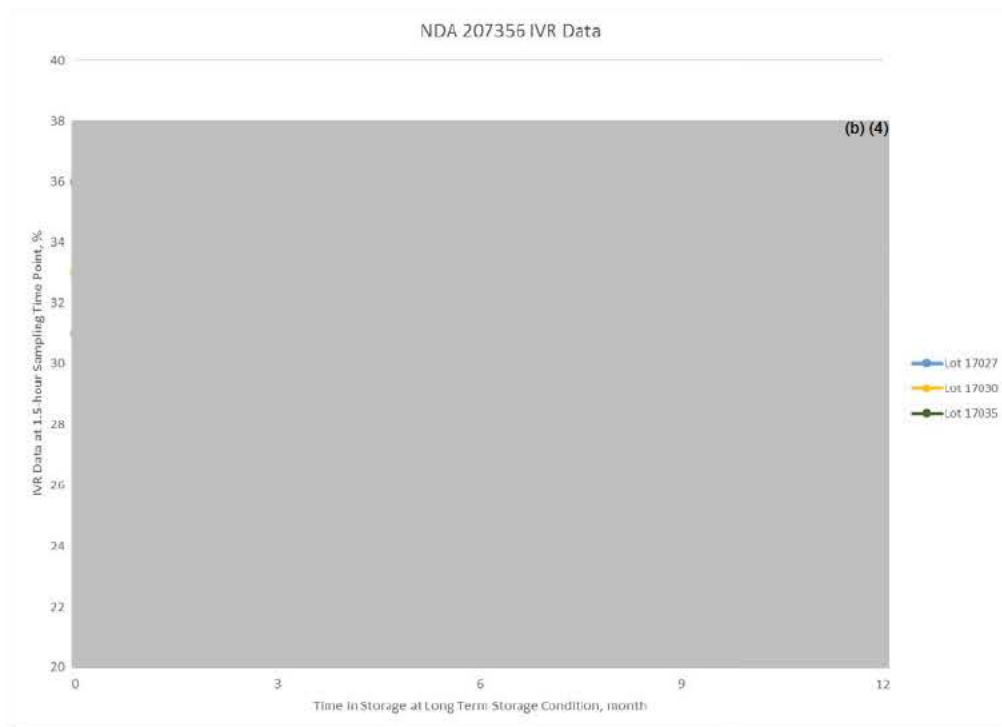


Figure 1. In-Vitro Release (IVR) Long Term Storage Stability Data at the 1.5-hour Sampling Time Point Based on Table 2

In the response (SDN 53, 9/21/2018), the Sponsor acknowledged that the drug product is assigned a shelf life of 9 months when stored at 2°C to 8°C (before dispensing).

Drug product in-use storage

The IQA documented that the NDA provided data to support an in-use period (after dispensing) of 4 weeks stored at (b) (4) 25°C ((b) (4) 77°F) (b) (4) ALIS does not need to be protected from light. ALIS cannot be frozen.

Upon discussions with the Applicant, the following in-use storage statements are adopted in labeling. These statements are supported by the data provided in the NDA, and can be granted.

Store ARIKAYCE vials refrigerated at 2°C to 8°C (36°F to 46°F) until expiration date on vial. *Do not freeze.* Once expired, discard any unused drug.

ARIKAYCE can be stored at room temperature up to 25°C (77°F) for up to 4 weeks. Once at room temperature, any unused drug must be discarded at the end of 4 weeks.

This NDA is still recommended for Approval from the Product Quality perspective. All Product Quality aspects including facilities are found acceptable. Details of the review findings are provided in the Integrated Quality Assessment (IQA) dated 8/22/2018.



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Recommendation: Approval
NDA 207356
Review 1

Drug Name/Dosage Form	ARIKAYCE (amikacin liposome inhalation suspension)
Strength	590 mg/8.4 mL
Route of Administration	Oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Insmad Incorporated
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Orig-1</i>	<i>03/28/2018</i>	<i>All</i>
<i>Quality Amendment</i>	<i>04/20/2018</i>	<i>Drug Product, Biopharm</i>
<i>Quality Amendment</i>	<i>04/30/2018</i>	<i>Facilities</i>
<i>Quality Amendment</i>	<i>05/18/2018</i>	<i>Device</i>
<i>Quality Amendment</i>	<i>07/03/2018</i>	<i>Drug Product, Process, Device</i>
<i>Quality Amendment</i>	<i>07/12/2018</i>	<i>Quality Micro</i>
<i>Quality Amendment</i>	<i>07/17/2018</i>	<i>Drug Product</i>
<i>Quality Amendment</i>	<i>07/19/2018</i>	<i>Quality Micro</i>
<i>Quality Amendment</i>	<i>07/20/2018</i>	<i>Device</i>
<i>Quality Amendment</i>	<i>07/23/2018</i>	<i>Biopharm</i>
<i>Quality Amendment</i>	<i>07/27/2018</i>	<i>Biopharm</i>
<i>Quality Amendment</i>	<i>08/02/2018</i>	<i>Drug Product</i>
<i>Quality Amendment</i>	<i>08/06/2018</i>	<i>Quality Micro</i>
<i>Quality Amendment</i>	<i>08/06/2018</i>	<i>Device</i>
<i>Quality Amendment</i>	<i>08/09/2018</i>	<i>Quality Micro</i>
<i>Quality Amendment</i>	<i>08/13/2018</i>	<i>Biopharm</i>
<i>Quality Amendment</i>	<i>08/16/2018</i>	<i>Quality Micro</i>
<i>Quality Amendment</i>	<i>08/16/2018</i>	<i>Biopharm</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Katherine Windsor	Charles Jewell
Drug Product	Yushi Feng	Balajee Shanmugam
Process	Peter Guerrieri	Derek Smith

Microbiology	Jennifer Sykora	Elizabeth Bear/John Arigo
Facility	Peter Guerrieri	Derek Smith
Biopharmaceutics	Om Anand	Elsbeth Chikhale
CDRH Device	Deepika Lakhani	James Lee
CDRH Device Facilities	Rakhi Dalal	Nazia Rahman
Environmental Assessment	Raanan Bloom	Scott Furness
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Yushi Feng	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	DS DMF for Amikacin sulfate, see DS review				
Various	Type II, III, IV	See DP and QUALITY MICRO reviews				

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	108674, (b) (4)	IND for current NDA

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH Device	Complete	Approval	8/08/18	Deepika Lakhani
CDRH Device Facilities	Complete	Approval	5/22/18	Rakhi Dalal
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for **Approval** from the Product Quality perspective. All Product Quality aspects including facilities are found acceptable.

II. Summary of Quality Assessments

A. Product Overview

This NDA provides for ARIKAYCE® (amikacin liposome inhalation suspension) to be indicated for the treatment of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients. The drug substance, amikacin sulfate, is a semi-synthetic aminoglycoside antibiotic. The proposed product is a combination product consisting a white, milky suspension of amikacin sulfate encapsulated in liposomes with a unit dose of 590 mg/8.4 mL amikacin per vial and an eFlow Nebulizer System.

Proposed Indication(s) including Intended Patient Population	ARIKAYCE® (amikacin liposome inhalation suspension) is indicated for the treatment of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients.
Duration of Treatment	The recommended dose in adults is the once daily inhalation of the contents of one ARIKAYCE vial using the Lamira™ Nebulizer System. (b) (4)
Maximum Daily Dose	Once daily oral inhalation of the contents of one ARIKAYCE vial 590 mg/8.4 mL.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

Amikacin sulfate, a semisynthetic aminoglycoside derived from kanamycin A, has been available for over 30 years for human use as a parenteral antibiotic. There are USP and Ph. Eur. monographs for amikacin sulfate.

The applicant cross-referenced the CMC information for amikacin sulfate drug substance to DMF (b) (4). DMF (b) (4) was reviewed by Katherine Windsor, Ph.D. (final signature 01-AUG-2018) and was found adequate to support NDA 207356.

The specified impurities routinely observed in drug substance produced by the proposed commercial manufacturer (b) (4) were qualified at or above the respective proposed limits by nonclinical studies. Stability data from the DMF holder support a retest period of (b) (4) months for amikacin sulfate drug substance manufactured at (b) (4) and stored at (b) (4) °C/60% RH.

For additional details, see the Drug Substance review below.

Drug Product:

The proposed drug product ARIKAYCE® (amikacin liposome inhalation suspension or ALIS) is a sterile, aqueous, liposome suspension for oral inhalation in a single-use glass vial containing a nominal dose of 590 mg of amikacin. The white, milky suspension consists of amikacin sulfate encapsulated in liposomes. The liposomes are composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol, (b) (4).

The concentration of the active ingredient is expressed in terms of amikacin (b) (4) and is nominally 70 mg/mL. Compendial excipients include Cholesterol (b) (4), (b) (4), (b) (4), Sodium Hydroxide, Sodium Chloride, Water for Injection. They will comply with the appropriate monographs and general USP/NF and Ph. Eur. requirements. The non-compendial excipient dipalmitoylphosphatidylcholine (DPPC) has been used in other approved products with a similar route of administration (e.g., Surfaxin, intratracheal administration to the lung). The route of administration, inhalation, is new for cholesterol. The Nonclinical reviewer was consulted and confirmed that no concerns on using DPPC and cholesterol in this inhalation product at the proposed levels.

The drug product is filled into a 10-mL, (b) (4) glass vial, stoppered with a (b) (4) stopper and sealed with an (b) (4). Each vial is (b) (4) to contain (b) (4) of ALIS to deliver (b) (4) (8.4 mL) of the suspension. Suitability of the container closure system was demonstrated by the registration stability studies, and the extraction study for vial and stopper on extractables/leachables and potential elemental impurities.

The proposed drug product specifications include appearance, Identification of Amikacin, Identification of Sulfate, pH, osmolality, amikacin concentration, percent associated amikacin, amikacin degradation products, content uniformity, DPPC concentration, cholesterol concentration, lipid to drug ratio, (b) (4) degradation products, (b) (4), particulate matter, liposome particle size, aerodynamic particle size distribution (APSD) post nebulization using the next generation impactor (NGI), percent associated amikacin post nebulization, in-vitro release, sterility, and bacterial endotoxins. The proposed drug product specification is adequate to ensure the quality of the drug product over its expiration date, and the tests and acceptance criteria are appropriately justified. The analytical procedures have been shown to be

appropriate for the intended use, the stability-indicating methods have been adequately validated.

Batch analysis data of 145 batches are provided for batches of the earlier formulations with amikacin concentrations of (b) (4) mg/mL, and for all nonclinical studies, clinical studies (Phases 1, 2 and 3), and drug product stability studies. Although several sites of manufacture were employed during development of the drug product, batches filled in 10-mL vials were manufactured at Ajinomoto Althea Technologies and Therapure Biopharma, Inc., the proposed commercial manufacturing sites for ALIS. All results met specification at the time of release. Batch analysis data on the (b) (4) Ajinomoto Althea: (b) (4), Ajinomoto Althea: (b) (4), Therapure Biopharma: (b) (4) show comparable results.

Regarding the (b) (4) degradation product of (b) (4):

Initially, the drug product specification acceptance limit on the (b) (4) degradation product of (b) (4) was proposed at NMT (b) (4) %. This limit was found not acceptable by the Nonclinical Reviewer. Upon request, the Applicant agreed to revise this limit to NMT (b) (4) %. Accordingly, the proposed shelf life for the drug product was revised from (b) (4) months to 24 months for long term (before dispensing) refrigerated storage and the in-use period (after dispensing) from (b) (4) weeks to 4 weeks for room temperature storage so the product under these conditions will meet the revised limits.

The results of the real time stability studies at the proposed storage conditions, the accelerated stability studies, and three special stability studies (temperature cycling study (7 cycles between 24 hours at 40°C and 1-3 days at 2-8°C), thermal exposure study (7 days at 40°C then returned to 2-8°C for up to 6 months), freeze-thaw study (2-3 days at -20°C then placed at either 2-8°C or 25°C for 2 days)), and photostability per ICH Q1B option 2 support the proposed expiration dating: Long-term storage of ALIS for 24 months when stored under refrigerated conditions of 2-8°C. The in-use period of the product is 4 weeks storage at (b) (4) 25°C (b) (4) 77°F (b) (4). ALIS does not need to be protected from light. ALIS cannot be frozen and will be recommended as such in the label. The data presented across manufacturing sites (Althea and Therapure) suggested comparability of these drug product manufacturing facilities.

For additional details, see the Drug Product review below.

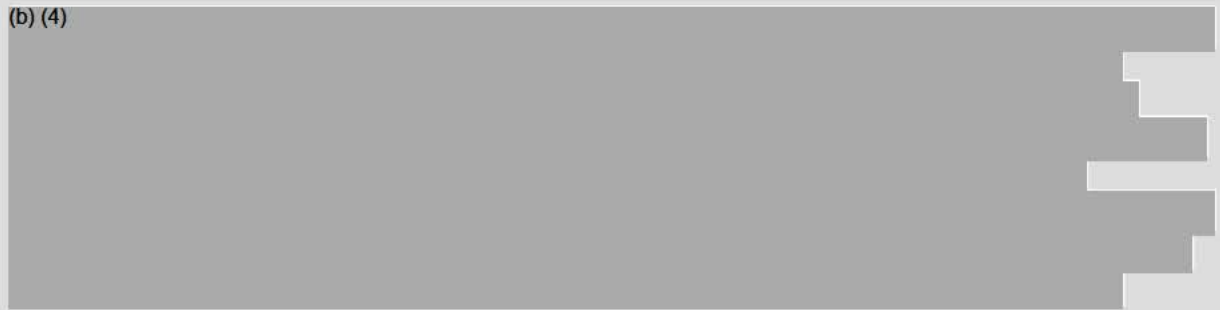
Process:

The application involves a sterile combination product, the amikacin sulfate liposomal suspension for inhalation, which is filled in 10 mL, single-use glass vials, and delivered with a product-specific Eflow nebulizer (Lamira Nebulizer System). The bulk manufacture consists of (b) (4)

(b) (4)



(b) (4)



For additional details, see the Process review below.

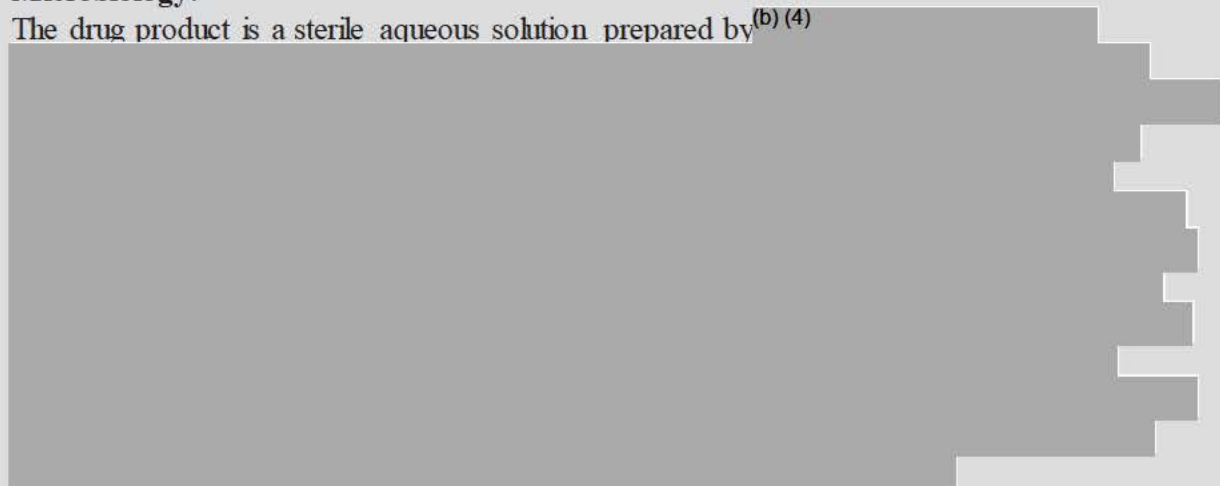
Facilities:

A review of the application and inspectional documents of the facilities responsible for manufacturing ALIS has determined that there are no significant outstanding risks. A pre-approval inspection was recommended and completed for Therapure Biopharma, Inc., and resulted in a recommendation of approval. All listed facilities are acceptable to manufacture product for NDA 207356.

For additional details, see the Facilities review below.

Microbiology:

The drug product is a sterile aqueous solution prepared by (b) (4)



For additional details, see the Microbiology review below.

Biopharmaceutics:

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting (1) the proposed in vitro release method and acceptance criteria, and (2) bridging between the proposed commercial product and the product used in the pivotal clinical studies. The Biopharmaceutics review findings are summarized as follows:

In Vitro Release (IVR) Method and Acceptance Criteria: The Quality Control (QC) in vitro release method and in vitro release acceptance criteria shown in the Table below are found acceptable, **on an interim basis**, for the routine QC of amikacin liposome inhalation suspension, 590 mg, for batch release and stability testing.

Apparatus/speed	Volume	Medium	Acceptance Criteria	
			Time (hours)	% Release
			0.5	NMT ^{(b) (4)} %
			1.5	^{(b) (4)} %
USP 2 (paddle) small vessel/150 rpm	Volume varies at each sampling time point [30 to 105.7 mL]	Triton/PBS buffer pH 7.2 at 37°C	3.0	NLT ^{(b) (4)} %

Biowaiver Request: A biowaiver is not needed nor submitted.

Bridging: The Phase 2 and 3 formulation composition is same as the commercial formulation. ^{(b) (4)}

^{(b) (4)} were used for the manufacturing of the clinical and commercial batches. ^{(b) (4)} are the commercial manufacturing processes. The Phase 3 clinical trial, NTM (INS-212), used various batches manufactured using ^{(b) (4)}. Since drug product manufactured using ^{(b) (4)} were all used in the clinical studies supporting safety and efficacy, there is no need for additional in vitro or in vivo bridging between products manufactured using ^{(b) (4)}. Nevertheless, drug products manufactured by ^{(b) (4)} exhibit comparable drug release profiles. Regarding the reliance of this NDA on published literature, reference is made to the Pharmacology/Toxicology and Clinical Reviews.

Recommendation: From a Biopharmaceutics perspective, NDA 207356 for Arikayce (amikacin liposome inhalation suspension), 590 mg is **recommended for APPROVAL with a Post-Marketing Commitment [PMC]**. The Applicant agreed to use the interim drug release method and acceptance criteria until a more optimal in vitro drug release method is approved. The Applicant agreed to a Post-Marketing Commitment [PMC Number 3480] to develop a new optimal in vitro drug release method in which only the drug released from the liposomes (free drug) is sampled and analyzed. The Applicant agreed (T-Con, dated 08/22/2018) to provide the requested reports as prior approval supplements, 06 months (interim report) and 12 months (final report) post NDA approval.

For additional details, see the Biopharmaceutics review below.

Environmental Assessment:

Based on modeled and available data, a low environmental risk is expected due to approval of this application. Extraordinary circumstances are not indicated. The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance is acceptable.

For additional details, see the Environmental review below.

CDRH Device:

In NDA 207356, Inmed Incorporated has proposed a formulation of Amikacin Liposome Inhalation Suspension (ARIKAYCE®) to be delivered by the eFlow Nebulizer System. The eFlow Nebulizer System is manufactured by PARI Respiratory Equipment (PRE) and is specifically designed to deliver amikacin liposome inhalation suspension (ALIS) drug product and hereafter referred to as ALIS eFlow. The ALIS eFlow is a portable, hand-held, electronic nebulizer intended for single patient use that uses a vibrating micro-perforated membrane to generate an inhalable aerosol.

The ALIS eFlow is a modified version of the Altera® K100380, a PARI Respiratory Equipment FDA-cleared electronic nebulizer system. The ALIS eFlow is also similar to two other FDA-cleared PARI Respiratory Equipment Nebulizer System: the Trio® K033833 (originally named the eFlow Nebulizer System) and the eRapid® K112859. The ALIS eFlow, Altera, Trio, and eRapid nebulizer systems all use the same micro-perforated vibrating membrane technology to aerosolize liquid medications. While the ALIS eFlow proposed under the current NDA submission has similar operating principles and components, it has undergone modifications to the controller, nebulizer handset, reservoir cap, and aerosol head. These changes can impact the performance, electrical safety, and biocompatibility of the device and require a new device review. To aid in the device review, additional sub-consults were sent in the following review areas: Electrical Safety, EMC, and Device Biocompatibility.

Additional information was recommended from the sponsor regarding their device software, performance and electrical safety. This information was requested from the sponsor via information requests. The sponsor provided adequate responses through interactive review which adequately addressed the outstanding software, performance and electrical safety.

For additional details, see the Device review memo below.

CDRH Device Manufacturing Facilities:

The NDA 207356 was assessed for applicable documentation, compliance with the applicable Quality System Requirements under 21 CFR Part 4. The Office of Compliance (OC) at CDRH has completed the evaluation of NDA 207356 and has considered the Application review complete. The NDA 207356 is recommended Approvable with Post Approval Inspection.

For additional details, see the Device Facilities review memo below.

C. Special Product Quality Labeling Recommendations (NDA only)

Recommendations have been conveyed to the OND PM for consideration as the labeling is finalized. See the OPQ Labeling review below.

D. Final Risk Assessment (see Attachment)



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MICROBIOLOGY[IQA Review Guide Reference](#)**Product Background:**

NDA: 207356

Drug Product Name / Strength: ARIKAYCE (Amikacin Liposome Inhalation Suspension or ALIS)

Route of Administration: Inhalation

Applicant Name: Inmed Inc, 1- Finderne Ave, Bridgewater, NJ 08807 USA

Manufacturing Sites:

**Ajinomoto Althea, Inc, (b) (4) and
Therapure Biopharma, Inc, (b) (4)**

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions Being Reviewed: 3/28/2018, 7/12/2018 (in Seq 0020), 8/6/2018 (in Seq 33), 8/9/2018 (in Seq 0035), 8/16/2018 (in Seq 0039)

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This drug product is an orphan drug and is under priority review.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents:

- **DMF (b) (4) for cholesterol (b) (4) used to manufacture the drug product at (b) (4)**

- DMF^{(b) (4)} microbiology review^{(b) (4)}, dated 10/27/2016 (DARRTS date 10/27/2016, Acceptable).
- DMF^{(b) (4)} for the^{(b) (4)} of the^{(b) (4)} rubber stoppers by^{(b) (4)}.
- DMF^{(b) (4)} microbiology review^{(b) (4)} c, dated 2/28/2017 (Adequate).
- DMF^{(b) (4)} for the manufacture and sterilization by^{(b) (4)}.
- DMF^{(b) (4)} microbiology review^{(b) (4)}, dated Aug 3, 2018 (Adequate).

Note: The reason this review is significantly longer than a normal DMA review is due to the following: 2 different manufacturing facilities, the use of different sets of equipment^{(b) (4)}, but also different sets of^{(b) (4)} and^{(b) (4)} sterilization. In addition, the firm did not properly submit validation studies for sterilization methods and multiple rounds of Information Requests were needed.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – ARIKAYCE is a white, milky suspension consisting of amikacin sulfate encapsulated in liposomes. The liposomes are composed of dipalmitoylphosphatidylcholine (DCCP) and cholesterol^{(b) (4)}. The sterile, single-use, drug product solution is filled in a 10 mL^{(b) (4)}, single-use vial. The vials are stoppered with a^{(b) (4)} of ALIS to deliver^{(b) (4)} (8.4 mL; ~ 590 mg drug product in total) of the suspension to a product-specific eFLOW nebulizer (Lamira Nebulizer System) manufactured by PARI Respiratory Equipment, Inc..
- **Drug product composition** –

Ingredient	Content per mL	Function
Amikacin Sulfate	70 mg	API
DPPC	(b) (4)	(b) (4)
Cholesterol ^{(b) (4)} NF, Ph. Eur	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sodium hydroxide, USP/Ph. Eur/ JP	(b) (4)	pH adjuster
Sodium chloride, USP/Ph. Eur	(b) (4)	(b) (4)
WFI, USP/Ph. Eur	(b) (4)	(b) (4)

- **Description of vial container closure system** –

Component	Description	Manufacturer Part number	Part Number at TBI	Part Number at Althea	Manufacturer
Vial	(b) (4)	(b) (4)			
Stopper					
Seal					

Reviewer's Assessment: *Adequate*

The firm provided a sufficient description of the composition of the drug product.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity (b) (4)

(b) (4)

The firm provided sufficient information on the actions concerning the product when there is a media fill failure at Althea with involvement of the Quality team and the Material Review Board.

P.5 Control of Drug Product

P.5.1 Specification

The product release specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria	Exhibit Batch Results
Bacterial Endotoxins	USP <85>.	(b) (4)	All < 0.15 EU/mg
Sterility	USP <71>		All conform

In section 1.6.3, the firm included information on previous correspondence with the firm. A preliminary meeting held on July 3, 2014 discussed if the Agency had any comments regarding proposed product quality attributes and specifications for the drug product. The Agency responded that the sterility and bacterial endotoxins (b) (4) EU/mg) specifications for the drug product at release and shelf life are acceptable from a microbiology product quality standpoint. Reference was given to the 2002 Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation which does not require endotoxins testing for inhalation products. No further information is necessary.

The firm also provided batch results for earlier formulations including concentrations of (b) (4) mg/mL. The 3 most recent batches from each TBI (17035, 17030, and 17027) and 3 recent batches from Althea (3-FIN-2703, 3-FIN-2702, and 3-FIN-2700) of the correct batch size and formulation had adequate results for sterility and endotoxins testing (reported in table above).

Reviewer's Assessment: *Adequate*

The firm provided sufficient information the control of drug product release specifications.

P.5.2 Analytical Procedures -- See P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Endotoxins

(See 3.2.P.5.3 in VAL-DOC-0118.pdf)

(b) (4)

(b) (4)

Reviewer's Assessment: *Adequate*

Bacterial endotoxins testing is not required for inhalation products as per the 2002 Guidance for Industry - Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation; however, the method suitability results support the endotoxins test method. It is also noted that the package insert does not indicate that the drug product is non-pyrogenic.

Sterility

(b) (4)

Finished lot # 17035, 17030, 17027 met the release specification of “conforms” for the TBI facility batches. Finished lot # 3-FIN-2703, 3-FIN-2702, and 3-FIN-2700 met the release specification of “conforms” for the Althea facility batches.

Reviewer’s Assessment: *Adequate*

The firm provided sufficient information on sterility testing for the commercial drug product.

P.7 Container Closure – See P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(See 3.2.P.8.1)

Proposed Expiry: (b) (4) months when stored at 2-8°C. The in-use period of the product is (b) (4) weeks when stored at (b) (4) 25°C (b) (4).

Thirteen development batches were manufactured and studied on stability at the clinical (b) (4) scale using (b) (4) (equivalent to commercial (b) (4)). These batches are held at 2-8°C and 25°C ± 2°C for up to (b) (4) months. At (b) (4) months, the batches are tested for sterility (specification: conforms).

Reviewer’s Assessment: *Adequate*

The firm provided sufficient information in the stability summary to support the proposed expiry of the drug product.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(See 3.2.P.8.2)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP <71>	Conforms

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 2-8°C

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
Sterility	X				X			X	X

Post Approval Stability Commitment

The applicant has placed first three commercial lots of the subject drug product into their stability program. And they commit, thereafter, on an annual basis, one production lot from each facility will be added to the stability program.

Reviewer's Assessment: Adequate

The firm provided sufficient information on the post-approval stability program of the commercial drug product.

P.8.3 Stability Data

Batch numbers ENG 1505, 16034, 17027, 17030, and 17035 were studied upright at 25°C/60% RH and 2-8°C underwent sterility testing at the scheduled intervals according to USP <71> and each "conformed." The batches did not undergo bacterial endotoxins testing. The batch sizes noted as (b) (4) correspond to the (b) (4) batch size (see 3.2.P.8.3 in "Stability Data – TBL.pdf").

At Althea, batches 3-FIN-0904, 3-FIN-1068, 3-FIN-1072, 3-FIN-1074, 3-FIN-1389, 3-FIN-1931, 3-FIN-1393, 3-FIN-1395, 3-FIN-1444, 3-FIN-1757, 3-FIN-1618, 3-FIN-1649, and 3-FIN-1653 were tested for sterility in the upright position at 2-8°C at time (b) (4) months. Batch numbers 3-FIN-1068, 3-FIN-1072, and 3-FIN-1074 were tested for sterility in the upright position for (b) (4) months at 2-8°C and then 1 additional month at 25°C. Batch numbers 3-FIN-1618, 3-FIN-1649, and 3-FIN-1653 were tested for sterility in the upright position at 25°C at time zero only. Batch numbers 3-FIN-1757, 3-FIN-1618, 3-FIN-1649, 3-FIN-1653 were tested for sterility in the inverted position at 25°C at time zero only. Batch numbers 3-FIN-1757, 3-FIN-1618, 3-FIN-1649, and 3-FIN-1653 were tested for sterility in the inverted position at 2-8°C at time (b) (4) months.

Batch numbers 3-FIN-2179, 3-FIN-2181, 3-FIN-2303, 3-FIN-2108, 3-FIN-2110 were tested for sterility in the upright position at 2-8°C at time (b) (4) months. Batch number 16D03AA has been tested for sterility in the upright position at 2-8°C at time zero. All batches tested have conformed to sterility testing.

The batches did not undergo bacterial endotoxins testing, which is not required for inhalation products.

Reviewer's Assessment: Adequate

The firm provided sufficient detail on the stability data at both facilities to maintain a sterile drug product.

A Appendices

A.2 Adventitious Agents Safety Evaluation

In section 3.2.P.4.5 (found in section 3.2.P.4 NA), the firm describes that the excipients used in the manufacture of ALIS with potential TSE/BSE risk are dipalmitoylphosphatidylcholine (DPPC) and cholesterol. DPPC is derived from (b) (4) raw materials thus has no risk of TSE/BSE. The cholesterol is derived from (b) (4) and has been granted a certificate of suitability from the supplier, (b) (4) which certifies that the cholesterol meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the EP..

The firm also provides a LOA dated June 23, 2016 for DMF (b) (4) held by (b) (4) for their Cholesterol (b) (4). Microbiology review (b) (4) pdf (dated Oct 17, 2016) reviewed the processing of cholesterol from starting material including viral inactivation and TSE/BSE control and they were deemed Adequate.

Lastly, in section 3.2.P.4 in document titled "Specifications.pdf", the firm provided specifications for excipients and additional testing for cholesterol (b) (4). The firm states that the cholesterol is evaluated in accordance with USP <61>, USP <85>, and USP <231> (Heavy Metals) by the supplier. No further information is needed.

Reviewer's Assessment: Adequate

The firm provided sufficient information and reference to microbiological control of cholesterol in the manufacture of the sterile drug product.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: *see A.2*

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: *see A.2*

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: *see A.2*

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: *see A.2*

R Regional Information

Executed Batch Records

Executed lot #(s): 16034 (TBI), 3-FIN-1011 (Althea), and 3-FIN-2110 (Althea)

The batch records confirm that (b) (4) and (b) (4) (b) (4) were used for the manufacture of the exhibit batch.

Reviewer's Assessment: *Adequate*

The firm provided sufficient information on the executed batch records for the drug product.

Comparability Protocols - No CP was included in the application.

Reviewer's Assessment: N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

- **Post-dilution/constitution hold time**

The drug product does not get diluted or reconstitute prior to administration.

Storage temperature: 2-8°C ; Route of administration: Inhalation ;

Container: Single dose/dose

Reviewer's Assessment: *Adequate*

The firm provided sufficient information on the package insert for the storage conditions and route of administration for the sterile drug product.

Post-Approval Commitments:

Reviewer's Assessment: *N/A*

List of Deficiencies: *None*

Primary Microbiology Reviewer Name and Date: Jennifer Sykora, Ph.D. on Aug 17, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Elizabeth Bearr, Ph.D. on Aug 22, 2018



Elizabeth
Barr

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Comments: The majority of the primary review for this NDA was performed by Jennifer Sykora. Primary review of the applicant's IR responses dated 8/16/2018 and 8/21/2018 was performed by Elizabeth Barr with John Arigo as secondary reviewer.



John
Arigo

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QUALITY A QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics



NDA/ Type of Submission: 207356-ORIG-1; 505(b)(2)

Drug Product Name/Strength: Amikacin liposome inhalation suspension / 590 mg per vial

Route of Administration: Oral inhalation

Applicant Name: Inmed

Submission Date: 03/28/2018 (Original Submission)

Background: The Applicant submitted this 505(b)(2) NDA seeking approval of the proposed drug-device combination product, Arikayce (amikacin liposome inhalation suspension or ALIS), 590 mg to be used with a product-specific eFlow[®] nebulizer (Lamira Nebulizer System), for the treatment of patients with of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium Avium Complex (MAC) as part of a combination antibiotic regimen for adult patients.

The ALIS clinical development program in NTM lung disease is based upon one ongoing adequate and well controlled pivotal Phase 3 Study INS-212; one completed, randomized, controlled Phase 2 supportive Study TR02-112; and one ongoing uncontrolled supportive Study INS-312, which is the extension study to INS-212. In each of these studies, ALIS was administered using a Lamira[™] nebulizer device. The Applicant relied in part on published literature to support the nonclinical pharmacology, nonclinical toxicology and clinical summary of efficacy. The safety and efficacy of the liposome formulation containing amikacin was evaluated in the ALIS clinical development program using the proposed drug product.

ALIS is a white, milky suspension consisting of amikacin sulfate encapsulated in liposomes, composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol with a mean diameter in the range of (b) (4). The drug product is filled into a 10-mL, single-use glass vial. The vial contains (u) (4) grams (u) (4) mL) of ALIS to deliver (b) (4) grams (8.4 mL containing 590 mg amikacin) of the suspension to the patient, using a product-specific eFlow[®] nebulizer (Lamira Nebulizer System).

The Phase 2 and 3 formulation composition is the same as the commercial formulation. A 10-mL vial containing (b) (4) ALIS at the same concentration of 70 mg amikacin/mL was used in NTM Phase 2 study (Study TR02-112) and NTM Phase 3 studies (Study INS-212 and Study INS-312): a Lamira commercial Nebulizer was used in the Phase 2 and Phase 3 studies.

Review Summary: The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting (1) the proposed in vitro release method and acceptance criteria, and (2) bridging between the proposed commercial product and the product used in the pivotal clinical studies. The Biopharmaceutics review findings are summarized as follows:

In Vitro Release (IVR) Method and Acceptance Criteria: The Quality Control (QC) in vitro release method and in vitro release acceptance criteria shown in the Table below are found acceptable, **on an interim basis**, for the routine QC of amikacin liposome inhalation suspension, 590 mg, for batch release and stability testing.

Apparatus/speed	Volume	Medium	Acceptance Criteria	
USP 2 (paddle) small vessel/150 rpm	Volume varies at each sampling time point [30 to 105.7 mL]	Triton/PBS buffer pH 7.2 at 37°C	Time (hours)	% Release
			0.5	NMT ^{(b) (4)} %
			1.5	^{(b) (4)} %
			3.0	NLT ^{(b) (4)} %

Biowaiver Request: A biowaiver is not needed nor submitted.

Bridging: The Phase 2 and 3 formulation composition is same as the commercial formulation. ^{(b) (4)} processes, ^{(b) (4)} (used at the Althea facility) and ^{(b) (4)} (used at the Therapure facility) were used for the manufacturing of the clinical and commercial batches. ^{(b) (4)} and ^{(b) (4)} are the commercial manufacturing processes. The Phase 3 clinical trial, NTM (INS-212), used various batches manufactured using ^{(b) (4)}. Since drug product manufactured using ^{(b) (4)} were all used in the clinical studies supporting safety and efficacy, there is no need for additional in vitro or in vivo bridging between products manufactured using ^{(b) (4)}. Nevertheless, drug products manufactured by ^{(b) (4)} exhibit comparable drug release profiles. Regarding the reliance of this NDA on published literature, reference is made to the Pharmacology/Toxicology and Clinical Reviews.

Recommendation: From a Biopharmaceutics perspective, NDA 207356 for Arikayce (amikacin liposome inhalation suspension), 590 mg is **recommended for APPROVAL with a Post-Marketing Commitment [PMC]**. The Applicant agreed to use the interim drug release method and acceptance criteria until a more optimal in vitro drug release method is approved. The Applicant agreed to a Post-Marketing Commitment [**PMC Number 3480**] to develop a new optimal in vitro drug release method in which only the drug released from the liposomes (free drug) is sampled and analyzed. The Applicant agreed (T-Con, dated 08/22/2018) to provide the requested reports as prior approval supplements, 06 months (interim report) and 12 months (final report) post NDA approval.



Signatures:

Primary Biopharmaceutics Reviewer:

Om Anand, Ph.D. 08/14/2018
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer:

Elsbeth Chikhale, Ph.D. 08/22/2018
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

1. List of Submissions Reviewed:

eCTD sequence #	Received date	Document
0001	03/28/2018	Original NDA submission
0028	07/27/2018	Quality/Response to Quality/Biopharmaceutics IR
0031	08/13/2018	Quality/Response to Quality/Biopharmaceutics IR
0040	08/16/2018	Quality/Response to Quality/Biopharmaceutics IR
	08/22/2018	T-Con with the Applicant

2. BCS Designation: (N/A)

Solubility: Amikacin is a white or almost white powder which is freely soluble in water. The pKa for amikacin is 8.1. The BCS designation is not applicable because the drug product is for inhalation, targeting lung delivery.

3. Polymorphism:

Amikacin sulfate is crystalline in nature. The Applicant reported that no other polymorphic forms are known in the literature.

4. Particle Size:

Amikacin is (b) (4). The product was developed to target a mean liposome particle size below (b) (4) to allow for transport of the liposomes within the aerosol droplets.

5. Formulation:

Arikayce (amikacin liposome inhalation suspension or ALIS) is a white, milky suspension consisting of amikacin sulfate encapsulated in liposomes, composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol with a mean diameter in the range of (b) (4) to (b) (4). The concentration of the active ingredient is expressed in terms of amikacin (b) (4) and is 70 mg/mL. The drug product is filled into a 10-mL, glass single-use vial. The vial contains (b) (4) of ALIS to deliver (b) (4) (8.4 mL) of the suspension to the patient using a product-specific eFlow[®] nebulizer (Lamira Nebulizer System). The composition of ALIS is provided in Table 1.

Table 1: Arikayce (amikacin liposome inhalation suspension or ALIS) composition

Component	Quality Standard	Function	Amount per mL	Amount per dose (nominal 8.4 mL) ^a	Theoretical amount per vial (8.9 mL)
Amikacin Sulfate	USP, Ph. Eur.	API	70 mg ^b	590 mg ^b	623 mg ^b
DPPC	Non-compendial, In-house	(b) (4)			
Cholesterol (b) (4)	NF, Ph. Eur., JP	(b) (4)			
(b) (4)					
Sodium Hydroxide	NF, Ph. Eur., JP	To adjust pH	(b) (4)		
Sodium Chloride	USP, Ph. Eur., JP	(b) (4)			
Water for Injection	USP, Ph. Eur.	(b) (4)			
(b) (4)					
NA = Not applicable					

ALIS is delivered using the Lamira Nebulizer System. The Lamira device is a high efficiency electronic nebulizer that uses a vibrating perforated membrane to generate inhalable aerosols. The device consists of a controller and a nebulizer handset. The nebulizer handset consists of the reservoir cover, medication reservoir, aerosol head, inhalation valve, aerosol chamber and mouthpiece. The device controller provides the electrical power to drive the aerosol head to produce aerosols and provides the user interface for operation information. The ALIS eFlow nebulizer system (Lamira) is shown in Figure 1.

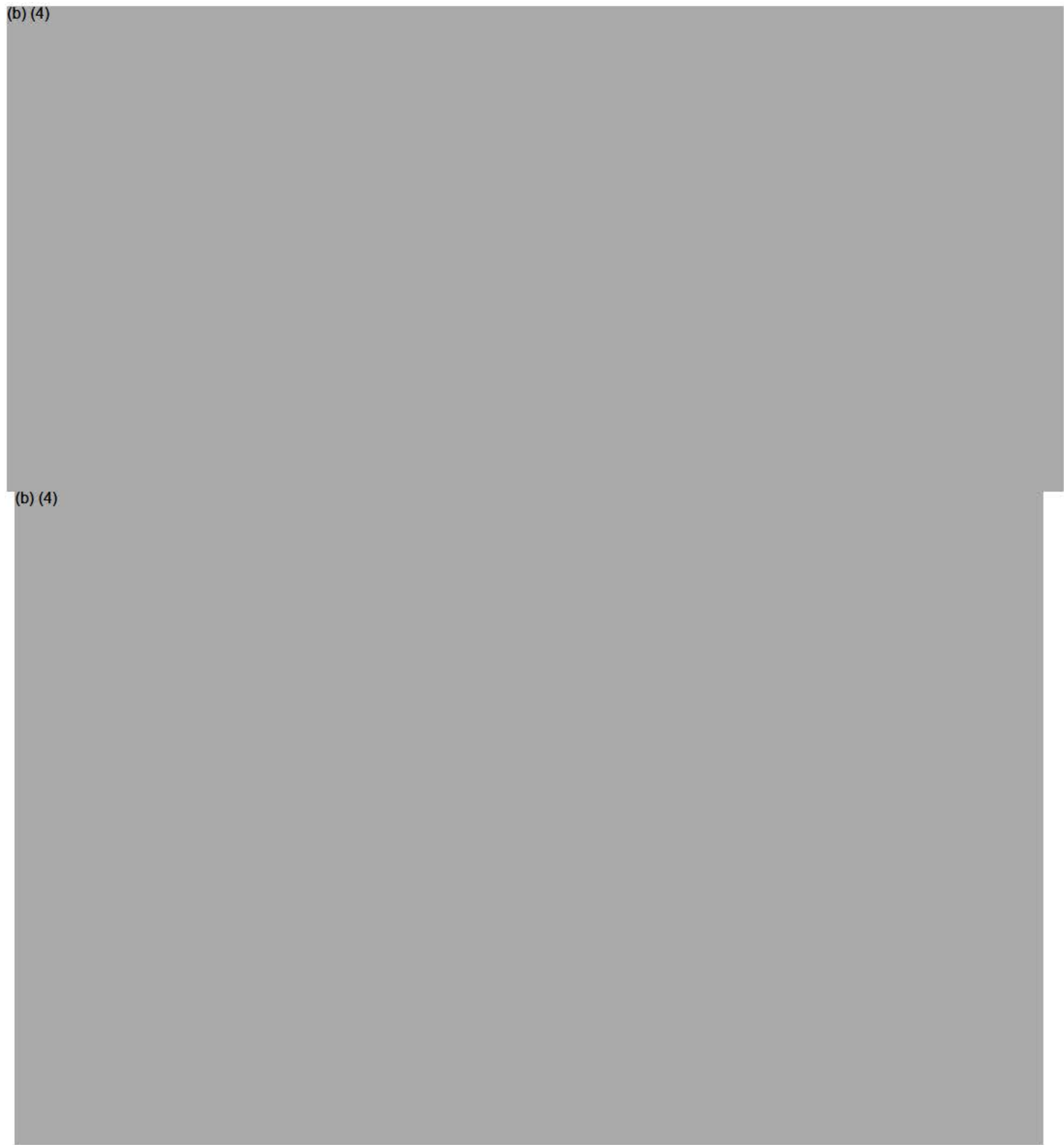
Figure 1: ALIS eFlow Nebulizer System (Lamira)



6. In Vitro Release (IVR) Method Development:

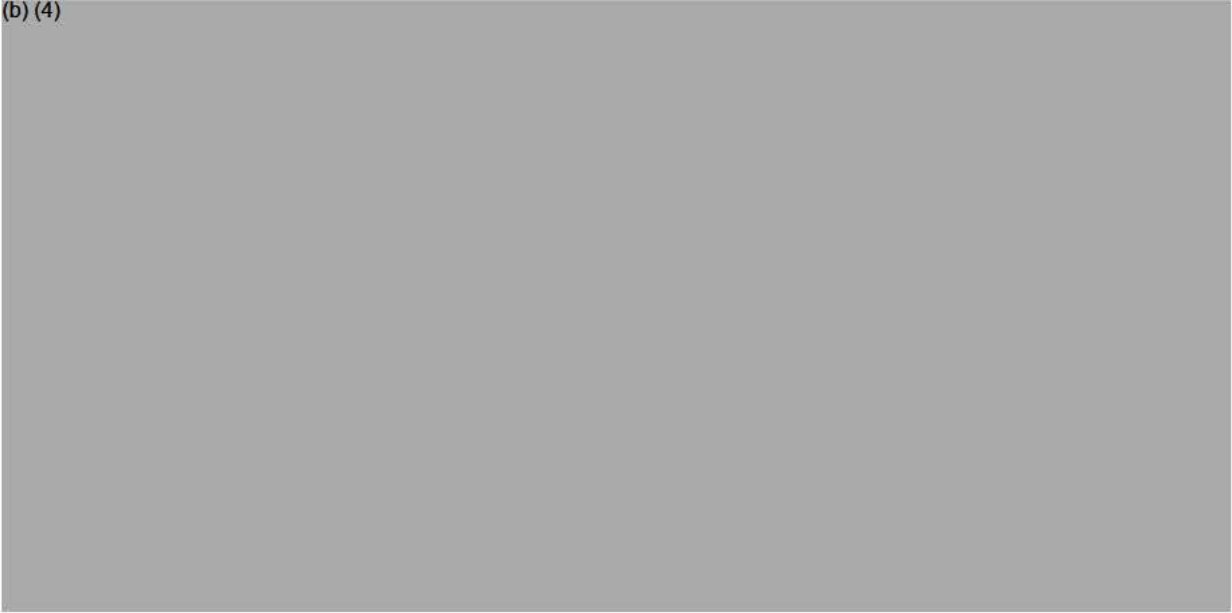
(b) (4)

(b) (4)



(b) (4)

(b) (4)



(b) (4)



(b) (4)



(b) (4)

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(b) (4)

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¹ Liposomal Amikacin for Inhalation (LAI) is same as ALIS

(b) (4)

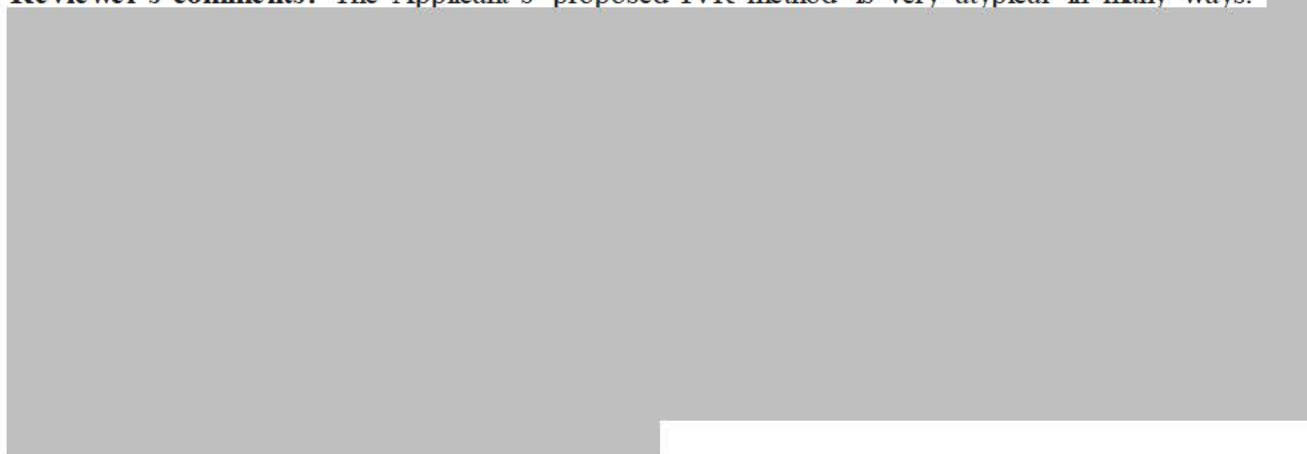


(b) (4)



Reviewer's comments: The Applicant's proposed IVR method is very atypical in many ways.

(b) (4)



In an IR (dated 07/21/2018), the Applicant was asked to provide address the above concerns regarding the proposed drug release method. The Applicant was recommended to develop a new optimal *in vitro* drug release method in which only the drug released from the liposomes (free drug) is sampled and analyzed. The Applicant was also recommended to consider using USP apparatus IV (flow through) for developing a new drug release method.

In a response² (dated 07/27/2018) to the IR, the Applicant reiterated that the current *in vitro* release method is suitable for quality control purposes. The Applicant also provided additional information

² <\\cdsesub1\evsprod\nda207356\0031\m1\us\quality-info-request-20jul2018.pdf>

demonstrating that the samples

(b) (4)

The Applicant also stated that due to

(b) (4)

the USP Dissolution Apparatus IV, may not be an option.

The Applicant agreed to continue to develop an optimal IVR method. The Applicant proposed to update the Agency on the progress of the method development as a post marketing commitment (PMC).

In this effort, the Applicant stated that they are exploring a technique

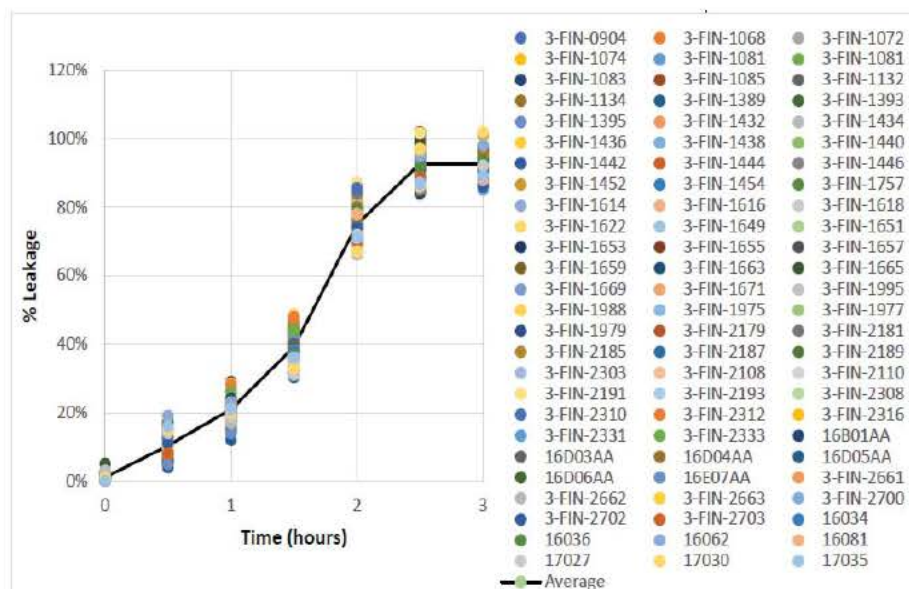
(b) (4)

7. In Vitro Release Acceptance Criteria:

The Applicant's originally proposed in vitro release acceptance criteria for the proposed drug product were: 0.5 hours: NMT ^{(b) (4)}%, 1.5 hours: NMT ^{(b) (4)}% and 3 hours: NLT ^{(b) (4)}%.

Comparative in vitro release profiles of registration and clinical batches: The *in vitro* release profiles of 79 ALIS batches manufactured by both the two proposed manufacturers (Althea and Therapure) along with an overall average release profile are provided in Figure 6.

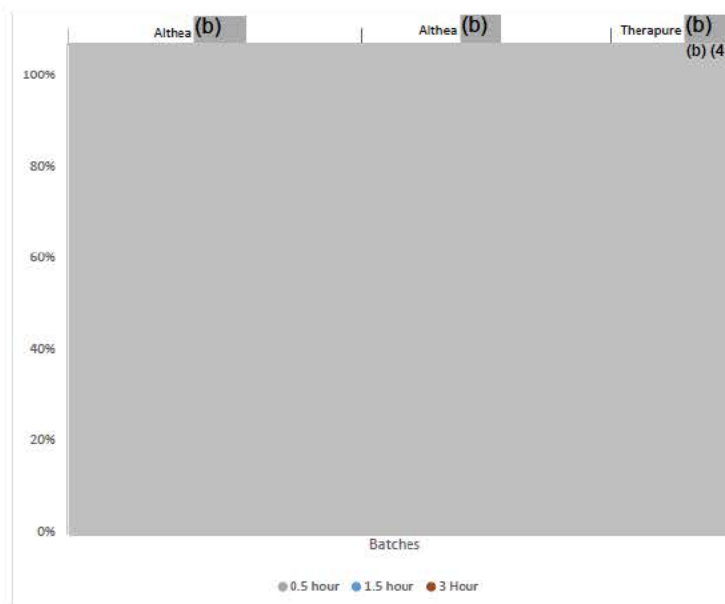
Figure 6: In vitro release profiles of representative ALIS Lots
(30 mL composite of four vials in one vessel)



The following batches³ were used in Phase 3 clinical, NTM (INS-212) trials: 3-FIN-2185, 3-FIN-2187, 3-FIN-2189, 3-FIN-2303, 3-FIN-2108, 3-FIN-2110, 3-FIN-219, 3-FIN-2193, 3-FIN-2308, 3-FIN-2310, 3-FIN-2312, 3-FIN-2316, 3-FIN-2331, 3-FIN-2333, 16D05AA, 16062, 3-FIN-2662, 3-FIN-2700, 3-FIN-2702, 3-FIN-1988, 3-FIN-1975, 3-FIN-1977, and 3-FIN-1979.

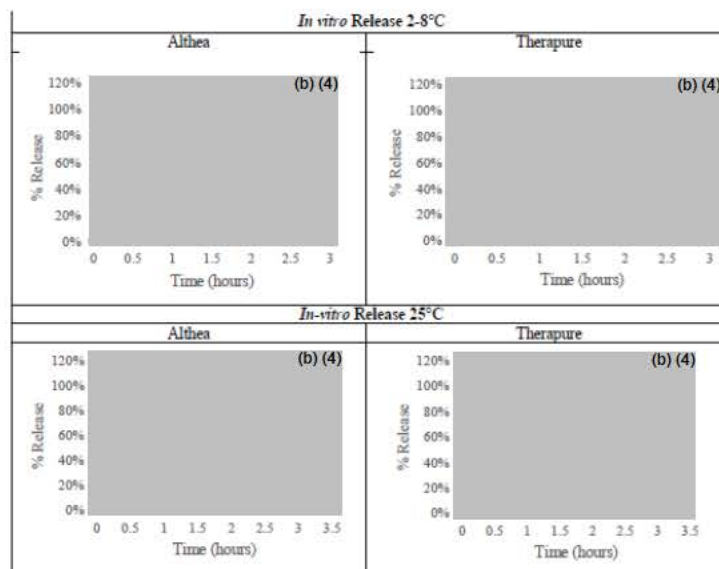
The following are the registration and the stability batches: 3-FIN-0904, 3-FIN-1068, 3-FIN-1072, 3-FIN-1074, 3-FIN-1389, 3-FIN-1391, 3-FIN-1393, 3-FIN-1395, 3-FIN-1444, 3-FIN-1757, 3-FIN-1618, 3-FIN-1649, 3-FIN-1653, 3-FIN-2179, 3-FIN-2303, 3-FIN-2110, and 16D03AA.

**Figure 7: Summary of the in vitro release data at “batch release”
(each dot represents an individual vessel measurement)**



³ **Note:** Six batches studied on stability were manufactured at the (b) (4) g commercial scale (b) (4) of which three of these batches are process validation batches (batch 3-FIN-2303, 3-FIN-2108, and 3-FIN-2110) (Anjinomoto Althea, Inc. (Althea)). One development batch, manufactured at Therapure, using the commercial process (b) (4), was placed on stability for six months at both 2-8°C and 25°C ± 2°C/60%RH ± 5%RH. Four additional batches (batch (b) (4)) manufactured at the (b) (4) commercial scale are being studied on stability; three of these batches are process validation batches (Therapure Biopharma, Inc. (Therapure)). (Details in sections 3.2.P.8.3].

Figure 8: Summary of the in vitro release data at “Stability” (each dot represents an individual vessel measurement)



Reviewer’s comments:

- The Applicant claimed that the storage temperature has no impact on the in-vitro release. However, this Reviewer notes that there are significant changes in the in vitro release of the stability batches, in particular, there is an apparent decrease in the release at 1.5 hours (presented in Figures 10 and 11) when stored at 2-8°C and 25°C.
- In a response to IR (dated 08/16/2018), it was clarified that the provided IVR data are not mean data for each batch, but are individual data (n=1), which is not appropriate and which makes it difficult to set appropriate acceptance criteria.
- The proposed in vitro release acceptance limit (NMT (b) (4) %) is reasonable for the first sampling time point (0.5 hour). However, for 1.5 hours sampling time point, a (b) (4) % range around the observed drug release data for the clinical batches should be set. Therefore, the Applicant should revise the dissolution acceptance criteria for the 1.5 hours sampling time point.

Information Request (IR) conveyed to the Applicant (dated 08/07/2018): In an IR (08/07/2018), the FDA acknowledged that the Applicant agreed to develop a new optimal in vitro drug release method in which only the drug released from the liposomes (free drug) is sampled and analyzed, as a post approval commitment. The currently proposed in vitro drug release method is acceptable on an interim basis, provided n=6 is used for batch release. In addition, based on the in vitro release data provided for the pivotal clinical and registration/stability studies of the proposed Amikacin liposome inhalation suspension, the FDA recommended the following in vitro release acceptance criteria:

Table 5: Recommended in vitro release acceptance criteria

Time (hours)	% Release
0.5	NMT (b) (4) %
1.5	(b) (4) %
3.0	NLT (b) (4) %

In addition, the Applicant was asked to provide a revised drug product specification table and update the stability protocol accordingly. For batch release and stability testing, USP<711> (Level 1, 2, and 3), should be followed.

The IR and the response (dated 08/13/2018) can be located at the following link:
<\\cdsesub1\evsprod\nda207356\0038\m1\us\quality-info-request-08aug2018.pdf>

Briefly, the Applicant summarized the in vitro drug release data at “batch release” and during “stability” testing as presented in Figure 9 below. In addition, the Applicant proposed new acceptance criteria as presented in Table 6 below:

Table 6: Newly proposed in vitro release acceptance criteria

Time (hours)	% Release
0.5	NMT (b) (4) %
1.5	(b) (4) %
3.0	NLT (b) (4) %

Figure 9: Batch release and stability data of IVR at the 1.5-hour time point (each dot represents an individual vessel measurement)



Reviewer's comments: As presented in Figure 9, there are several batches which are showing in vitro release at the 1.5-hour time point above (b) (4) % and below (b) (4) %. The identities (clinical batches or not) of these batches are not clear. Therefore, the Applicant was asked to provide several clarifications in an IR dated 08/15/2018.

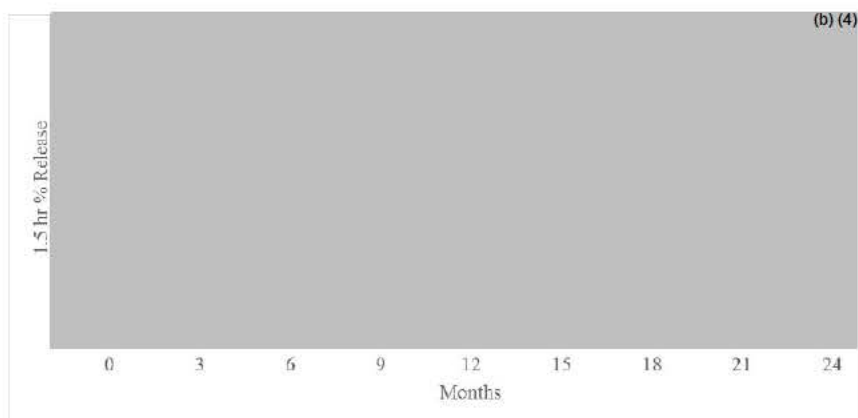
The IR (dated 08/15/2018) and the response (dated 08/16/2018) can be located at the following link:
<\\cdsesub1\evsprod\nda207356\0040\m1\us\quality-info-request-15aug2018.pdf>

Briefly, the Applicant clarified that the dots (in Figure 9 above) represent individual vessel data; provided a table that identifies each release value that is (b) (4) % and above and (b) (4) % and below (see Table 7) and submitted data generated for the batches tested on stability [2-8°C (Figure 10) and 25°C/60%RH (Figure 11)].

Table 7: Summary information for IVR results at (b) (4) % and above or (b) (4) % and below

Batch Number	% Release at 1.5 hour								Use-Clinical Study Number	Process	Manufacture Location (Date of Mfg)
	0	3	6	9	12	18	24	36			
3-FIN-1068	(b) (4)								TR02-108 (CF Phase 3)	(b) (4)	Althea (25MAR2011)
3-FIN-1078	(b) (4)								TR02-108 (CF Phase 3)	(b) (4)	Althea 11JUN2011
3-FIN-1389	(b) (4)								TR02-110 (CF Phase 3) TR02-112 (NTM Phase 2)	(b) (4)	Althea (22JUN2012)
3-FIN-1391	(b) (4)								TR02-110 (CF Phase 3)	(b) (4)	Althea (28JUN2012)
3-FIN-1444	(b) (4)								TR02-110 (CF Phase 3)	(b) (4)	Althea (11OCT2012)
3-FIN-1452	(b) (4)								TR02-110 (CF Phase 3)	(b) (4)	Althea (13DEC2012)
3-FIN-1618 Upright	(b) (4)								TR02-110 (CF Phase 3)	(b) (4)	Althea (09MAY2013)
3-FIN-1655	(b) (4)								TR02-110 (CF Phase 3)	(b) (4)	Althea (11JUL2013)
3-FIN-2181	(b) (4)								INS-212 (NTM Phase 3)	(b) (4)	Althea (04MAR2014)
3-FIN-2185	(b) (4)								INS-212 (NTM Phase 3)	(b) (4)	Althea (18MAR2015)
3-FIN-2303	(b) (4)								INS-212 INS-312 (NTM Phase 3)	(b) (4)	Althea (17JUN2015)
16D03AA	(b) (4)								Compassionate Use	(b) (4)	Althea (06APR2016)
16034	(b) (4)								INS-312 (NTM Phase 3)	(b) (4)	Therapure (08JUN2016)
17027	(b) (4)								Commercial Inventory	(b) (4)	Therapure (12APR2017)
17030	(b) (4)								Commercial Inventory	(b) (4)	Therapure (19APR2017)

(Green = values at (b) (4) % and above
Yellow = values at (b) (4) % and below
nt = not tested
S = scheduled

Figure 10: IVR (% Release) at 1.5-hour for stability samples stored at 2-8°C**Figure 11: IVR (% Release) at 1.5-hour for stability samples stored at 25°C**

Reviewer's comments: As presented in Table 7 and Figures 10-11 above, when the batches were stored at 2-8°C, they released the drug between (b) (4) %. However, there is a slight decline in the drug release when the batches were stored at 2-8°C and 25 °C. The drug product is proposed for storage at 2-8 °C throughout the shelf life, however, the drug product can be stored at room temperature 25 °C for up to (b) (4) weeks.

Telephone Conference (T-Con) (dated, 8/22/2018): The Agency requested a T-Con with the Applicant to discuss and resolve the remaining Biopharmaceutics review issues. During the T-Con (dated 8/22/2018) the Applicant agreed to perform the drug release test in 6 vessels instead of 1 vessel, and will implement USP Level 1, Level 2, and Level 3 testing as needed. In addition, the drug release acceptance criteria at 1.5 hours were discussed with the Applicant. The FDA recommended acceptance criteria of (b) (4) % at 1.5 hours [0.5 hours and 3 hours were previously found acceptable]. The Applicant agreed with the proposed acceptance criteria of (b) (4) % at 1.5

hours, and submitted a revised drug product specification Table. During this T-Con, the Applicant also agreed with the PMC timelines as follows:

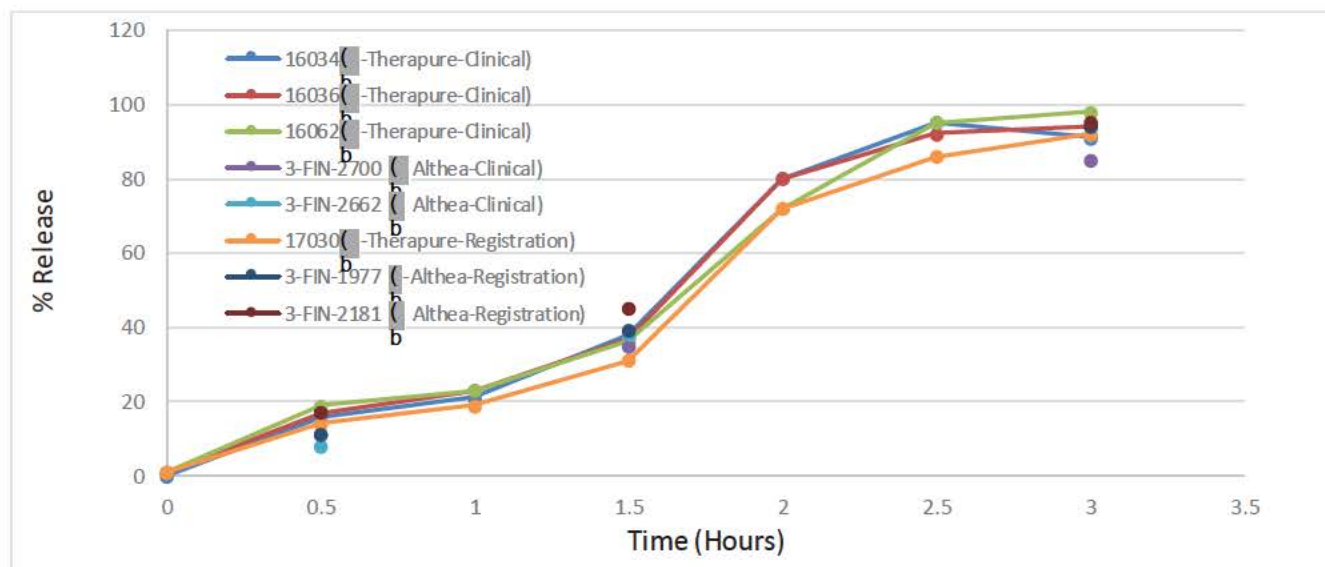
- Submission of Interim PMC Report 6 months after NDA approval (as part of a Prior Approval CMC Supplement to the NDA)
- Submission of Final PMC Report 12 months after NDA approval (as part of a Prior Approval CMC Supplement to the NDA)

8. Bridging:

The Phase 2 and 3 formulation composition is the same as the commercial formulation. A 10-mL vial containing (b) (4) mL ALIS at the same concentration of 70 mg amikacin/mL was used in NTM Phase 2 study (Study TR02-112) and NTM Phase 3 studies (Study INS-212 and Study INS-312). A Lamira (commercial Nebulizer) was used in Phase 2 and Phase 3 studies.

(b) (4) (used at the Althea facility) and (b) (4) (used at the Therapure facility) were used for the manufacturing of the clinical and commercial batches. (b) (4) and (b) (4) are the commercial manufacturing processes. The Phase 3 clinical trial, NTM (INS-212), used various batches manufactured using (b) (4). Since drug product manufactured using (b) (4) were all used in the clinical studies supporting safety and efficacy, there is no need for additional in vitro or in vivo bridging between products manufactured using (b) (4). Nevertheless, drug products manufactured by (b) (4) exhibit comparable drug release profiles (Figure 12). Regarding the reliance of this NDA on published literature, reference is made to the Pharmacology/Toxicology and Clinical Reviews.

Figure 12: Comparison of in vitro release profiles of the batches manufactured using different processes (each dot represents an individual vessel measurement)



Note (b) (4) are the different processes.



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Elsbeth
Chikhale

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ENVIRONMENTAL**R Regional Information***Environmental Analysis*

Application: NDA 207356

API: Amikacin

Drug Product: liposome inhalation suspension



Indication: ARIKAYCE (amikacin liposome inhalation suspension) is an aminoglycoside antibacterial indicated for the treatment of nontuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* Complex (MAC) as part of a combination antibiotic regimen for adult patients.

MOA: Amikacin is an aminoglycoside antibiotic that binds prokaryotic ribosomes to inhibit protein synthesis in susceptible bacteria

Claim of categorical exclusion: The drug sponsor has submitted a claim of categorical exclusion (21 CFR 25.31(b)) with supporting information. A statement of no extraordinary circumstances is provided as follows: "As far as Insmed is aware, there are no extraordinary circumstances surrounding the approval of the registration application for ARIKAYCE that could significantly affect the quality of the environment." Data are provided for estimated sales volume. No data are provided for environmental depletion mechanisms or environmental effects.

Aquatic exposure: For peak US forecast calculations ((b)(4) vials manufactured at California facility; Production volume = (b)(4)), the drug sponsor correctly estimated a WWTP effluent concentration (Estimated Introductory Concentration or EIC) of (b)(4) per billion (ug/L).

The fish plasma model (FPM; see references) was used to calculate an "effects ratio" > 1,000, indicating that it is unlikely that amikacin will cause effects in fish at estimated environmental concentration.

Potential for interaction with estrogen and androgen receptors: The interaction of amikacin with estrogen receptors was determined as **INACTIVE** in binding, agonist and antagonist ER models. The evaluation was made using predictions for Estrogen receptor activity as reported in Mansouri et al., 2016 (CERAPP project paper). Predictions for Androgen receptor activity was determined as **INACTIVE** in binding, agonist and antagonist AR models. The evaluation was made using used COMPARA models.

Aquatic toxicity predictions for amikacin are reported in the Danish QSAR toolbox database:

Fathead minnow: 96h LC₅₀: Leadscope model: 272401 mg/L; SciQSAR model: 4408 mg/L.

Daphnia magna: 48h EC₅₀: Leadscope model: 933 mg/L; SciQSAR model: 3.5E-5 mg/L

Pseudokirchneriella s. 72h EC₅₀: Leadscope model: 5958 mg/L; SciQSAR model: 8.9 mg/L; Battery: 2983 mg/L

Predicted acute toxicity concentrations are much higher than the EIC, except for the SciQSAR model for *Daphnia magna* acute toxicity, which predicted toxicity at the same order of magnitude as the EIC (approx (b) (4) mg/L). Additional *in vivo* studies would be required to further evaluate model predictions.

Relevant PUBMED publications on amikacin:

Chen et al., 2012. Fin reduction is a novel and unexpected teratogenic effect of amikacin-treated zebrafish embryos. *Toxicology Mechanisms and Methods*. 22(2): 151-158.

- Decreased survival rate of zebrafish embryos and fin malformation starting at 2 ppm = 2 mg/L (lowest concentration tested)
- EIC amikacin = (b) (4) mg/L; >1000x lower

Analogues: Kanamycin (used in the synthesis of amikacin)



Muller, 1982. Sensitivity of *Daphnia magna* Straus against eight chemotherapeutic agents and two dyes. *Bull. Environm. Contam. Toxic.* 28, 1-2.

- Acute toxicity for kanamycin sulfate: 24h-72h EC₅₀s range from 32 mg/L to > 128 mg/L.

Based on the above results, a low risk of environmental impacts to aquatic organisms from patient use and disposal of amikacin is anticipated.

References:

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Nallani G, Venables B, Constantine L, Huggett D. 2016. Comparison of measured and predicted bioconcentration estimates of pharmaceuticals in fish plasma and prediction of chronic risk. Bulletin of Environmental Contamination and Toxicology, 96(5):580-584.

Reviewer's Assessment: Adequate

Based on modeled and available data, a low environmental risk is expected due to approval of this application. Extraordinary circumstances are not indicated.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance is acceptable.

Primary Environmental Reviewer: Raanan A. Bloom, Ph.D.

Secondary Reviewer: Scott Furness, Ph.D.



Raanan
Bloom

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Michael
Furness

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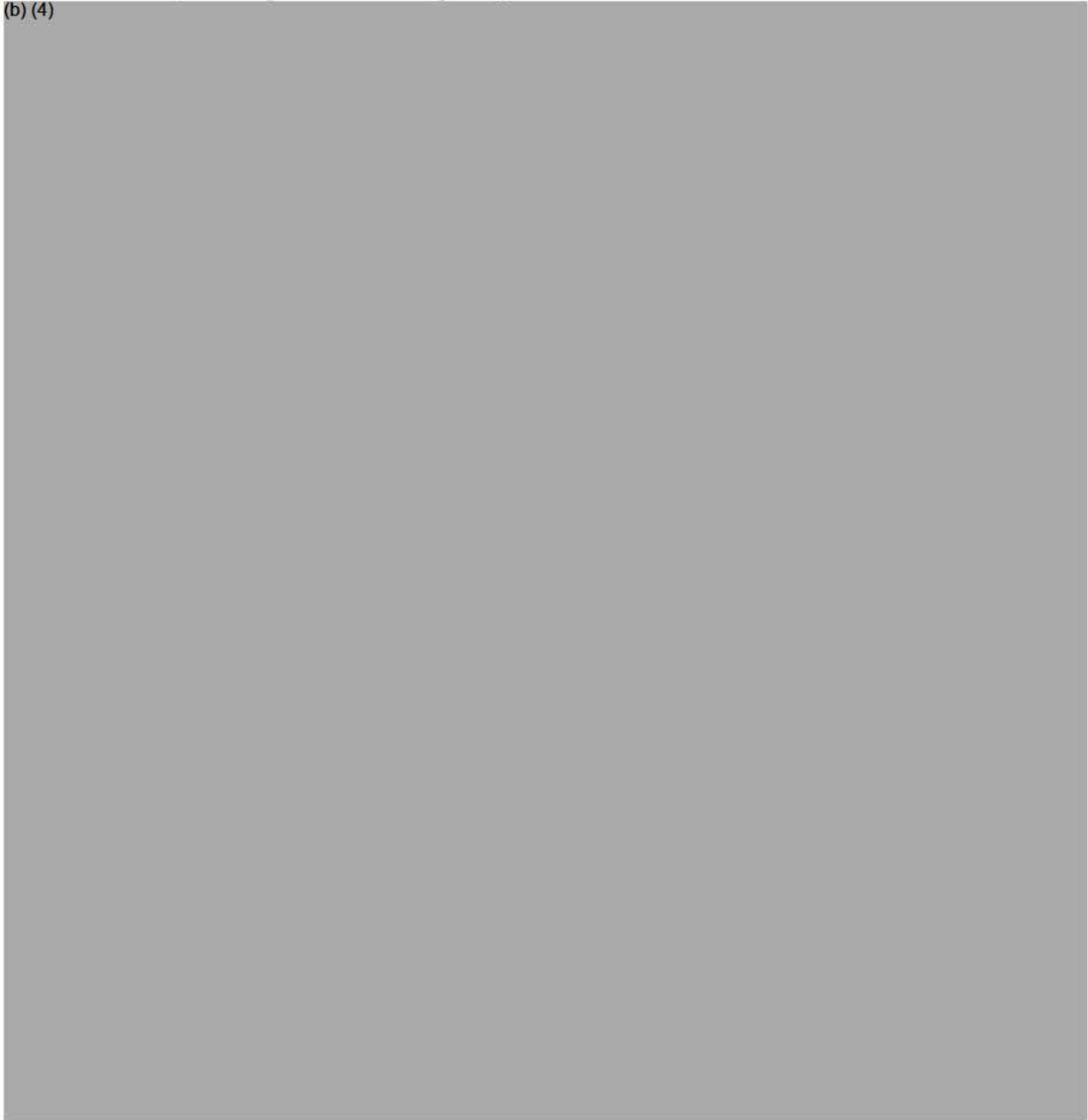
LABELING

I. Package Insert (SDN 8, eCTD Sequence 0008, Submitted on 5/25/2018)

1. Highlights of Prescribing Information

ARIKAYCE® (amikacin liposome inhalation suspension), for oral inhalation use

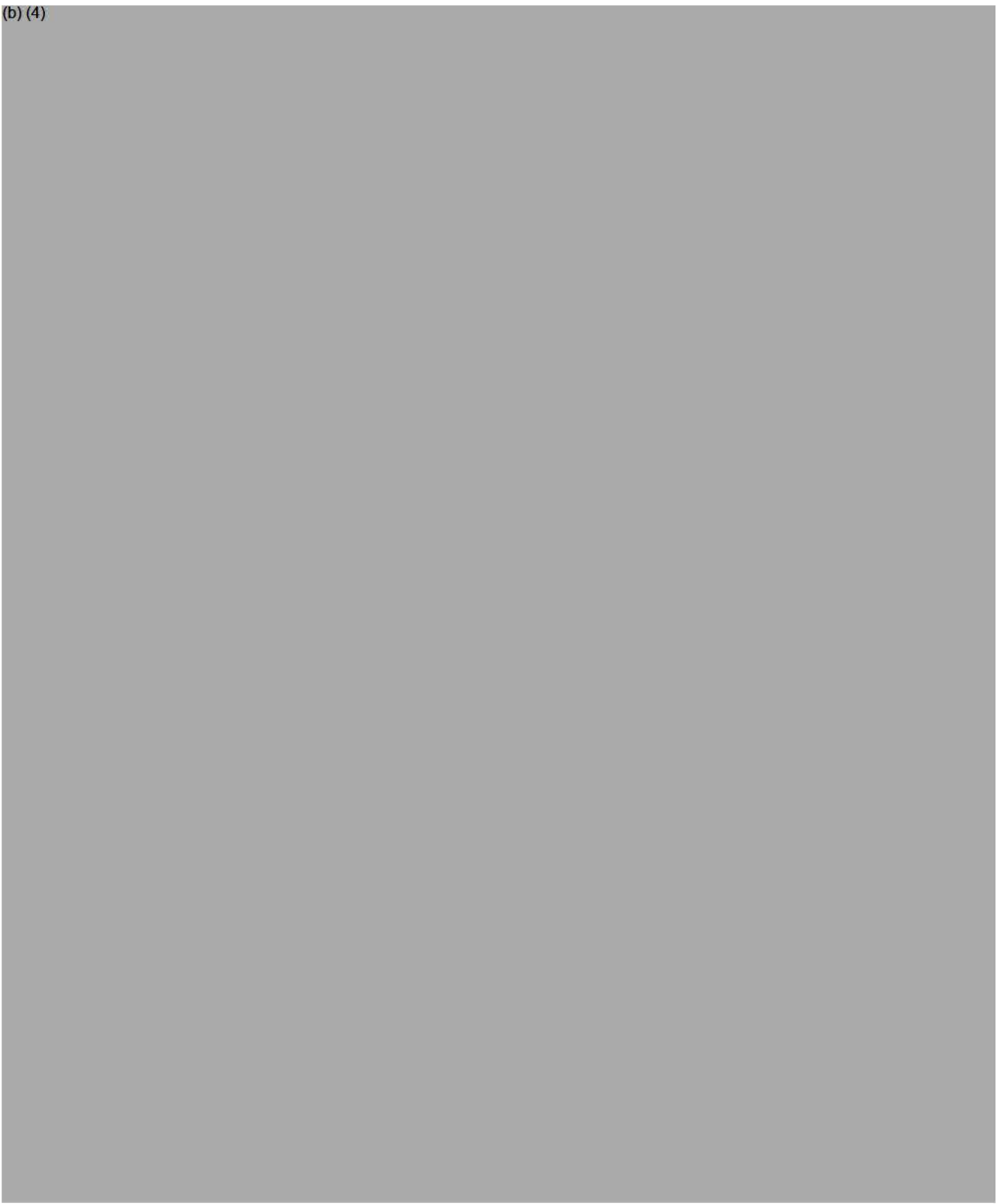
(b) (4)



(b) (4)



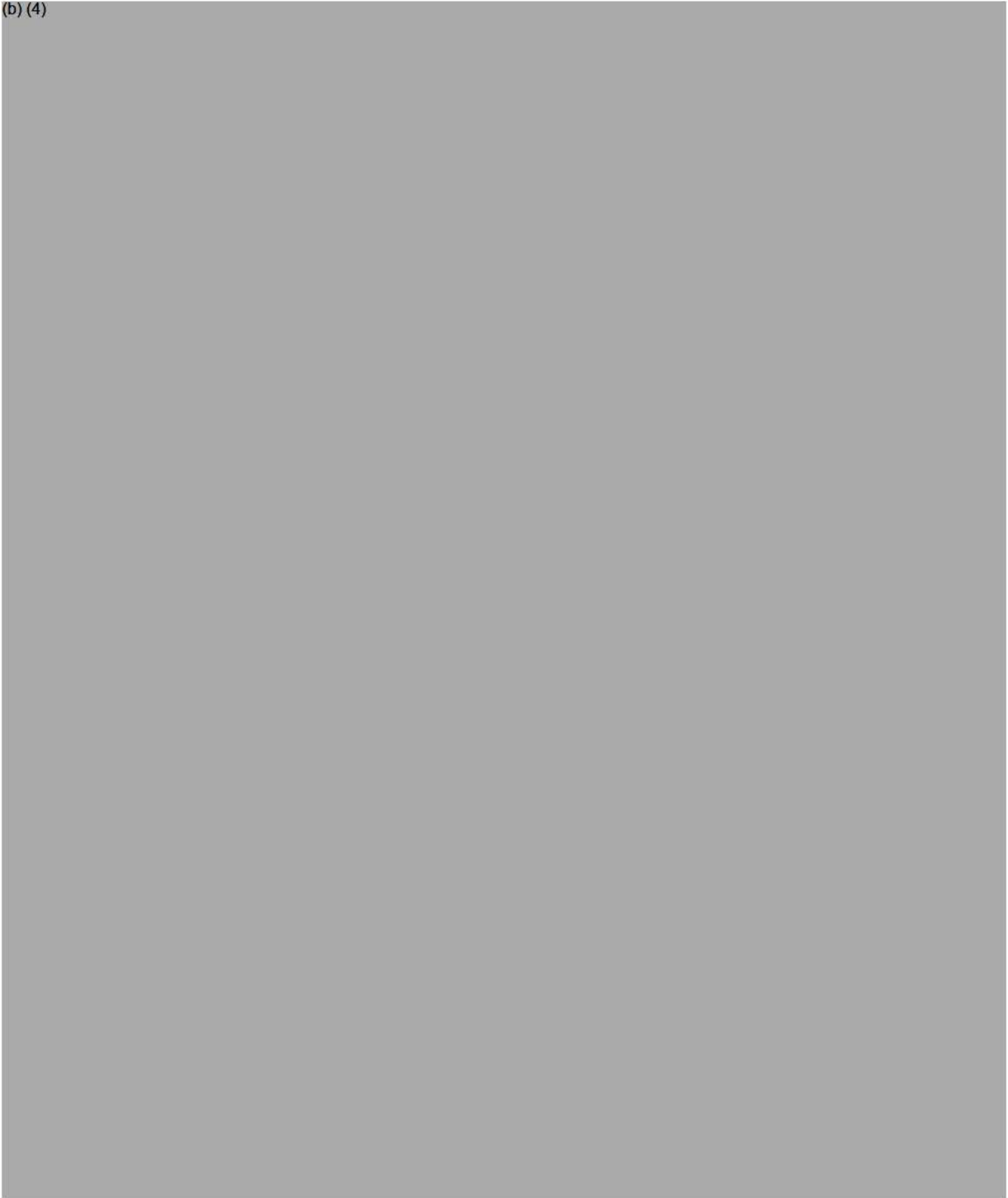
(b) (4)



(b) (4)



(b) (4)



Reviewer's Assessment of Package Insert: Changes recommended

Statements in Sections 11 & 16 regarding the device will be evaluated by the Device reviewer.

Refer to the assessment on container labels below regarding the storage condition statements.

For recommended changes, see the List of Deficiencies below.

II. Labels:**1. Container and Carton Labels**

(SDN 1, eCTD Sequence 0001, Submitted on 03/28/2018)

Vial Label

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

The following container labels will be reviewed by the Device and DMEPA reviewer:

- *Sleeve Insert*
- *Carton Exterior – Device*
- *Controller Launch*
- *Controller Preventative Film*
- *Controller Bottom Plate*
- *Carrying Bag*
- *AC Adapter*
- *Aerosol Head – Launch*
- *Aerosol Head – Post-Launch*
- *Aerosol Head Outer Packaging – Front*
- *Aerosol Head Outer Packaging – Back*
- *Handset – Launch*
- *Handset – Post-Launch*
- *Handset Outer Packaging*

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ADEQUATE	N/A
Dosage strength	Changes recommended	N/A
Net contents	Changes recommended	N/A
“Rx only” displayed prominently on the main panel	ADEQUATE	N/A
NDC number (21 CFR 207.35(b)(3)(i))	ADEQUATE	N/A
Lot number and expiration date (21 CFR 201.17)	ADEQUATE	N/A
Storage conditions	Changes recommended	N/A
Bar code (21CFR 201.25)	ADEQUATE	N/A
Name of manufacturer/distributor	ADEQUATE	N/A
And others, if space is available	N/A	N/A

Reviewer’s Assessment of Labels: Changes recommended

Salt equivalency statement is not included on the vial label, given the small label with limited space, this is acceptable. Salt equivalency statement is to be added to the carton exterior label.

Regarding the storage condition statements:

The proposed product storage conditions as supported by primary & in-use stability data in the NDA are:

Before dispensing:

24 months when stored under refrigerated conditions of 2-8°C

After dispensing:

4 weeks storage at (b) (4) 25°C (b) (4) 77°F (b) (4)

Current storage condition statements in the proposed labeling are:

(b) (4)

For consistency, the following storage condition statements are recommended:

Prior to Dispensing (Prior to Dispensing statement in Package Insert, and Prior to Dispensing statement on Carton Exterior label):

Store at 2°C to 8°C (36°F to 46°F). Do not freeze.

For all after dispensing labeling situations (Dispensing Instructions statement in Package Insert, Patient Information, Dispensing Instructions statement on Carton Exterior label, Inner Sleeves, and Vial Label):

Store at room temperature up to 25°C (77°F) until the Discard After Date indicated on the outer carton. Do not freeze.

For recommended changes, see the List of Deficiencies below.

List of Deficiencies:**For the Package Insert and Patient Information:**

- Remove the words "(b) (4)" from Sections 3 & 16.
- Change the package type term from single use to unit-dose per USP General Chapter (659) PACKAGING AND STORAGE REQUIREMENTS.
- No data could be located in the NDA to support the statement of handling: "shaking the vial well for at least 10 to 15 seconds, until the contents appear uniform and well mixed". IR to request supporting data has been sent.
- Update the salt equivalency statement in Sections 3 & 11 to read: containing amikacin 590 mg/8.4 mL (equivalent to amikacin sulfate 623 mg/8.4 mL).
- Sort inactive ingredients alphabetically in Section 11.
- Add a statement on the pH of the product in Section 11.
- Change Dispensing Instructions in Section 16 to read: Dispense with a 4-week "Discard After" dating and specify "Store at room temperature up to 25°C (77°F) until the Discard After Date indicated on the outer carton. Do not freeze."
- Change the storage condition statement in the How should I store ARIKAYCE? section of the Patient Information to read: Store ARIKAYCE vials at room temperature up to 25°C (77°F) until the Discard After Date indicated on the outer carton. Do not freeze.

For the Container Labels:

- Add the statement of sterility to all container labels.
- Change the strength/net content on all container labels to read: 590 mg / 8.4 mL.
- Change the storage condition statement on the Dispensing Instructions statement on Carton Exterior label to read: Dispensing Instructions: Dispense with a 4-week "(b) (4)" dating and specify "Store at room temperature up to 25°C (77°F) until the Discard After Date indicated on the outer carton. Do not freeze."
- Change the storage condition statements on the Vial Label to read: Store at room temperature up to 25°C (77°F) until the Discard After Date indicated on the outer carton. Do not freeze. See full prescribing information for room temperature storage and complete information on dosage and directions for use.
- Add the names of all inactive ingredients (sort alphabetically) on the Carton Exterior label.
- Add the salt equivalency statement "Each vial contains amikacin 590 mg/8.4 mL (equivalent to amikacin sulfate 623 mg/8.4 mL)" on the Carton Exterior label.
- Add "Rx only", lot number and expiration date, name of manufacturer/distributor, and the statement of "see package insert for dosage information" on all four Inner Sleeve labels.

Overall Assessment and Recommendation:

From the ONDP perspective, this application is not recommended for approval per 314.125(b)(6) until the deficiencies are satisfactorily resolved (see the List of Deficiencies)

Primary Labeling Reviewer Name and Date:

Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
Aug 17, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):



Yushi
Feng

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Balajee
Shanmugam

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Date: 8/19/2018 08:32:56PM

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations/ Comments
Assay, stability (impurities/degradation products)		L		Acc	
Physical stability (phase separation)		L		Acc	
Uniformity of Dose		L		Acc	
(b) (4) degradation products		M	Controlled in the drug product specifications with appropriate acceptance limits	Acc	
Osmolality		M	Controlled in the drug product specifications with appropriate acceptance limits	Acc	
Liposome particle size		H	Controlled in the drug product specifications with appropriate acceptance limits	Acc	
Aerodynamic particle size distribution		H	Controlled in the drug product specifications with appropriate acceptance limits	Acc	
In vitro release test Dissolution for Suspension only		M	Controlled in the drug product specifications. Current method and acceptance criteria are acceptable on an interim basis. The Applicant has agreed for an improved method via a prior approval supplement PMC.	Acc	
Sterility		H	Controlled in the drug product specifications with appropriate acceptance limits; additional controls through adequate manufacturing process controls and container closure	Acc	
Extractables and leachables		H	Extractables and leachables testing has been carried out and the results are satisfactory	Acc	



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Feng

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance

Date: May 22, 2018

To: Anh-Thy Ly, CDER/OPQ/OPRO/DRBPMI/RBPMI, E-mail: Anh-Thy.Ly@fda.hhs.gov
Office of Combination Products at Combination@fda.gov

Through: Nazia Rahman, Lead, OC, CDRH, E-Mail: Nazia.Rahman@fda.hhs.gov

Shanika Booth, Branch Chief, Respiratory, Ear/Nose/Throat, General Hospital, and Ophthalmic Devices Branch
Division of Product Labeling and Compliance, OC, CDRH
E-mail: Shanika.Booth@fda.hhs.gov

From: Rakhi Dalal, Ph.D., Respiratory, Ear/Nose/Throat, General Hospital, and Ophthalmic Devices Branch
Division of Manufacturing and Quality, OC, CDRH
E-mail: Rakhi.Dalal@fda.hhs.gov

Applicant: Insmed Incorporated
10 FINDERNE AVE
BRIDGEWATER, NJ 08807
FEI# 3010930003

Application # NDA 207356
CTS #: ICC1800288
Combination
Product Name: Amikacin Liposome Inhalation Suspension
Trade Name: ARIKAYCE® (Conditionally Approved)
Intended Use: ARIKAYCE® is for the treatment of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients.

Device Constituent: Nebulizer (Direct Patient Interface, i.e. eFlow® nebulizer (Lamira™ Nebulizer System), co-packaged and cross-labelled

Consult Request: Please indicate if this is fillable by 04/26/2018. Review dates will be update after filling

Pre-Approval
Inspection: No
Documentation
Review: Complete

CDRH/OC**Recommendation:**

1. **APPROVAL** of NDA 207356.
2. **Post Approval Inspection** of the Insmed Inc (NDA Sponsor) due to Orphan Drug Designation (3/25/13) with Fast Track and Breakthrough Therapy Designation.

Background:

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the (b) (4)

CDER also requested feedback on compliance status of the manufacturing site, and whether any inspection is necessary.

PRODUCT DESCRIPTION

The ARIKAYCE® (amikacin liposome inhalation suspension or ALIS) is a sterile aqueous, white, milky liposomal suspension consisting of amikacin sulfate encapsulated in liposomes. The drug product contains amikacin sulfate as the active ingredient. ARIKAYCE is comprised of amikacin sulfate encapsulated in liposomes composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol in a 2:1 ratio; other inactive excipients include sodium chloride, sodium hydroxide for pH adjustment and water for injection (WFI).

Amikacin sulfate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin which showed to be active against a broad spectrum of gram-negative organisms and some gram-positive organisms. Amikacin has been available for more than 30 years for human use as a parenteral antibiotic for susceptible infecting organisms. Amikacin, like other aminoglycosides, interferes with protein synthesis in susceptible microorganisms. Amikacin is actively transported across the bacterial cell membrane, binds to a specific receptor protein on the 30S subunit of bacterial ribosomes and interferes with the initiation complex formed between the messenger RNA and 30S subunit inhibiting protein synthesis.

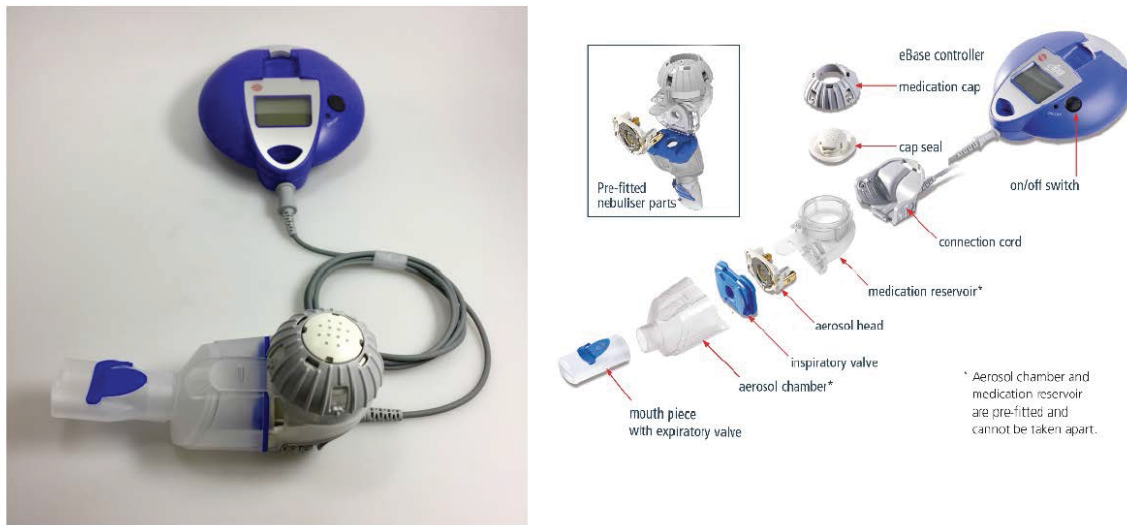
ARIKAYCE is formulated at a target concentration equivalent to 70 mg amikacin/mL and is provided in a unit dose configuration consisting of a single-use, (b) (4) glass vial with a (b) (4) using a closure system consisting of a (b) (4) stopper and a (b) (4) seal. The recommended dose for ARIKAYCE is one vial (590 mg amikacin) administered once daily, by inhalation for the treatment of Nontuberculous Mycobacterial (NTM) lung infection caused by *Mycobacterium avium* Complex (MAC) as a part of a combination antibiotic regimen for adult patients. The vial contains (b) (4) (8.4 mL) of the suspension to a product-specific eFlow® nebulizer (Lamira™ Nebulizer System). ARIKAYCE provides the opportunity to effectively target infection in the lung with once daily dosing while limiting systemic exposure and thereby systemic toxicity.

Device Constituent:

The device constituent of the ARIKAYCE is a single patient use and as per the device intended use, it is for 28 days use, as prescribed by their healthcare provider. The device for the

ARIKAYCE is based on an eFlow Nebulizer System provided by PARI Respiratory Equipment, Midlothian, VA, a subsidiary of PARI Pharma GmbH, Germany, and is provided as the Lamira™ nebulizer handset along with the eFlow® rapid control unit. ALIS is delivered through the mouthpiece of the Lamira™ Nebulizer System. The Lamira™ device is a high efficiency electronic nebulizer that uses a vibrating perforated membrane to generate an inhalable aerosol. The nebulizer handset consists of the reservoir cover, medication reservoir, aerosol head, inhalation valve, aerosol chamber and mouthpiece. The device includes a controller, which provides the electrical signal to drive the aerosol head and provides the user interface for turning the nebulizer handset on and off. The ALIS eFlow configuration with the nebulizer handset (hand-held unit), the connection cord and the controller is shown in Figure 1. The device is powered by either AA batteries or an AC adapter.

Figure 1 ALIS eFlow Device Configuration (left) and Components Overview (right)



Mechanism of aerosolization of drug:

The PRE nebulizer system uses the micro-perforated vibrating membrane technology to aerosolize liquid medications (Figure 3). This technology uses a wafer-thin plate of stainless steel, the so-called membrane, which is perforated with numerous laser-drilled holes. This micro-perforated membrane vibrates at high frequencies against a body of fluid. The vibration source is the (b) (4) actuator that is activated by an electronic drive circuit. The actuator and the perforated membrane are the main components of the aerosol head that is in contact with the liquid medication to be aerosolized. Liquid jets are created as an inertial response to the vibration of the membrane. These jets disperse to produce a stream of precisely controlled droplets.

Figure 3 Micro-Perforated Vibrating Membrane Technology for Aerosol Generation

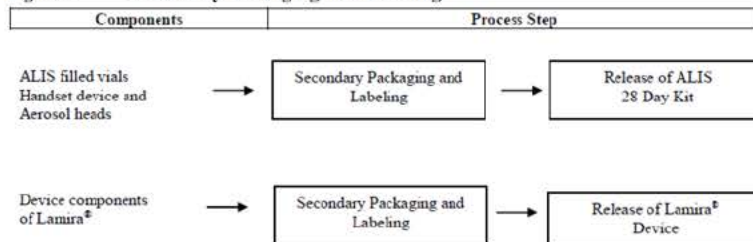


Advantages of nebulization Technology

- **Rapid Delivery.** Because devices using this technology nebulize at a faster rate than conventional jet or ultrasonic nebulizers, the duration of each treatment is shortened. These faster treatments are intended to help increase patient compliance.
- **Efficiency.** The technology enables the device to nebulize the dose to the lung with little waste. Further, the volume of residual liquid medication left in the device when the nebulization has ceased is negligible.

The drug is provided (co-packaged) with one Lamira™ Nebulizer Handset and 4 aerosol heads. The Lamira™ nebulizer system package, which includes the eFlow® Controller, is provided with the initial prescription and is considered as a cross-labelled combination product.

Figure 7 Secondary Packaging and Labeling



Device Component Description

The ALIS eFlow consists of three main components: The Nebulizer Handset, the controller, and the connection cord as depicted in Figure 2. The ALIS eFlow Nebulizer Handset (Figure 4) includes: the medication cap with cap seal (1), the medication reservoir (2), the aerosol head (3), the inhalation valve (4), the aerosol chamber (5) and the mouthpiece (6) with exhalation valve (7).

Figure 4 ALIS eFlow Nebulizer Handset

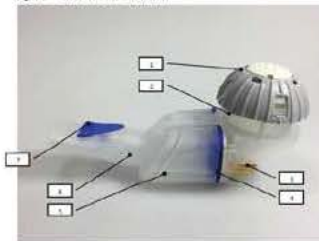


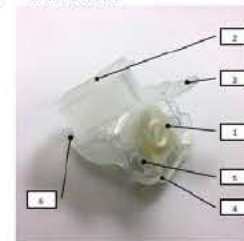
Figure 5 Fluid Feed Assembly



Figure 6 Medication Cap



Figure 7 Medication Reservoir



2.6.1. The Fluid Feed Assembly, Figures 5-7

The fluid feed assembly (Figure 5) is the nebulizer handset part that contains the medication cap (1) and medication reservoir (2).

The medication cap (Figure 6) is constructed of a rigid plastic lid (1) and a sealing cap (2), the latter of which is made with a hard and soft component. This cap's purpose is to create a seal with the inside of the medication reservoir, thereby causing the medication to maintain a slight negative pressure on the aerosol head. The medication reservoir (Figure 7) is the part where the medication is poured into the device and held pending aerosolization. It is designed to hold nominal volume of 8.4 mL of ALIS. The cup-shaped reservoir is made of (b) (4) membrane (1) as shown in Figure 7 at the base of the reservoir creates a seal with the aerosol head providing direct contact of medication with the atomizing head unit. The upper part of the reservoir is the fill opening (2) which, after filling, is firmly closed with the medication cap by a twist-lock. Once capped, the device can be turned upside down without spilling any medication. The design of the reservoir allows for minimal residue of the medication in the reservoir at the end of the nebulization process. The medication reservoir is attached to the aerosol chamber with a latch (3) and hinge (4) which allows the two parts to be opened for cleaning and insertion of the aerosol head. The reservoir has slots (5) to receive the aerosol head and a snap lock (6) for attaching the connection cord horse shoe connector.

2.6.2. Aerosol Head, Figure 8

The aerosol head (Figure 8) is the core component of the nebulizer essential for the aerosol generation. It is located between the fluid feed assembly and the aerosol chamber, and consists of a non-detachable, perforated membrane unit in the center mounted on a rigid plastic head-mount.

The aerosol head consists of a dome-shaped, wafer-thin (b) (4), stainless steel membrane with laser-drilled holes (1) that is (b) (4) to a stainless-steel (b) (4) (2) held in place by a (b) (4) head mount (3). Figure 8 on the left shows the side of the aerosol head that contacts with the drug solution. On the right side of Figure 8 the aerosol side is depicted. A ring-shaped (b) (4) actuator (not visible) is sandwiched between the stainless-steel (b) (4) (2) and the reddish-black flexible circuit which is (b) (4) (4). A stainless-steel membrane protector (5) protects the membrane from inadvertent damage during handling. The membrane protector additionally identifies the aerosol head. The aerosol head's two (b) (4) coated electrical connectors (6) provide the electrical contact to the (b) (4) actuator. These contacts fit through slots in the medication reservoir to mate with the connection cord's horseshoe connector contacts.



When electrically powered by the controller, the (b) (4) actuator vibrates the membrane forcing the liquid medication through the membrane's holes and aerosolizes it. The aerosol then passes into the aerosol chamber where it is held pending inhalation by the patient. The aerosol head is trade/drug-specific labelled.

2.6.3. Inhalation Valve, Figure 9

The inhalation valve is made of (b) (4) and is located between the aerosol chamber and the fluid feed assembly. It has openings through which the aerosol is injected into the aerosol chamber and two adjacent one-way butterfly-shaped valves (1). The valve is press-fit into the back side of the aerosol chamber so that it may be detached for cleaning. The static position of the one-way valves is the closed position. During patient inhalation, air is drawn into the aerosol chamber and the two one-way valves open into the chamber to carry the aerosolized droplets with the inhaled air. During patient exhalation, the valves return to their static CLOSED position.

Figure 9 Inhalation valve with two adjacent one-way butterfly-shaped valves (1)

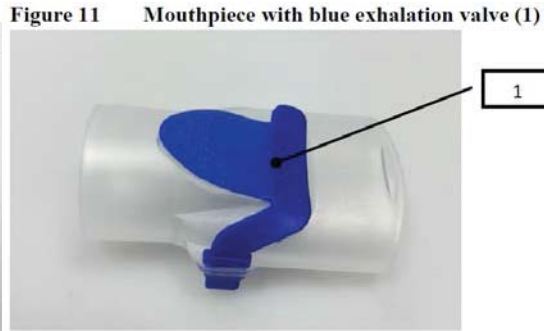


2.6.4. Aerosol Chamber, Figure 10

The (b) (4) aerosol chamber serves as a holding chamber for the aerosol, pending inhalation by the patient. The inhalation valve press-fits into its open back side (1), while the mouthpiece press-fits over the circular front outlet (2, patient side) of the aerosol chamber. It has a snap-fit hinge at its bottom (3) that locks with the fluid feed assembly. The top of the aerosol chamber has a snap-fit catch (4) for locking the chamber against the fluid field assembly. For cleaning, the snap-fit is unlocked, and the chamber rotates (on the snap-fit hinge) down and away from the fluid feed assembly. The aerosol chamber is trade-specific labelled.

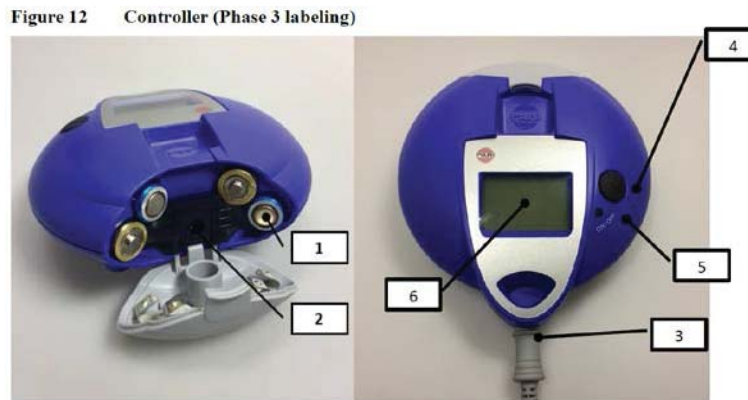
2.6.5. Mouthpiece, Figures 10 - 11

The mouthpiece (Figure 11) is made of (b) (4) which is connected to the front (patient side) outlet of the aerosol chamber (2) in Figure 10 to allow for the patient's respiratory flow. Press-fitted onto the mouthpiece is a (b) (4) one-way exhalation valve (1) in Figure 11. The exhalation valve is closed during inhalation and opens during exhalation by the patient. The mouthpiece may be removed for cleaning between use.



2.6.6. Controller, Figure 12

The controller contains the electronics in a disc-shaped plastic housing, which is approximately 5 inches in diameter and 1.6 inches in height. The controller conducts power pre-processing, monitors the nebulizer's aerosol generation through incorporated software, and generates optical and acoustical feedback to the user on nebulization status and out-of-range parameters.



2.6.8. Connection Cord, Figure 13

The connection cord of the ALIS eFlow device provides the connectivity between the nebulizer handset and the controller for tethered operation. On the handset end, the cord has contacts (1) that mate with the nebulizer handset's fluid feed assembly. The electrical contacts are wired through to an electrical connector on the opposite end (2) which mates with the controller. The connection cord used by the ALIS eFlow is identical to the connection cord used by existing eFlow devices listed in Table 1.



2.6.9. Accessories

2.6.9.1. AC Adapter

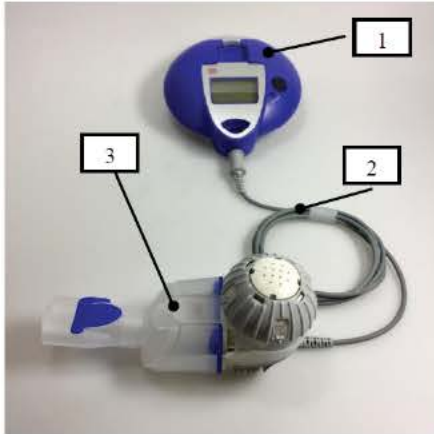
The controller can be powered by either 4 AA batteries or by the supplied medical-grade 12 V AC adapter. The AC adapter ALIS eFlow commercial product will be slightly smaller in size than the AC Adaptor used for the investigational studies. The AC adapter for the ALIS eFlow commercial product would have no difference in specification critical to ALIS eFlow and is described in Section 3 – Device Change History. Information concerning electrical safety of the proposed AC adapter is provided in Section 8 - EMC and Electrical Safety (deferred to ODE review).

Device constituent Development:

The nebulizer systems that was used in the clinical development of ALIS is provided in Table 6. For early clinical studies a commercially available LC STAR Jet Nebulizer (PARI) was used. For Phase 2 clinical studies were conducted using the 70 mg/mL ALIS formulation with the PARI eFlow Electronic Nebulizer (K033833). The time required to administer an ALIS dose of 560 mg amikacin (a total of about 8 mL) was found to be approximately 20 minutes. The nebulizer reservoir could only accommodate 4 mL of ALIS and therefore patients were required to fill the nebulizer twice. This eFlow device was modified prior to the Phase 3 studies to reduce nebulization time and reduce the number of times the patient must fill the device. Aerosol properties of ALIS delivered by the different variants of the eFlow Nebulizer Systems were considered as comparable. Details on the modifications and comparability between the eFlow nebulizers are discussed in Section 3.2.R.3 3 Device Change History. **Sponsor proposed that for commercialization, the nebulizer system used in the Phase 3 studies (the Lamira™ handset and aerosol head with the PARI eBase controller) will be used.** The device information of the Lamira is provided in Section 3.2.R.3 Device Module.

Per eCTD 3.2.R, Section 3.4. Proposed Commercial eFlow Nebulizer System, the commercial version of the ALIS eFlow Nebulizer System (launch version & post launch version) will introduce specific changes from the version used in the Phase 3 clinical studies (INS-212, INS-312) as described in Table 4 (Section 3.2.R.3 3 Device Change History), such as change to AC Adaptor, controller circuit board upgrade, material of construction, etc. Per the sponsor, these changes would have no impact on device performance, functionality, material of construction or aerosol performance. The function, the mode of operation and the aerosol performance would remain unchanged. Per the applicant, the minor device changes implemented were driven by scale up activities including replacement of electronic components as in Table 4. Comparison of the current device with K033833 is also provided for describing equivalence to other nebulizers, Table 1.

Table 4 **Comparative Description of the Investigational eFlow Nebulizer System vs. the ALIS eFlow for Commercial (Launch/Post launch)**

	Investigational eFlow Nebulizer System (INS-212; INS-312)	ALIS eFlow for commercial (launch & post launch version) which will be implemented after the drug and device brand names have been cleared.	Rationale & Assessment
Device Image	 Main Components: The Nebulizer System consists of a controller (1) and a Nebulizer handset (3) connected via a connection cord (2)		The function, the mode of operation and the aerosol performance were not changed. The minor device changes which were implemented were driven by scale up activities as discussed below.
Technical Specification	(b) (4)		The technical specifications were not changed.
Materials Nebulizer Handset			The materials were not changed.
Materials Aerosol Head			

	Investigational eFlow Nebulizer System (INS-212; INS-312)		ALIS eFlow for commercial (launch & post launch version) which will be implemented after the drug and device brand names have been cleared.		Rationale & Assessment
Controller/ Circuit Board		The controller contains the integrated circuit board that drives the aerosol head (b) (4) vibrating element. The controller is powered by 4-AA batteries or an AC adapter. The controller features a liquid crystal display (LCD) for status indication. The circuit board contains the electronic components, the display and the battery compartment to operate the aerosol head.		The commercial eBase Controller US will be implemented. The eBase Controller is essentially the same as the investigational Controller except for specific labeling and implementation of changes to fulfill the new requirements according to IEC 60601-1-2 4th edition. A Supplier and type of (b) (4) diode has been changed. (b) (4) To ensure compliance with IEC60601-1-2 4th edition, additional (b) (4) (b) (4) to pass the electrostatic discharge test. A transistor is discontinued and was replaced by a similar one. To prevent unintended shutdown of the controller if the patient wobbles on the connector of the power adaptor (b) (4) (b) (4) (b) (4) have been installed.	These changes involved an upgrade of the controller to the one used in the commercially available Altera and eRapid. The function, the mode of operation and the aerosol performance were not changed. All applicable electrical safety and EMC standards are fulfilled. The software of the controller was validated according IEC 62304 and FDA requirements.
	Investigational eFlow Nebulizer System (INS-212; INS-312)		ALIS eFlow for commercial (launch & post launch version) which will be implemented after the drug and device brand names have been cleared.		Rationale & Assessment
Housing Lower of Controller		N/A		Ribs (1) have been enlarged and holes (2) have been implemented to protect the circuit board from vertical water droplets.	The lower housing of the controller was optimized to meet IP21 rating.
AC Adapter				A new AC adapter model will be introduced.	The function, the mode of operation, the aerosol performance and materials were not changed. The proposed AC adapter fulfills the upcoming EMC IEC 60601-1-2 (Edition 4.0 2014-02) requirements and will be UL approved.

Table 1 Comparison of the ALIS eFlow with Other FDA Cleared PRE-Electronic Nebulizers

	ALIS eFlow Nebulizer System	Altera Nebulizer System	Trio Electronic Nebulizer System	eRapid Nebulizer System
Figure				
510(k) Clearance date	Not Applicable	K100380 February 22, 2010	K033833 May 5, 2004	K112859 May 30, 2012
Use	ALIS only This NDA (NDA 207356)	Cayston® only NDA 050-814	General Use	General Use
Drug solution fill volume	8.4 mL	1 mL	Maximum of 4 mL	Maximum of 6 mL
Aerosol head	Customized and medication-specific	Customized and medication-specific	Standard general use	Standard general use
Aerosol generation technology	eFlow® micro-perforated Vibrating Membrane Technology			

2.3. Intended Use

The ALIS eFlow is intended specially for the aerosolization of ALIS (amikacin liposome inhalation suspension) using vibrating membrane technology. The device is intended for administration to patients who have been prescribed ALIS, and may be used by health care professionals in hospitals, hospital-type facilities, nursing homes, sub-acute institutions, and by care givers in home settings.

At the time of treatment initiation, each patient will receive the ALIS eFlow and a drug kit containing 28 vials of ALIS drug product, four aerosol heads (for weekly changing of the aerosol head), and the nebulizer handset for use during 28-day treatment. Patients receive a new drug kit every 28 days, as prescribed by their healthcare provider.

REGULATORY HISTORY

Facility which may be subject to applicable 21 CFR Part 4 and 21 CFR part 820:

Firm, Address, FEI	Responsibilities	Inspection History and Review Comments
Insmmed Incorporated 10 FINDERNE AVE BRIDGEWATER, NJ 08807 FEI# 3010930003	NDA-207356 Applicant (Form 356h) and therefore considered responsible for the device constituent part used in the NDA and subject to QS requirements. Responsible for the finished combination product.	No inspection history in FACTS. Per NDA 207356, the commercial form of the device constituent part is a modified K033833 device, eFlow Electronic Inhaler/Nebulizer. The modified device is not cleared or approved by the FDA for interstate

		commerce. In the NDA 207356, the modified eFlow Electronic Inhaler/Nebulizer is cross-labelled and co-packaged in a kit prior to release. Recommendation: As the NDA-207356 has an Orphan Drug Designation (3/25/13) with Fast Track and Breakthrough Therapy Designation, a Post Approval inspection is recommended.
(b) (4)		Review deferred to CDER
		Review deferred to CDER
		Review deferred to CDER
		Review deferred to CDER
		Review deferred to CDER.

(b) (4)		Review deferred to CDER.
PARI Respiratory Equipment, Inc (PRE) 2412 PARI Way Midlothian, VA 23112 FEI: 1000142942	Manufacturing, release, and labeling of the nebulizer device components.	Last inspection (Surveillance, routine QSIT, Baseline Level II): (b) (4), VAI No recall found at this FEI in RES. No inspection required.
(b) (4)		Last inspection (QSIT, covered CAPA, P&PC of automated assembly of (b) (4) NAI.
		No recall found at this FEI in RES. No inspection required.

Per the Section 2.3.P.3.1, the product is a co-packaged drug-device combination product subject to 21 CFR part 4. All the facilities comply with cGMP in accordance with 21 CFR 210 and 211. (b) (4) also complies with cGMP in a streamlined approach in accordance with 21 CFR 820. PARI Respiratory Equipment, Inc. complies with current cGMP in accordance with 21 CFR 820.

Inspection Recommendation: Post-approval Inspection required.

DOCUMENTATION REVIEW

The application was evaluated for the applicable 21 CFR part 820 regulations under the 21 CFR Part 4.

Management Responsibility, 21 CFR 820.20:

The Management Responsibility for the cross labelled device constituent for the ARIKAYCE, under 21 CFR 820.20 is provided in eCTD 3.2.R.3.10 Quality System Information, Insmmed Incorporated Number: MFG-QLT-000122, Version: 3.0, Approved date: 01/30/2018. The PARI Quality Manual in the Document No. 42-06, SOPC Number: 17S005 Effective Date: 2/17/17, provides general policies and procedures for the manufacturing, packaging, testing, storage, and distribution of PARI products and services. The Management Review, SOP 56-01 describes the procedure applies to the management review system for PARI in the Americas (PitA). The Internal Quality Audits, SOP 82-02 describes the standard method for evaluating the PARI Quality Management System through an internal audit program. This procedure applies to all procedures and policies related to the design, manufacture, packaging, labeling, storage,

distribution, installation, and/or servicing of PARI in the Americas (PitA) products and processes. As the 21 CFR 820.20 was related to PARI, additional information under the 21 CFR 4.4 Call-outs was requested in an IR (as below).

According to the NDA 207356, the commercial form of the device constituent part is a modified K033833 device, eFlow Electronic Inhaler/Nebulizer. The modified device is not cleared or approved by the FDA for interstate commerce. In the NDA 207356, the modified eFlow Electronic Inhaler/Nebulizer is cross-labelled and co-packaged in a kit prior to release. Per the Section 2.3.P.3.1, the co-packaged drug-device combination product is subject to 21 CFR part 4. In the NDA 207356, only the PARI Quality System (QS) information is provided for the device constituent part. We are unable to locate the QS Call-Out information that relate to 21 CFR part 4.4 applicable to the NDA 207356, ARIKAYCE®. Please provide the following information for review.

- 1. A summary of how Insmed Incorporated's management structure with executive responsibility who manage, perform, and assess work affecting quality of the product and related controls, ensure that the firm's quality policies are appropriately implemented and followed, and the product is appropriately designed and manufactured in conformance with cGMP requirements, including quality system requirements as per 21 CFR 820.20.*

Firm's response (5/21/2018): Per the sponsor, Insmed's management structure includes a

(b) (4)

. The Quality Policy includes the identification of quality objectives, the definition and allocation of resources and responsibilities, and the use of formal Quality System reviews. Per the firm, Insmed recognizes that the effective operation of the Quality System is dependent on clearly identified authorities, responsibilities and interactions for all personnel. (b) (4)

assures that the procedures and control systems are implemented and followed to assure that the products are appropriately designed and manufactured in conformance with cGMP requirements including Quality System requirements as per 21 CFR 820.20, and the objectives of that policy. (b) (4)

The Quality Policy is provided in document title "Insmed Incorporated Number: POL-QA-000001, Version 2.0, Quality Policy, Effective Date: 9/14/2017", Attachment 1 of the response.

The Management Responsibility information as provided in the NDA 207356 to support the 21 CFR 820.20 Call-Out requirements for the ARIKAYCE® is deemed acceptable and adequate.

Design Controls, 21 CFR 820.30

The Design Control activities for the cross labelled device constituent for the ARIKAYCE is provided under the eCTD 3.2.R.3, Section 10.1 Design Control, Insmed Incorporated Number: MFG-QLT-000122, Version: 3.0, Approved date: 01/30/2018. Individual elements of the design

controls is provided for the device constituent part. Design Control SOP 73-01 described the PARI Respiratory Equipment (PRE) standard method for controlling and verifying new products. (b) (4) of SOP 73-01 outlined the steps for planning, design input, verifying the output meets the design output, and validation that the design meets user requirements. The PRE design control process is (b) (4)

(b) (4)

(b) (4)

Design verification is done as (b) (4) to confirm the design output meets the design input. The design validation is planned as part of (b) (4) per SOP 73-01 and SOP 75-08 to confirm the design output meets the customer's needs. = Design transfer is complete at the end of (b) (4) per SOP 73-01. In this phase, (b) (4)

(b) (4)

as per Design Control, SOP 73-01 and Document/Engineering Change Control, SOP 42-03. Furthermore, (b) (4). Design control information provided in NDA 207356 is acceptable and no issues remain. Per the 05/21/2018 sponsor's response to the IR, the (b) (4) specific to the modified eFlow Electronic Nebulizer (Lamira™ nebulizer) is located (b) (4).

The Design Control information as provided in the NDA 207356 to support the 21 CFR 820.30 Call-Out requirements for the ARIKAYCE® is deemed acceptable and adequate.

Purchasing Controls, 21 CFR 820.50

The cross-labeled and co-packaged device constituent of the ARIKAYCE® is provided in 3.2.R.3.10 Quality System Information, under Purchasing, SOP 74-01. The SPR provides a standard method for conducting purchasing activities. This procedure applies to all materials, parts, and services that impact PARI in the Americas' Quality Management System. There are purchasing and quality agreements with supplier(s) of critical components. Suppliers of critical components are audited at planned intervals.

As the CDRH/OC could not locate information that related to Insmmed's Purchasing Control under the 21 CFR 820.50 Call-Out or the Supplier Agreements between the NDA sponsor and the device constituent contract manufacturers (PARI Respiratory Equipment, Inc (PRE) and (b) (4)), including qualification of the combination products, an IR was sent to the firm as below:

3. *Summary of information pertaining to the Purchasing Control as per 21 CFR 820.50 to demonstrate controls and documentation for components, products, and/or services received at the Insmmed Incorporated's facility for use in the manufacture of the combination product. The summary should include the applicant's evaluation process of their suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in the firm's Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final combination product. For review, please provide the copies of the Supplier Agreements between Insmmed and the contract manufacturers including PARI Respiratory Equipment, Inc. for the device constituent parts, the (b) (4) for the secondary packaging and labeling, etc.*

Firm's response (5/21/2018): Insmmed acknowledged FDA's comment on the reference to Purchase Control as per 21 CFR 820.50 and indicated that the firm has procedures and systems that include requirements for establishing and communicating specifications to suppliers, performing qualification and approval of suppliers and materials prior to utilizing them, monitoring the performance of the suppliers and directing periodic reassessments. The Vendor Management Standard Operating Procedure (SOP), Attachment 2, contains the evaluation process for the suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Additionally, copies of the Quality Agreements executed between Insmmed and PARI Respiratory Equipment and (b) (4) are provided with this response in Attachments 3 and 4, respectively.

Purchasing control information as provided in the NDA 207356 to support the 21 CFR 820.50 Call-Out requirements for the ARIKAYCE® is deemed acceptable and adequate.

Corrective and Preventive Actions (CAPA), 21 CFR 820.100

The CAPA procedures are provided in the Insmmed Incorporated Number: MFG-QLT-000144, Version 2.0, Approved Date: 1/22/2018. The PARI Corrective and Preventive Action, Doc. No. 85-02, Rev. No. J1/17, SOPC Number: 17S001, Effective Date: 1/5/17, provides a standard method for documenting investigations into nonconformities and potential nonconformities.

Per the document, this procedure applies

(b) (4)

in accordance with SOP 56-

01. Per section 6.5, the Corrective and Preventive Action Report records are maintained including investigation records, memos, and fax transmission records as appropriate in the Corrective and Preventive Action Report file.

As the above information was associated only for PARI and not for Insmmed, additional information was requested in an IR, as below.

4. *Summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.*

Firm's Response (5/21/2018): Per the response, Insmmed has procedures established for the investigating the deviations, failures and customer complaints to determine the root cause and identify appropriate and effective corrective actions to prevent recurrence. In addition, the investigation into failure of the device constituent part is documented in the PARI Respiratory Equipment, Inc. CAPA system,

(b) (4)

The Quality system at Insmmed included

(b) (4)

actions required to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions per 21 CFR 820.100 as detailed in Insmmed's Corrective and Preventive Actions SOP, Insmmed Incorporated Number: SOP-QA-000017, Version 3.0, Effective Date: 3/31/2017. Additionally, Insmmed

(b) (4)

to identify adverse trends and opportunities for improvement for the implementation of preventive actions. There is a system for tracking the CAPAs to assure they have been implemented, and confirmed to be effective as shown in Insmmed's

(b) (4)

SOP, Insmmed Incorporated Number: SOP-QA-000062, Version 2.0, Effective Date: 5/18/2018.

Corrective and Preventive Actions information as provided in the NDA 207356 to support the 21 CFR 820.100 Call-Out requirements for the ARIKAYCE® is deemed acceptable and adequate.

Manufacturing

Following is the Production flow provided. eCTD 3.2.R, Section 10.15.2. Production and Process Controls, 820.70 contains the Control of Facilities, SOP 63-01.

(b) (4)



(b) (4)



DOCUMENTATION REVIEW RECOMMENDATION

The NDA 207356 was assessed for applicable documentation, compliance with the applicable Quality System Requirements under 21 CFR Part 4. As information related to Insmid Inc., 21 CFR 820 Call out requirements could not be located, an IR request was sent to the firm. On May 21, 2018, sponsor responded to the IR deficiencies. The response was reviewed and found to be

adequate. Currently, there are no outstanding issues remaining for review. Information in NDA 207356 is considered acceptable.

CDRH Office of Compliance Recommendation

The Office of Compliance (OC) at CDRH has completed the evaluation of NDA 207356 and has considered the Application review complete. The NDA 207356 is recommended Approvable with Post Approval Inspection.

Rakhi Dalal, Ph.D.

Prepared: RDalal, Ph.D.:05/22/2018

Reviewed:

CTS No.: ICC1800288

NDA 207356