APPLICATION NUMBER:

207356Orig1s000

OTHER REVIEW(S)
1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revisions for the following components of the Arikayce product (Appendix A):

- Container Labels
- Carton Labeling – Exterior, Weekly Sleeve, and Aerosol Head
- Headset Packaging Outer Labeling
- Instructions for Use (IFU)
- Quick Start Guide (QSG)
- Prescribing Information (PI)
- Medication Guide (MG)

DAIP’s request was for DMEPA to determine if these components are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

Additionally, the Applicant has requested approval under the Limited Population Antibacterial Drug (LPAD) pathway for use in the treatment of nontuberculous mycobacterial lung disease

caused by *Mycobacterium avium* complex in adult patients who have limited or no alternative treatment options. To comply with 21 USC 356(h), specific language was included on the carton labeling, and in the Prescribing Information (PI), Quick Start Guide (QSG), Medication Guide (MG), and Instructions for Use (IFU). The language is intended to convey that the product has been shown to be safe and effective only for use in a limited population. For more information on this limitation, see the draft guidance, *Limited Population Pathway for Antibacterial and Antifungal Drugs Guidance for Industry*. b

2 CONCLUSION

The revised labels and labeling for Arikayce are acceptable from a medication error perspective. We have no further recommendations at this time.

b Draft Guidance: Limited Population Pathway for Antibacterial and Antifungal Drugs Guidance for Industry
Accessed on September 25, 2018
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/s/

JAMES H SCHLICK
09/26/2018

OTTO L TOWNSEND
09/26/2018
Date: September 20, 2018

To: Sumathi Nambiar, MD, MPH
   Director
   Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

From: Sharon Williams, MSN, BSN, RN
   Senior Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)
   David Foss, Pharm. D., BCPS
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ARIKAYCE (amikacin liposome)

Dosage Form and Route: inhalation suspension, for oral inhalation use

Application Type/Number: NDA 207356

Applicant: Insmed, Inc.
1 INTRODUCTION

On March 28, 2018, Insmed, Inc submitted for the Agency’s review an Accelerated Approval seeking marketing authorization for a drug-device combination for ARIKAYCE (amikacin liposome inhalation suspension) administered by oral inhalation using the product-specific Lamira™ Nebulizer System and is to be indicated for the treatment of nontuberculous mycobacteria (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients. Orphan designation was granted on March 25, 2013. Fast Track and Breakthrough Therapy designations were granted on June 28, 2013 and June 16, 2014 respectively. The designation as a Qualified Infectious Disease Product (QIDP) was granted on June 28, 2013.

During labeling meetings the decision was made for the sponsor to change the submitted Patient Package Insert (PPI) to a MG based on the Boxed Warning and significant serious side effects. After discussion with the Regulatory Project Manager (RPM) for the application on September 7, 2018, the decision was made to use the submitted PPI labeling as the basis for the pending MG due to the essence of time in approving the application. Shortly upon completion of a review of the PPI the sponsor submitted a MG.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infective Products (DAIP) on April 12, 2018 for DMPP and OPDP to review the Applicant’s proposed MG.

2 MATERIAL REVIEWED

- Draft ARIKAYCE (amikacin liposome inhalation suspension) proposed MG, IFU received on September 11, 2018, and received by DMPP and OPDP on September 12, 2018.

- Draft ARIKAYCE (amikacin liposome inhalation suspension) Prescribing Information (PI) received on March 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on September 4, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.
In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

4 CONCLUSIONS
The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS
- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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

SHARON W WILLIAMS
09/20/2018

DAVID F FOSS
09/21/2018

LASHAWN M GRIFFITHS
09/21/2018
Date: September 11, 2018

To: Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

David Foss, Pharm. D., MPH, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) Instructions for Use (IFU) and Quick Reference Guide (QRG)

Drug Name (established name): ARIKAYCE (amikacin liposome)
Dosage Form and Route: inhalation suspension, for oral inhalation use
Application Type/Number: NDA 207356

Applicant: Insmed, Inc.
1 INTRODUCTION

On March 28, 2018, Insmed, Inc submitted for the Agency’s review an Accelerated Approval seeking marketing authorization for a drug-device combination for ARIKAYCE (amikacin liposome inhalation suspension) administered by oral inhalation using the product-specific Lamira™ Nebulizer System and is to be indicated for the treatment of nontuberculous mycobacteria (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients. Orphan designation was granted on March 25, 2013. Fast Track and Breakthrough Therapy designations were granted on June 28, 2013 and June 16, 2014 respectively. The designation as a Qualified Infectious Disease Product (QIDP) was granted on June 28, 2013.

During labeling meetings the decision was made for the sponsor to change the submitted Patient Package Insert (PPI) to a MG based on the Boxed Warning and significant serious side effects. After discussion with the Regulatory Project Manager (RPM) for the application on September 7, 2018, the decision was made to use the submitted PPI labeling as the basis for the pending MG due to the essence of time in approving the application.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infective Products (DAIP) on April 12, 2018 for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) that has been reviewed as a MG, Instructions for Use (IFU), and Quick Reference Guide (QRG) for ARIKAYCE (amikacin liposome inhalation suspension), for oral inhalation use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review fo the IFU was submitted on July 18, 2018.

2 MATERIAL REVIEWED

- Draft ARIKAYCE (amikacin liposome inhalation suspension) proposed PPI reviewed as a MG, IFU, and QSG received on March 28, 2018, and received by DMPP and OPDP on September 4, 2018 and August 31, 2018 respectively.
- Draft ARIKAYCE (amikacin liposome inhalation suspension) Prescribing Information (PI) received on March 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on September 4, 2018.
- ARIKAYCE (amikacin liposome inhalation suspension) and Lamira™ Nebulizer System Review (IND 108674) of IFU and QRG submitted to the Division of Medication Error Prevention and Analysis (DMEPA) on October 5, 2017.
3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the MG, IFU, and QSG we:

• simplified wording and clarified concepts where possible
• ensured that the MG, IFU, and QSG are consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the MG, IFU, and QSG are free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the MG, IFU, QSG meet the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
• ensured that the MG meets the Regulations as specified in 21 CFR 208.20
• ensured that the MG, IFU, QSG are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG, IFU, QSG are acceptable with our recommended changes.

5 RECOMMENDATIONS

• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

• Our collaborative review of the MG, IFU, and QSG are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG, IFU, and QSG.

Please let us know if you have any questions.
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/s/

SHARON W WILLIAMS
09/11/2018

DAVID F FOSS
09/11/2018
Memorandum

Date: September 10, 2018

To: Hiwot Hiruy
Division of Anti-Infective Products (DAIP)

Deborah Wang, Regulatory Project Manager, (DAIP)

Abimbola Adebowale, Associate Director for Labeling, (DAIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ARIKAYCE® (amikacin liposome inhalation suspension), for oral inhalation use

NDA: 207356

In response to DAIP's consult request dated May 9, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Arikayce.

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on August 31, 2018, and are provided below.

**PPI/Medication Guide/IFU:** A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI, Medication Guide, and IFU will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 28, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.
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/s/

DAVID F FOSS
09/10/2018
Division of Pediatric and Maternal Health Review

Date: September 4, 2018          Date consulted: July 2, 2018

From: Jin Chen, MD, PhD, DABT, Medical Officer, Maternal Health Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director Division of Pediatric and Maternal Health

To: Division of Anti-Infective Products (DAIP)

Drug: Arikayce (amikacin liposome inhalation suspension)

NDA: NDA 207-356

Applicant: Insmed Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients.

Materials Reviewed:
- DAIP consult request form dated July 2, 2018
- Original NDA 207-356 submitted on March 28, 2018
- Updated labeling of Arikayce submitted on May 25, 2018
- DPMH consult review of TOBI (tobramycin inhalation solution, NDA 50-753) by Dr. Carrie Ceresa on October 26, 2017
- Current labeling of amikacin injectable (March 2016)
Consult Question:

"Please evaluate the proposed PLLR labeling for this new formulation of amikacin (amikacin liposome inhalation suspension)"

INTRODUCTION AND BACKGROUND

On March 28, 2018, the Applicant, Insmed Inc., submitted a 505(b)(2) NDA for a new formulation of amikacin, liposome inhalation suspension of amikacin delivered by Lamira™ Nebulizer System, with a tradename ARIKAYCE. The novel route of administration is intended to achieve greater local concentrations of amikacin in the lung, while minimizing systemic concentrations. The proposed indication 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”. The recommended dosage is the once daily oral inhalation of amikacin 590 mg.

- Amikacin is a semisynthetic aminoglycoside with a broad antimicrobial activity and has been marketed in US as an injectable formulation since July 1976 (under NDA 50-495) “for the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including Pseudomonas species, Escherichia coli, species of indole-positive and indole-negative Proteus, Providencia species, Klebsiella-Enterobacter-Serratia”. The NDA was withdrawn in 1993 but not due to safety or efficacy reasons. There have been seven generic versions of amikacin injectable products on the market for the same indication as the original NDA. The overall safety profile of amikacin is similar to the aminoglycoside class, including effects on pregnancy and lactation.

- No officially approved inhalation formulation of amikacin has been marketed anywhere in the world. Injectable formulations of amikacin have been used off-label to treat lower airway infections through nebulization and inhalation for decades.

- The proposed product, Arikayce, is a drug-device combination, which was submitted through the 505(b)(2) pathway by referencing published literature for amikacin and the aminoglycosides class of antibiotics. Arikayce does not rely on a specific Listed Drug for efficacy, safety or labeling.

- Arikayce was granted orphan designation on March 25, 2013, Fast Track on June 28, 2013, and Breakthrough designation on June 16, 2014.

The proposed Pregnancy and Lactation Labeling Rule (PLLR) labeling for Arikayce, submitted in this NDA, is largely based on historical information of amikacin and other aminoglycoside antibiotics administered via injection. The Applicant did not conduct any new studies on inhaled amikacin in pregnant and lactating women or animals to support the proposed PLLR labeling of Arikayce.
REVIEW

PREGNANCY

Clinical Experience:
There are no clinical studies on inhaled amikacin exposure in pregnant women for assessment of embryofetal risk of Arikayce. In the proposed PLLR labeling, the Applicant primarily adapted the clinical information from published data for amikacin and other aminoglycoside antibiotics based on intravenous (IV) or intramuscular (IM) administration. See the Literature Review below for details.

Of note, the systemic exposure of amikacin through inhalation appears significantly lower than other parenteral routes of administration at the highest recommended dose through cross-labeling comparisons. Based on the Applicant’s pharmacokinetic (PK) study, a single dose of Arikayce (590 mg) has a Cmax that is approximately 16 times lower than IV infusion (500 mg) and 8 times lower than IM injection (500 mg).

In the clinical program of Arikayce, female subjects with a positive pregnancy test were excluded from the study or discontinued from the study if pregnancy testing became positive during the study. Two pregnancies from two female subjects were reported from two different clinical trials. As summarized below, one case resulted in a miscarriage with a temporal relationship to Arikayce treatment and the other had a normal pregnancy outcome but without a temporal relationship to Arikayce treatment.

Case# TR02-105-PL2-003 (normal pregnancy): This was an 18-year-old female with cystic fibrosis (CF) and P. aeruginosa infection. The patient had a positive pregnancy test at 21 days (about 90x half-life of amikacin) after the completion of the 28-day dosing cycle and at the end of 56 days off-drug [Reviewer: may need to clarify the onset time because 21+28 ≠ 56]. Although no abnormal pregnancy outcome was observed, there was also no temporal relationship between amikacin exposure and pregnancy. Thus, no adverse pregnancy outcome does not mean amikacin exposure is safe during pregnancy.

Case# TR02-107-101-013 (miscarriage): This was a 20-year-old female with non-CF bronchiectasis and Pseudomonas aeruginosa infection. The patient’s pregnancy test was positive on the last day of dosing (during safety evaluation visit), and the patient experienced an “incomplete abortion” 13 days after the positive pregnancy test. This suggests that there was at least a temporal relationship between amikacin exposure and the event. Although it may be confounded by underlying infection, the miscarriage was still “possibly related” to amikacin either alone or due to drug-disease interactions.
Nonclinical Experience
No nonclinical studies on Arikayce or amikacin inhalation were conducted by the applicant or identified in literature. The Applicant provided a literature summary based on two published studies that described animal reproductive studies conducted in pregnant mice and rats. Amikacin was subcutaneously administered to pregnant rats (Gestation Days 8-14) and mice (Gestation Days 7-13) at doses of 25, 100, or 400 mg/kg to assess developmental toxicity. Overall, these doses did not cause fetal visceral or skeletal malformations in mice. The high dose was excessively maternally toxic in rats (nephrotoxicity and mortality were observed), precluding the evaluation of offspring at this dose. Fetal malformations were not observed at the low or mid dose in rats. Otoxicity was not adequately evaluated in offspring in animal developmental toxicology studies. The reader is referred to the current Pharmacology/Toxicology review (by Dr. Amy Ellis) for details.

Review of Pharmacovigilance Database
Arikayce has not been marketed outside the U.S. and there no post-marketing pharmacovigilance database has been established. However, the product has been offered for compassionate use internationally through Compassionate Use Programs. As of July 7, 2017, a total of 72 subjects received Arikayce through this program. Overall, 29 adverse events (AEs) were reported in 16 subjects. Of these, 11 events were serious AEs (SAEs) and reported in 8 subjects, including 3 deaths. There were no events related to pregnancy, lactation or human fertility that were reported from this program. All SAEs and deaths are confounded by underlying infections but appear to be consistent with the safety profile established from clinical trials with Arikayce.

The applicant did not conduct a review of the pharmacovigilance database for other formulations of amikacin (injectable or oral) related to pregnancy.

Review of Literature
Applicant’s literature review:
The Applicant did not perform thorough literature search in the current submission to support the proposed PLLR labeling. Instead the Applicant provided a brief literature review in the ISS, which included four clinical studies and two review articles published between 1974 and 1982. As summarized in Table 1 of Appendix A, the literature suggests:


Reference ID: 4315431
• Systemic exposure to aminoglycosides, primarily from studies on streptomycin, in pregnant women has been associated with total, irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy.
• Amikacin can rapidly cross the placenta into the fetal circulation and amniotic fluid.
• Amikacin distributes to most fetal tissues (particularly accumulated in kidneys), but not the brain and cerebrospinal fluid.

DPMH review of literature:
DPMH conducted a literature search in PubMed, EMBASE and MicroMedex, using search terms or keywords “amikacin” with and without “inhaled” AND “pregnancy” for all types of publication, and “aminoglycosides” with and without “inhaled” AND “pregnancy” for review article only. No relevant publications were identified on the use of inhaled aminoglycosides, including amikacin, during pregnancy. The most relevant publications on amikacin and other aminoglycosides, given by other routes of administration, related to pregnancy were those published in 1970s and 1980s as the Applicant cited in the proposed labeling. There were four publications that described the use of aminoglycoside antibiotics during pregnancy, and these studies are described below.

Wang et al (2017)³ published a case control study in infants with low birth weight and hearing impairment (n=12) and infants with normal hearing (n=297). Maternal exposure to multiple risk factors during pregnancy were assessed, including parenteral or oral gentamicin. The odds ratio of gentamicin exposure between impaired and normal hearing was 3.62 with a statistical significance (95% CI: 1.67-7.82). The study suggests that low birth weight infants may be more susceptible to ototoxicity if the mother was exposed to aminoglycosides during pregnancy.

Reviewer Comment:
In addition to intrinsic limitations of a case-control study, the compatibility between the two groups appear questionable because no matching criteria and method for selection of the control group (normal hearing infants) were provided in the study report.

Czeizel et al (2000)⁴ conducted a population-based case-control study using the national register databases (years 1980-1996) in Hungary to assess potential association of teratogenicity with maternal exposure to aminoglycoside antibiotics during pregnancy. The aminoglycoside exposure included parenteral gentamicin, streptomycin and tobramycin, and oral neomycin. A total of 22,865 (cases) infants with congenital structural abnormalities and 38,151 (matched control) infants without congenital abnormalities were included in the study. The matching criteria for selection of control infants included sex, birth week and residence but without maternal characteristics. The exposure data were obtained prospectively through antenatal care logbooks and other medical documents and retrospectively by questionnaires completed by mothers. The odds ratios of maternal aminoglycoside exposure during pregnancy associated with their infant congenital abnormality.

abnormalities were up to 9.0, but with no statistical significance (95% CI across 1.0). The study concluded that maternal exposure to aminoglycoside antibiotics during pregnancy had no detectable teratogenic risk to the fetus in “structural developmental disturbance”. Nephrotoxicity and ototoxicity were not reported or discussed, except that the author stated in the conclusion “the risk of deafness cannot be excluded, but the magnitude is estimated as small”.

Reviewer Comment:
*It appears that this study is the largest case-control study to date assessing potential teratogenicity of aminoglycosides in pregnant women. However, the study had the following limitations: maternal characteristics were not used as part of control matching criteria, congenital abnormalities were focusing on only structural developmental abnormalities, overall exposure rates of aminoglycosides in both study groups were lower, and high variations of odds ratios.*

Pacifici (2006)\(^5\) published a literature review to discuss placental transfer of various classes of antibiotics, including aminoglycosides. The PK data of seven aminoglycosides antibiotics, including amikacin, in maternal blood and umbilical cord blood were summarized from studies published between 1945 to 2005. The ratios of aminoglycosides between cord and maternal blood were from 0.19 (gentamicin) to 0.59 (amikacin). Although aminoglycosides cross the placenta, the authors described aminoglycosides as having “incomplete” placental transfer where concentrations of the drugs were lower in the cord than in the maternal plasma.

Mylonas (2011)\(^6\) published a brief review to discuss potential risks associated with prenatal exposure of aminoglycoside antibiotics. The authors concluded that infant ototoxicity and nephrotoxicity are most likely a class effects of aminoglycosides associated with maternal exposure during pregnancy, and that aminoglycosides “should generally not be administered during the first 4 months of pregnancy.”

Reviewer Comment:
*No clinical or nonclinical studies on inhaled amikacin have been conducted to assess embryofetal developmental risks. Although systemic exposure to amikacin from Arikayce is expected to be low compared to IM and IV formulations, the safety margin of systemic amikacin exposure is unknown and thus it is reasonable to take a conservative approach to use the aminoglycoside class labeling language, regarding the risk of ototoxicity associated with aminoglycoside exposure during pregnancy, for Arikayce labeling. The Applicant’s proposed ototoxicity language appears consistent with the literature findings as reviewed above and with the labeling of injectable formulations of amikacin and other aminoglycosides.*

\(^6\) Mylonas I: Antibiotic chemotherapy during pregnancy and lactation period: aspects for consideration. *Arch Gynecol Obstet* 283:7–18, 2011
LACTATION

Nonclinical Experience
No data from animal lactation studies on amikacin administered by any routes of administration in the proposed labelling and the NDA submission.

Review of Pharmacovigilance Database
Arikayce has not been marked anywhere in the word and thus no pharmacovigilance database has been established. There were also no lactating women in the Compassionate Use Programs for Arikayce. The applicant did not conduct a review of pharmacovigilance database for other formulations of amikacin (injectable or oral) related to lactation.

Review of Literature
Applicant’s Literature Review:
The Applicant did not provide any literature search strategy and method. Instead the Applicant cited four publications in the annotated labeling: three individual study reports [(b)(4)]; Matsuda et al 1974 and [(b)(4))] as summarized in Table 1 of Appendix A, and one textbook (Brigg’s Drugs in pregnancy and lactation, 2017). Under the Lactation labeling, the applicant proposed the statement [(b)(4)].

The publications cited in the annotated labeling were not reviewed or discussed by the applicant.

Among three individual study publications, two were irrelevant [(b)(4)] because no information about the use of amikacin during lactation was reported. The third study (by Matsuda 1974) did report a “trace” amount of amikacin present in milk based on two lactating women. The Applicant’s proposed labeling statements appears to be adapted from [(b)(4)]

DPMH Literature Review:
DPMH conducted a literature search in PubMed, EMBASE MicroMedex and LactMed using keywords “amikacin” AND “lactation” or “lactating” or “nursing”. No relevant publications or documents were identified except the following summaries from MicroMedex and LactMed.

MicroMedex states the following:
“Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding”.

LactMed (updated on March 10, 2015) states the following;
“Amikacin is poorly excreted into breast milk. Newborn infants apparently absorb small amounts of other aminoglycosides, but serum levels with typical three times daily dosages are far below those attained when treating newborn infections and systemic effects of amikacin are unlikely.”

In addition, the following information is presented in LactMed from five women exposed to intramuscular amikacin and reported from three articles published in the early 1970s\textsuperscript{8,9} and 1980s\textsuperscript{10}.

“Maternal Levels. Two women were given a single dose of 100 mg amikacin intramuscularly, and milk levels were measured at 2 and 6 hours after the dose. Only trace levels were detected. In one woman on amikacin therapy, the peak amikacin milk level was 1.5 mg/L 2.5 hours after a 100 mg dose by injection.

Two women were given a single 200 mg dose of amikacin intramuscularly and milk levels were measured hourly for 6 hours. They had only trace levels in milk 6 hours after the dose.

A woman given a single dose of amikacin 100 mg intramuscularly had undetectable milk amikacin levels 1 and 2 hours after the dose and only trace amounts in milk at 4 and 6 hours after the dose.”

Reviewer Comment:
No information is available regarding the presence of amikacin through inhalation exposure in lactating women and animals. However, the Applicant also did not present any information from studies in lactating animals treated with amikacin by other routes of administration (such as intravenous or intramuscular injection), nor discussed this information in the ISS. Limited literature reports from case reports with lactating women exposed to intramuscular amikacin suggest that amikacin is poorly excreted into human milk with undetectable or trace amounts seen in human milk. No new studies or information on amikacin in lactating women can be identified from further literature search.

**FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

Nonclinical Experience
Per the Applicant’s ISS submitted with this NDA, no animal fertility studies were conducted with inhaled amikacin. The Applicant relied on information from animal fertility studies with intraperitoneal administration of amikacin to rats prior to mating until early organogenesis at doses of 0, 25, 100, or 200 mg/kg/day. There were no effects observed on fertility and reproductive indices in either male or female rats.

Review of Pharmacovigilance Database
Arikayce has not been marketed anywhere in the world and thus the Applicant did not conduct a pharmacovigilance review. The Applicant also did not conduct a review of pharmacovigilance databases of other amikacin products (such as injectable and oral).

Review of Literature
*Applicant’s Literature Review:*

\textsuperscript{8} Matsuda S et al Evaluation of amikacin in the obstetric and gynecologic field. *Jpn J Antibiot* 27:633-6, 1974

\textsuperscript{9} Yuasa M. Evaluation of amikacin in gynecological and obstetric field. *Jpn J Antibiot* 27:377-81, 1974

\textsuperscript{10} Matsuda S. Transfer of antibiotics into maternal milk. *Biol Res Pregnancy Perinatol* 5:57-60, 1984
The Applicant did not identify any relevant publications in literature regarding amikacin and effects on fertility; however, no literature search method was provided.

**DPMH Literature Review:**
DPMH conducted a literature search in PubMed, EMBASE and MicroMedex using the keywords “amikacin” AND “fertility”. No relevant publication or documents were identified.

**Reviewer Comment:**
*There are no human fertility data related to amikacin. In addition, the animal fertility study was negative. Thus, according the PLLR guidance (2014), subsection 8.3 should be omitted.*

**DISCUSSION AND CONCLUSIONS**

**Pregnancy**
There are no clinical or nonclinical data on Arikayce available to assess embryofetal developmental risks. The Applicant’s proposed ototoxicity language appears consistent with the literature findings as reviewed above and with the labeling of injectable formulations of amikacin and other aminoglycosides.

The Applicant also presented the following language under the proposed Pregnancy labeling (b)(4)

Therefore, DPMH does not agree with including the statement proposed by the applicant.

**Lactation**
The limited information from published literature suggests that amikacin is poorly excreted in human milk after systemic exposure (injection). With low systemic exposure to Arikayce, which is expected via inhalation, infants would be less likely to receive a meaningful exposure to amikacin through breastfeeding. Therefore, DPMH recommends that the proposed language related to (b)(4) in the labeling should be removed.

**Females and Males of Reproductive Potential**
This subsection can be omitted because no human data are available regarding amikacin and effects on fertility, and the animal fertility study on amikacin through systemic exposure was negative.
LABELING RECOMMENDATIONS

DPMH revised sections 5.8, 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the DAIP on July 24, 2018. DPMH recommendations are below and reflect the discussions with DAIP. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling on Arikayce

HIGHLIGHTS OF PRESCRIBING INFORMATION

------------------------WARNINGS AND PRECAUTIONS----------------------

• Embryofetal toxicity: aminoglycosides can cause total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero (5.8, 8.1)

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.8 Embryofetal toxicity

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycoside antibiotics, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero. Patients who use ARIKAYCE during pregnancy or become pregnant while taking ARIKAYCE should be apprised of the potential hazard to the fetus [see Use in Specific Populations, Pregnancy (8.1)].

8.1 Pregnancy

Risk Summary
There are no data on ARIKAYCE use in pregnant women to evaluate for any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Although systemic absorption of amikacin following oral inhalation is expected to be low [see Clinical Pharmacology (12.3)], systemic exposure to aminoglycoside antibiotics may be associated with, total, irreversible, bilateral congenital deafness when administered to a pregnant woman [see Warnings and Precautions (5.8)]. Advise pregnant women of the potential risk to a fetus.

Animal reproductive toxicology studies have not been conducted with inhaled amikacin. Subcutaneous administration of amikacin to pregnant rats (up to 100 mg/kg/day) and mice (up to 400 mg/kg/day) during organogenesis was not associated with fetal malformations. Ototoxicity was not adequately evaluated in offspring in animal studies.

The estimated background risk of major birth defects and miscarriage for the indicated
populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
Amikacin was subcutaneously administered to pregnant rats (Gestation Days 8-14) and mice (Gestation Days 7-13) at doses of 25, 100, or 400 mg/kg to assess developmental toxicity. These doses did not cause fetal visceral or skeletal malformations in mice. The high dose was excessively maternally toxic in rats (nephrotoxicity and mortality were observed), precluding the evaluation of offspring at this dose. Fetal malformations were not observed at the low or mid dose in rats. Postnatal development of the rats and mice exposed to these doses of amikacin in utero did not differ significantly from control. Ototoxicity was not adequately evaluated in offspring in animal developmental toxicology studies.

8.2 Lactation
Risk Summary
There is no information regarding the presence of ARIKAYCE in human milk, the effects on the breastfed infant, or the effects on milk production. Although limited published data on other routes of administration of amikacin indicate that amikacin is present in human milk, systemic absorption of ARIKAYCE following inhaled administration is expected to be low [see Clinical Pharmacology (12.3)]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ARIKAYCE and any potential adverse effects on the breastfed child from ARIKAYCE or from the underlying maternal condition.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The squamous cell carcinomas may be the result of a high lung burden of particulates from ARIKAYCE in the rat lung. The relevance of the lung tumor findings with regards to humans receiving ARIKAYCE is unknown.

No evidence of mutagenicity or genotoxicity was observed in a battery of in vitro and in vivo genotoxicity studies with ARIKAYCE (in vitro microbial mutagenesis test, in vitro mouse lymphoma mutation assay, in vitro chromosomal aberration study, and an in vivo micronucleus study in rats).
17 PATIENT COUNSELING INFORMATION

**Embryofetal Toxicity:** Advise pregnant women that aminoglycosides, including ARIKAYCE, can cause irreversible congenital deafness when administered during pregnancy [see Warnings and Precautions (5.8) and Use in Special Population (8.1)].
## APPENDIX A.

### Table 1. Summary of literature that the Applicant cited to support the proposed PLLR labeling in the submission

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects</th>
<th>Drug/Dosage</th>
<th>Results</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single/multiple-dose cord blood, amniotic fluid and milk PK</td>
<td>N=5 pregnant women, N=2 lactating women</td>
<td>Amikacin Single &amp; multiple 100mg IM q12-hr x3</td>
<td>Amikacin concentration: Cord blood: 30-50% maternal blood (Cmax); Amniotic fluid Cmax: 1-2 ug/ml; Trace amount in milk; No safety data</td>
<td>Matsuda S et al (1974): <em>Japanese J Antibiotics</em> 27(5): 633</td>
</tr>
<tr>
<td>Single-dose PK in pregnant women (elective abortion) and fetal tissue</td>
<td>18 pregnant women</td>
<td>Amikacin Single 7.5 mg/kg IM</td>
<td>Amikacin concentration: Cord blood (Cmax): 8% maternal blood (26ug/ml); Amniotic fluid Cmax: 1.5ug/ml; Fetal urine: 24 ug/ml Fetal tissue: kidney&gt;placenta&gt;lung; undetectable in fetal brain and liver; No safety data</td>
<td>Bernard B et al (1974): <em>Antimicrobial Agents and Chemotherapy</em> 14th Annual Conference (abstract)</td>
</tr>
<tr>
<td>Review article On antituberculous drugs</td>
<td>Pregnant women</td>
<td>Streptomycin and others</td>
<td>Ototoxicity (8th nerve and vestibular damage) in children born from maternal TB therapy with streptomycin; Multiple case study reports on congenital deafness associated with streptomycin, with mixed (positive and negative) conclusions, overall toward to ototoxicity</td>
<td>Warkany J (1979): <em>Teratology</em> 20: 133-138.</td>
</tr>
<tr>
<td>Review article on amikacin</td>
<td>unknown</td>
<td>Amikacin vs. other aminoglycosides</td>
<td>Infants less susceptible to ototoxicity than adults; relative low nephrotoxicity with amikacin; Persistent high in fetal kidney and lung, amniotic fluid and placenta, but unknown outcome in fetus Amikacin-pregnancy: Amniotic fluid: 3-8ug/ml; fetal serum: 15-</td>
<td>Philips JB and Cassady G (1982): <em>Seminars Perinat.</em> 6(2): 166-171</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JIN CHEN
09/04/2018

MIRIAM C DINATALE
09/04/2018

LYNNE P YAO
09/05/2018
NDA 207356 – Regulatory Device Consult

Date: August 8, 2018

To: Anh-Thy Ly (CDER/OPQ/OPRO)
Through: James Lee, Branch chief (CDRH/ODE/DAGRID/RPDB)
From: Deepika A. Lakhani (CDRH/ODE/DAGRID/RPDB)
Applicant: Insmed Incorporated
Product Name: Amikacin Liposome Inhalation Suspension with eFlow Nebulizer System for use with Amikacin Liposome Inhalation Suspension (ALIS)
Indication: Nontuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* Complex (MAC) in adults

A. Executive Summary

In NDA 207356, Insmed 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.

CDRH Review Team:
To aid in the device review, additional sub-consults were sent in the following review areas:

<table>
<thead>
<tr>
<th>Name</th>
<th>Review Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandy Weininger  (CDRH/OSEL/DBP)</td>
<td>Electrical Safety</td>
</tr>
<tr>
<td>Howard Bassen (CDRH/OSEL/DBP)</td>
<td>EMC</td>
</tr>
<tr>
<td>Kiros Hailemariam (CDRH/ODE/DAGRID/INCB)</td>
<td>Device Biocompatibility</td>
</tr>
</tbody>
</table>
Additional information was recommended from the sponsor regarding their device software, performance and electrical safety. This information was requested from the sponsor via IR dated June 21, July 13 and July 27 2018. The sponsor provided adequate responses through interactive review which adequately addressed the outstanding software, performance and electrical safety.

**RECOMMENDATION:** The device is recommended for approval.

### B. 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.

### C. Device Description

**Device Description per Sponsor:**

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, which is a modified version of the Altera® by PRE, which was cleared under K100380. The ALIS eFlow configuration with the nebulizer handset (hand-held unit), the connection cord and the controller is shown in Figure 1.

The following figures show the device configuration which was used in the phase 3 clinical trials. For commercialization, the controller circuit board will have to be upgraded to meet new regulations for EMC, the AC adapter will be changed to a newer model and the device labeling will be replaced with commercial labeling. None of the proposed changes impact the device performance or the material of construction. Further details are described in Section 3 - Device Change History.
Table 1  Comparison of the ALIS eFlow with Other FDA Cleared PRE-Electronic Nebulizers

<table>
<thead>
<tr>
<th></th>
<th>ALIS eFlow Nebulizer System</th>
<th>Altera Nebulizer System</th>
<th>Trio Electronic Nebulizer System</th>
<th>eRapid Nebulizer System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>ALIS only</td>
<td>Cayston® only</td>
<td>General Use</td>
<td>General Use</td>
</tr>
<tr>
<td></td>
<td>This NDA (NDA 207356)</td>
<td>NDA 050-814</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug solution fill volume</td>
<td>8.4 mL</td>
<td>1 mL</td>
<td>Maximum of 4 mL</td>
<td>Maximum of 6 mL</td>
</tr>
<tr>
<td>Aerosol head</td>
<td>Customized and medication-specific</td>
<td>Customized and medication-specific</td>
<td>Standard general use</td>
<td>Standard general use</td>
</tr>
<tr>
<td>Aerosol generation technology</td>
<td>eFlow® micro-perforated Vibrating Membrane Technology</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The ALIS eFlow, as well as the Altera, Trio, and eRapid nebulizer systems are identical in overall purpose, function, aerosol generation technology, and method of operation. They are single-patient use, reusable electronic nebulizers that can be used for inhalation therapy. All devices are hand-held and portable. Their main components are a nebulizer handset (1) and controller (3) connected to each other with a connection cord (2) as shown in Figure 2. The devices are powered by either AA batteries or an AC adapter.

Like the Altera, the ALIS eFlow is intended for use with a specific drug, whereas the Trio and the eRapid are non-drug specific nebulizers for use with medications prescribed by doctors for nebulization.

All PRE nebulizer systems use the same 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 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.
Advantages of this 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.

**Controller**

The controller (Figure 12) contains the electronics in a discus-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.

**Features**
The controller features: A built-in battery compartment (1) for 4 x AA-type batteries for battery operation; an electrical input slot (2) for connection to an AC adapter; an electrical output slot (3) for tethered operation of the nebulizer handset connected to the controller via the connection cord; an ON/OFF button (4) to start or stop the treatment; a green/orange light emitting diode (LED) (5); and a liquid crystal display (LCD) (6). The LCD combined with the LED and audible signal indicates the device’s operating status and informs the user in the event of a device malfunction.

**Device Change History**
Changes made to the clinical device during the clinical studies include:
- Adding a small indent on the outside of the nebulizer handset 8mL reservoir so it could be connected to the standard connection cord used on commercial eFlow handsets.
- Strengthen the hook and flexible joint on the connection cord that connects the handset to the controller.
- Update software with better Fluid Presence Sensor (FluPS) to confirm the absence of medication and to provide the patient the option to pause the controller during nebulization rather than turning off the controller.
- Update the circuit board with additional memory for the improved FluPS.
- Upgrading the controller to an IP21 rating by adding channels and holes to the controller housing to protect the circuit board from vertical water droplets.
- Replace the special connection cord with the standard connection cord used in all OS eFlow handsets.
- The connection cord outer sheathing will change because the plastic has been discontinued but the appearance and performance will not change.

The proposed commercial ALIS eFlow Nebulizer System will be identical to the Investigational eFlow except with the following changes:
- Update circuit board to meet EMC-Standard IEC60601-1-2 4th edition standards for radio frequency (RF) and electrostatic discharge, and to increase the capacity of the capacitor to allow for momentary disconnection from the AC adapter during operation.
- Update the software to accommodate the new circuit board.
- The AC adapter will be updated but it will continue to have the same performance and safety rating of the older AC adapter.
- The appearance of the battery pack of 4 AA batteries will change from a blister pack to shrink wrapped.
- The front side of the blister packaging of the aerosol head will change from blank white to printed.

**Reviewer’s Comments:** The differences between the previous eFlow used for Phase 3 studies and their proposed commercial eFlow are not expected to impact the aerosol performance. However, they could impact other aspects of the device review, such as the software verification/validation, electrical safety, EMC, and mechanical safety. Therefore, the sponsor was requested to confirm that the testing provided was conducted on their final eFlow device intended for market. This was confirmed by the sponsor in their response to our June 21, 2018 letter. Therefore, this is acceptable.

**Labeling:**
Insmed is proposing two commercial device configurations: an ALIS eFlow Nebulizer System and a 28-day drug kit. Both configurations contain the same ALIS eFlow Instructions for Use (IFU).
D. Cleaning, Disinfection, Maintenance and Shelf Life

To determine the cleaning efficacy and validate the cleaning process described in the IFU handset components were inoculated with a soil containing protein, and carbohydrate, and then subjected to a cleaning process that was less rigorous than that recommended in the IFU. Inoculation points included contact areas and locations that are difficult to clean. The differences between the cleaning process described in the IFU and the less rigorous cleaning process tested are outlined in Table 1.

<table>
<thead>
<tr>
<th>Steps of Cleaning Process Described in the IFU</th>
<th>Steps of the Tested Less Rigorous Cleaning Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean immediately after use.</td>
<td>Allow residue to dry on the device for 6 hours.</td>
</tr>
<tr>
<td>Rinse each component for 10 seconds under warm tap water.</td>
<td>Rinse each component for 10 seconds under room temperature (68±9°F / 20±5°C) tap water.</td>
</tr>
<tr>
<td>Soak the components for 5 minutes in soapy water made with liquid dish soap and warm tap water.</td>
<td>Soak the components for 5 minutes in soapy water (0.08%) made with liquid dish soap and room temperature (68±9°F / 20±5°C) tap water.</td>
</tr>
<tr>
<td>Rinse each component again for 10 seconds under warm tap water.</td>
<td>Rinse each component again for 10 seconds under room temperature (68±9°F / 20±5°C) tap water.</td>
</tr>
</tbody>
</table>

The testing activities involved:

1. Soiling the handset components with a mixture of protein and carbohydrate.
2. Allowing the soil to dry for 6 hours.
3. Cleaning the handset components using the less rigorous processing parameters described above.
4. Repeating the soiling, drying and cleaning steps (1-3) five (5) additional times before continuing to step 5.
5. After 6 cleaning cycles, performing exhaustive extraction using phosphate buffered saline until concentrations were below the detectable limit of the assays.

The above testing activities (steps 1-6) were performed on five different handset units. Testing indicated that the soiled handset components were successfully cleaned by the less rigorous process because residual protein and carbohydrate were below the AAMI TIR30:2011 benchmark levels of 6.4 µg/cm² and 1.8 µg/cm², respectively after cleaning.

Disinfection
To reduce the risk of contamination, the IFU instructs that the ALIS eFlow handset components be disinfected by boiling in distilled water after it is cleaned with warm soapy water. These cleaning and disinfecting methods are identical to the methods used for the 510(k)-cleared eRapid® (K112859) and the Altera® (K100380) nebulizer system handsets.

For validation of the disinfection procedure, the device handset components from 6 comparable devices (Altera) were inoculated with a mixture of six organisms (4 bacteria, 1 mold, and 1 fungus) allowed to dry and then placed in boiling water for 5 minutes. The IFU directs the user to clean the handset components before disinfection. However, to mimic worse case conditions, the handset components were not cleaned and the organisms were allowed to dry on to the handset components prior to initiating the disinfection procedure.

The handset components for each handset were extracted with cell medium, the extract filtered, and the filters applied to plates containing the appropriate growth medium. After a minimum of 48 hours, the colonies were counted. The first 6 results shown in Table 2 are for the comparable device (Altera). The study was repeated with Burkholderia cepacia because growth media used for the positive control did not grow well enough to demonstrate a 6-log change from disinfection during the first study. Since the handset is a single person device and not to be shared with others, the disinfection procedure was deemed effective because there was more than a 6-log reduction in microorganisms versus the control (SGS Report 09A1004020 with addendum 09A1005854 and repeat B. cepacia 09A1717223 - Disinfection Study).

### Table 2 Summary of the Validation Results of the Disinfection of 6 Devices

<table>
<thead>
<tr>
<th>Organism</th>
<th>Average bioburden before disinfection (CFU)</th>
<th>Average bioburden after disinfection (CFU)</th>
<th>Log Reduction (Log of the difference between before and after)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>$5.4 \times 10^7$</td>
<td>0</td>
<td>7.7</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>$3.4 \times 10^7$</td>
<td>0</td>
<td>7.5</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>$4.9 \times 10^7$</td>
<td>0</td>
<td>7.7</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>$4.3 \times 10^7$</td>
<td>0</td>
<td>7.6</td>
</tr>
<tr>
<td>Aspergillus niger S</td>
<td>$1.7 \times 10^7$</td>
<td>0</td>
<td>7.2</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>$5.2 \times 10^7$</td>
<td>0</td>
<td>5.7</td>
</tr>
<tr>
<td>Burkholderia cepacia (repeated)</td>
<td>$6.3 \times 10^7$</td>
<td>0</td>
<td>6.8</td>
</tr>
</tbody>
</table>

**Sterility:** The sponsor confirmed that the subject device is non-sterile.

**Shelf Life**

The sponsor indicated that ALIS eFlow handset is not sterile, it has very low risk degradation, and it treats a non-life-threatening condition. The sponsor used these arguments to support the conclusion that, expiration dating is not assigned or required.

The shelf life has been determined on five investigational eFlow devices after the devices have been stored for 4 years and 8 months at room temperature. The devices were characterized with
respect to mass median diameter (MMD) by laser diffraction technique and total output rate (TOR) using saline.

**Reviewer’s Comment:** Cleaning and validation data are ACCEPTABLE. A labeling IR was communicated to the Sponsor on June 21, 2018 to include better disposal methods for the antibiotic. The Sponsor acknowledged the comment. A cleaning consult was sent to review the cleaning and disinfection validation reports. The subject device is intended for single patient use, is not likely to be heavily soiled, employs a very effective disinfection process and does not have design features that present significant reprocessing concerns.

- It is noted that phosphate buffered saline was used as the extraction media. This media may not be effective in removing residual soil with insoluble elements, but is considered to be acceptable in for the soil used in the validation protocol for the tests soil on the subject device. The surfaces of the subject device considered to be accessible for the extraction.
- The assays employed are considered to be acceptable for the test protocol as they can provide acceptable quantitation of the intended soil markers.
- The protein and carbohydrate acceptance criteria of , have historical basis for acceptance as there is no metric to scientifically determine adequate cleaning, but the device is indicated to be assessed for visual cleanliness and there is not a significant risk of cross contamination from inadequate cleaning and disinfection as the device is single patient use.
- The disinfection validation shows appropriate reductions in test organisms. The test protocol does not address wash off, but this is not considered to be a significant concern due to the following reasons.
  - Initial challenges were 10 fold greater than the 10⁶ challenge needed for disinfection.
  - There is not significant mechanical action on the device during disinfection
  - There is not significant fluid flow on the device during disinfection
  - Established parameters for thermal high level disinfection include 1 minute at 90°C. The instructions indicated submersion in boiling water for 5 minutes resulting in likely thermal conditions of 95-105 °C for 5 minutes. This significantly exceeds conditions needed for thermal high level disinfection.

**E. Biocompatibility**

The ALIS eFlow nebulizer contains both direct and indirect patient-contacting components. The device is a prolonged exposure, external communicating device (tissue, bone and dentin). The outside of the mouthpiece is a prolonged exposure, surface-mucosal membrane contact component.

Even though the eFlow ALIS is identical to the Altera (510(k) K100380) in formulation, processing, and cleaning, and even though, many of the materials and processes used for the eFlow ALIS nebulizer are also used in the Zoom (510(k) K162785) and eRapid (510(k) K112859), biocompatibility testing was repeated, per the guidance contained in FDA Guidance, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process".

In its final finished form, the ALIS eFlow handset was tested and found not to be a health
hazard based on favorable outcome of the following tests:

- Cytotoxicity Elution Test – ISO 10993-5
- Intracutaneous (Intradermal) Reactivity Test – ISO10993-10
- Sensitization Test - Maximization Sensitization Test – ISO 10993-10
- Acute Systemic Toxicity – ISO 10993-11
- Subacute Toxicity – ISO 10993-11
- Genotoxicity Test, Cell-based - Reverse Mutation Assay – ISO 10993-3
- Genotoxicity Test, Mammalian-based – ISO 10993-3
- Implantation, Muscle Implantation – ISO 10993-6

The air path testing evaluated the presence of any emitted particulate matter (PM2.5), ozone (O3), carbon monoxide (CO), carbon dioxide (CO2), or volatile organic compounds (VOCs) in the handset air path as the device is being used. There is no evidence that the ALIS eFlow emits any PM2.5, VOC, CO and CO2, as well as O3 in its final form. The nebulizer meets the standards of FDA, OSHA, EPA, and ACGIH.

**Reviewer’s Comment:** A biocompatibility consult was conducted by Kiros Hailemariam to review the device biocompatibility information submitted. The biocompatibility reviewer concluded that biocompatibility data are ACCEPTABLE.

**F. Software**

Verification and validation testing was conducted in accordance with, and documentation was provided as recommended by FDA Guidance for the *Content of Premarket Submissions for Software Contained in Medical Devices, May 11, 2005* (FDA, 2005). The software for this device is of a “moderate” level of concern, based upon FDA guidance the device manufacturer received for previous eFlow technology submissions.

1.1. **Level of Concern – Adequate**

The sponsor adequately identified their software as having a Moderate Level of Concern.

1.2. **Software Description – Adequate**

The sponsor adequately described their software.

General

The software that will be used in the controller for the proposed ALIS eFlow nebulizer system is identical to the software used in the controller used for the commercially available eRapid Nebulizer System (510(k) K112859) and the commercially Altera Nebulizer System (510(k) K100380).

As with all eFlow Technology software, software was developed in-house, and is device-specific in design, i.e., it is not “off-the-shelf”. Further, it is not dependent for its operation on any external devices, such as a monitor, printer, keyboard or mouse.

The software’s programming language is . Program source codes were developed from a
1.3. Device Hazard Analysis – Adequate

The sponsor provided a risk assessment that did not include all the information recommended by our premarket software guidance. Interactive review deficiencies resolved the concerns associated with risk assessment.

1.4. Software Requirements Specifications (SRS) – Adequate

The sponsor provided an SRS document. The SRS document conflicts with the software description document regarding automated software quality checks. Interactive review deficiencies resolved the concerns associated with SRS.

1.5. Architecture Design – Adequate

The sponsor provided adequate architecture design documentation.

1.6. Software Design Specification – Adequate

1.7. Traceability Analysis – Adequate

The sponsor provided an adequate traceability document.

1.8. Software Development Environment Description – Adequate

The sponsor provided adequate software development environment documentation.

1.9. Testing (Verification/Validation) – Adequate

The sponsor did not provide any white-box unit testing as required for Class B software per the IEC 62304 standard. Interactive review resolved this deficiency. The sponsor did not provide the protocol with test steps for their verification testing. Further interactive review (dated July 21 and 27) resolved this deficiency.

1.10. Revision Level History – Adequate

The sponsor provided an adequate software revision level history document.

1.11. Unresolved Anomalies (Bugs or Defects) – Adequate

The sponsor stated they have no unresolved anomalies.

Reviewer’s Comment: The software reviewer provided the following conclusion: “The sponsor adequately addressed the deficiencies. I recommend approval for the software review.”

G. EMC and Electrical Safety
Electrical safety and electromagnetic compatibility (EMC) testing were conducted on the eFlow Nebulizer System and AC Adapter. The eFlow Nebulizer System’s controller and adapter are identical to the ALIS eFlow Nebulizer System’s controller and adapter. Testing was performed to confirm the devices meet the current EMC standards:

- IEC 60601-1, Edition 3.1 + AMD1:2012 CSV; Medical electrical equipment - Part 1: General requirements for basic safety and essential performance; 2012-08;
- IEC 60601-1-2, Edition 4.0; Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests (home, hospital, vehicle, and airplane); 2014-02
- IEC 60601-1-11, Edition 1.0; General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment; 2010-04

**Reviewer’s Comment:** The electrical safety reviewer identified concerns with the submitted FMEA and how the approach identifies hazards in general and those that may be outside the scope of the standards identified. Methods to comprehensively and systematically identify hazards include fault tree analysis and failure modes analysis. The device was recommended for approval from electrical safety and EMC perspective but it was noted that for future, methods to comprehensively and systematically identify hazards include fault tree analysis and failure modes analysis should be included. This is acceptable. EMC reviewer did not note any concerns, however labeling comments were communicated to the Sponsor that were acknowledged.

### H. Device Performance

**In vitro Aerosol Characterization of ALIS eFlow**

To evaluate the aerodynamic particle size distribution of ALIS nebulized with the ALIS eFlow nebulizer, a Next Generation Cascade Impactor (NGI) was used to test three lots of ALIS aerosolized with 10 different ALIS eFlow nebulizers. All 10 ALIS eFlow nebulizers met Insmed’s acceptance criteria for MMAD (\( \leq 4 \mu m \)) and FPD (\( \leq 4 \mu g \)) for all 3 lots of ALIS.

**Data Collected from the NGI of 3 Lots of ALIS and 10 ALIS eFlow Nebulizers**

<table>
<thead>
<tr>
<th>Lot No. ALIS</th>
<th>3-NFF-0205</th>
<th>3-FIN-1454</th>
<th>3-FIN-1699</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow Rate[L/min]</td>
<td>Mean</td>
<td>SD(^a)</td>
<td>RSD(^b)</td>
</tr>
<tr>
<td>15.0</td>
<td>-</td>
<td>-</td>
<td>15.0</td>
</tr>
<tr>
<td>Filled Drug Amount [mg](^c)</td>
<td>588</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Dose per Shot [mg]</td>
<td>547.8</td>
<td>13.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Calc Delivered Dose [mg]</td>
<td>529.1</td>
<td>13.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>
### Fine Particle Dose <5µm [mg]

<table>
<thead>
<tr>
<th></th>
<th>313.1</th>
<th>16.3</th>
<th>5.2</th>
<th>341.3</th>
<th>19.7</th>
<th>5.8</th>
<th>326.7</th>
<th>15.6</th>
<th>4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD</td>
<td>313.1</td>
<td>16.3</td>
<td>5.2</td>
<td>341.3</td>
<td>19.7</td>
<td>5.8</td>
<td>326.7</td>
<td>15.6</td>
<td>4.8</td>
</tr>
<tr>
<td>MMAD [µm]</td>
<td>4.5</td>
<td>0.2</td>
<td>3.4</td>
<td>4.4</td>
<td>0.1</td>
<td>2.7</td>
<td>4.4</td>
<td>0.1</td>
<td>2.6</td>
</tr>
<tr>
<td>GSD</td>
<td>1.58</td>
<td>0.02</td>
<td>1.3</td>
<td>1.59</td>
<td>0.01</td>
<td>0.7</td>
<td>1.61</td>
<td>0.01</td>
<td>0.6</td>
</tr>
<tr>
<td>Neb. time [min]</td>
<td>13.6</td>
<td>0.7</td>
<td>5.0</td>
<td>13.0</td>
<td>0.5</td>
<td>3.8</td>
<td>12.3</td>
<td>0.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Fill Weight [g]</td>
<td>8.809</td>
<td>0.013</td>
<td>0.14</td>
<td>8.800</td>
<td>0.004</td>
<td>0.04</td>
<td>8.803</td>
<td>0.002</td>
<td>0.02</td>
</tr>
<tr>
<td>Residual Weight [g]</td>
<td>0.256</td>
<td>0.150</td>
<td>58.5</td>
<td>0.197</td>
<td>0.107</td>
<td>54.1</td>
<td>0.200</td>
<td>0.111</td>
<td>55.3</td>
</tr>
<tr>
<td>TOR [mg/min]</td>
<td>632</td>
<td>35</td>
<td>5</td>
<td>662</td>
<td>24</td>
<td>4</td>
<td>699</td>
<td>38</td>
<td>5</td>
</tr>
</tbody>
</table>

- **a** Standard Deviation
- **b** Relative Standard Deviation
- **c** Calculated by multiplying the label claim of ALIS by the approximate amount poured into the reservoir (70mg/mL x 8.4 mL)
- **d** Calculated using all available digits

Breath simulation studies were performed to evaluate the delivered dose expected for adults. The studies were performed with three lots of ALIS and ten ALIS eFlow nebulizers. The three lots of ALIS were nebulized in an inspiratory filter connected to a breath simulator that was set to a tidal volume of 500 mL and 15 breaths per minute with an inhalation to exhalation ratio of 50:50. For each lot of ALIS, the mean delivered dose (DD) met the acceptance criteria of equal or greater than 90% of label claim.

**Breath Simulation of 3 Lots of ALIS with 10 ALIS eFlow Nebulizers**

<table>
<thead>
<tr>
<th>Lot No. ALIS</th>
<th>3-NFF-0205</th>
<th>3-FIN-1454</th>
<th>3-FIN-1699</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD [mg]</td>
<td>Mean</td>
<td>SD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RSD&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>309.4</td>
<td>9.4</td>
<td>3.0</td>
</tr>
<tr>
<td>DD [%]</td>
<td>52.6</td>
<td>1.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Res [mg]</td>
<td>93.5</td>
<td>20.5</td>
<td>21.9</td>
</tr>
<tr>
<td>Res [%]</td>
<td>15.9</td>
<td>3.5</td>
<td>21.9</td>
</tr>
<tr>
<td>DDR [mg/min]</td>
<td>23.8</td>
<td>2.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Neb time [min]</td>
<td>13.1</td>
<td>0.9</td>
<td>7.0</td>
</tr>
</tbody>
</table>

- **a** Standard Deviation
- **b** Relative Standard Deviation [%]

In order to investigate how the nebulizer handset holding angle influences the delivered dose, breath simulation studies were performed with ten ALIS eFlow nebulizer handsets tilted 15 degrees backwards, forwards and sideways. The results illustrate that a variation of the
holding angle of the ALIS eFlow nebulizer handset of 15 degrees has no significant effect on the delivery of ALIS. The mean delivered dose met the acceptance criteria of equal or greater than 90% of label claim.

### Delivered Doses with Different Handset Holding Orientations

<table>
<thead>
<tr>
<th>Angle</th>
<th>15° forward</th>
<th>15° backward</th>
<th>15° sideways</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>RSD</td>
</tr>
<tr>
<td>DD [mg]</td>
<td>313.2</td>
<td>11.5</td>
<td>3.7</td>
</tr>
<tr>
<td>DD [%]</td>
<td>53.3</td>
<td>2.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Res [mg]</td>
<td>82.8</td>
<td>11.7</td>
<td>14.2</td>
</tr>
<tr>
<td>Res [%]</td>
<td>14.1</td>
<td>2.0</td>
<td>14.2</td>
</tr>
<tr>
<td>DDR [mg/min]</td>
<td>24.0</td>
<td>1.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Neb time [min]</td>
<td>13.1</td>
<td>0.6</td>
<td>4.5</td>
</tr>
</tbody>
</table>

a Standard Deviation
b Relative Standard Deviation [%]

### Simulated Use Testing

The ACI testing showed that there is no significant change in MMAD, GSD and FPD with sonication, and the MMAD decreased from 3.88 µm at the beginning and 3.53 µm at end of 42 days. The total output rate is also improved with sonication as indicated by the RSD of the data at 8% with sonication, and 15% without sonication. Based on this data, it was concluded that using the sonication to clean the aerosol head every 7-day is appropriately implemented in the clinical studies to maintain the aerosol performance of the nebulizer. In addition, the study also indicates that handset is durable for 3 months of use.

### Summary of ACI Results for Group 1 (Aerosol heads 1, 3, 5) with Ultrasonic Cleaning

<table>
<thead>
<tr>
<th>Aerosol Head No.</th>
<th>Beginning of Study</th>
<th>Middle of Study (Day 42)</th>
<th>End of Study (Day 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 3 5 Mean SD</td>
<td>1 3 5 Mean SD</td>
<td>1 3 5 Mean SD</td>
</tr>
<tr>
<td>MMAD (µm)</td>
<td>3.70 3.83 3.96 3.83 0.13</td>
<td>3.71 3.57 3.72 3.67 0.08</td>
<td>3.54 3.37 3.77 3.56 0.20</td>
</tr>
<tr>
<td>GSD</td>
<td>1.73 1.76 1.74 1.75 0.01</td>
<td>1.79 1.78 1.78 1.78 0.00</td>
<td>1.73 1.74 1.78 1.75 0.02</td>
</tr>
<tr>
<td>FPD (D12)</td>
<td>43.8 39.3 38.5 40.5 2.8</td>
<td>33.8 39.6 36.1 36.5 2.9</td>
<td>42.0 43.8 38.1 41.3 2.9</td>
</tr>
</tbody>
</table>
### Summary of ACI Results for Group 2 (Aerosol heads 2, 4, 6) without Ultrasonic Cleaning

<table>
<thead>
<tr>
<th>Aerosol Head No.</th>
<th>Beginning of Study</th>
<th>Middle of Study (day 42)</th>
<th>End of Study (day 84)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>Mean</td>
</tr>
<tr>
<td>MMAD</td>
<td>3.88</td>
<td>3.89</td>
<td>3.91</td>
<td>3.89</td>
</tr>
<tr>
<td>GSD</td>
<td>1.79</td>
<td>1.76</td>
<td>1.75</td>
<td>1.76</td>
</tr>
<tr>
<td>FPD$^*$</td>
<td>42.2</td>
<td>36.8</td>
<td>38.1</td>
<td>39.1</td>
</tr>
</tbody>
</table>

$^*$ Normalized to the volume of ALIS nebulized (mg/mL)

### Device related complaints:

<table>
<thead>
<tr>
<th></th>
<th>INS-112</th>
<th>INS-212</th>
<th>INS-312</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects in the clinical study</td>
<td>89</td>
<td>224</td>
<td>163</td>
<td>476</td>
</tr>
<tr>
<td>Number of systems used in clinical studies</td>
<td>150</td>
<td>271</td>
<td>162</td>
<td>583</td>
</tr>
<tr>
<td>Number of replacement handsets used in clinical studies</td>
<td>272</td>
<td>483</td>
<td>375</td>
<td>1130</td>
</tr>
<tr>
<td>Total number of devices$^*$ used in studies</td>
<td>422</td>
<td>754</td>
<td>537</td>
<td>1713</td>
</tr>
<tr>
<td>Number of device related complaints</td>
<td>12</td>
<td>82</td>
<td>44</td>
<td>138</td>
</tr>
<tr>
<td>Number of device complaints that could not be investigated because the device was not returned</td>
<td>8</td>
<td>28</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Number of devices that were within specification</td>
<td>2</td>
<td>13</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Number of device complaints that were investigated</td>
<td>2</td>
<td>41</td>
<td>29</td>
<td>72</td>
</tr>
<tr>
<td>Number of device complaints confirmed</td>
<td>1</td>
<td>8</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>

### Results of root cause assessment

<table>
<thead>
<tr>
<th></th>
<th>INS-112</th>
<th>INS-212</th>
<th>INS-312</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power supply related</td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>7840/7845 = Defect of power supply</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controller related</td>
<td>N/A</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>7820/7833 = Loose contact plug socket - power supply</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7820/7831 = Defect of electronics</td>
<td>1</td>
<td>1</td>
<td>N/A</td>
<td>2</td>
</tr>
</tbody>
</table>
Reviewer’s Comment: During the clinical studies, it was noted that the weekly (7-day) ultrasonic cleaning requirement placed a burden on the patients, and it is impractical for commercial use. The Sponsor has proposed to replace the aerosol head every week (7-days) rather than requiring weekly ultrasonic cleaning of the aerosol head. Therefore, it was proposed that each 28-day kit contains 28 ALIS vials, one nebulizer, and four aerosol heads where the patient is instructed to replace the aerosol head after 7 days of use. After 28 days, the patient is supplied with a new 28-day kit of ALIS with the same content described above.

The complaints related to device failure rate of 6.8% (116/1713) led to the implementation of several device optimizations which are described in detail: (Sponsor's material)
Overall the device performance data is adequate to support the use of the device. The clinical study device failure’s analyses by the Sponsor has resulted in a reasonable approach of replacing the aerosol head every 7 days to prevent clogging.

The device performance data is ACCEPTABLE.

I. Human Factors

Reviewer’s Comment: A human factors consult was requested separately by DMEPA. I refer to the HF engineer’s (Dr. Hanniebey Wiyor) memo communicated to DMEPA on July 11, 2018. His conclusion noted: “Four (4) deficiencies were identified based on sponsor’s Human Factors engineering report (Nebulizer-engineering-report). However, this review defers to DMEPA to make the necessary and appropriate final determination given the public health considerations for the proposed product.”

J. Recommendation

The device is recommended for APPROVAL.
HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public ***

Date of This Review: July 18, 2018
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 207356
Product Type: Combination Product
Drug Constituent Name and Strength: Arikayce (amikacin liposome inhalation suspension), 590 mg/8.4 mL
Device Constituent: Nebulizer
Rx or OTC: Rx
Applicant/Sponsor Name: Insmed, Inc.
FDA Received Date: March 28, 2018 and May 25, 2018
OSE RCM #: 2018-674; 2018-686
DMEPA Safety Evaluator: Millie Shah, PharmD, BCPS
DMEPA Safety Evaluator: James Schlick RPh, MBA
DMEPA Team Leader: Otto L. Townsend, PharmD
DMEPA Associate Director for Human Factors: Quynh Nhu Nguyen, MS
1 REASON FOR REVIEW
The Division of Anti-Infective Products (DAIP) requested a consultative review of a human factors (HF) validation study report submitted under NDA 207356 for Arikayce (amikacin liposome inhalation suspension). This is a combination product with a proposed nebulizer device constituent part that is intended to treat nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients.

1.1 PRODUCT DESCRIPTION
Arikayce will be used with the Lamira nebulizer, which is a Pari eFlow brand nebulizer specifically designed for Arikayce. The Pari eFlow nebulizer was previously cleared through a 510(k) pathway. Compared to the Pari eFlow nebulizer, the Lamira nebulizer features an increased medication reservoir fill volume and the laser-drilled holes in the aerosol head membranes have a slightly different geometry. These changes optimize the delivery of the Arikayce liposome suspension product and have minimally altered the physical appearance of the device compared to the other Pari eFlow predicate devices. Importantly, despite these differences, the steps required to operate the Lamira nebulizer are nearly identical to the steps required to operate the Pari eFlow nebulizer.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT’S HUMAN FACTORS DEVELOPMENT PROGRAM
We previously reviewed the HF study protocol and provided comments to the Sponsor.1 Our review identified one new critical task of replacing the aerosol head every 7 days for Arikayce, which is different from other drugs that also use the Pari eFlow nebulizer platform. The aerosol head used with other drugs needs to be cleaned and disinfected, but does not need to be replaced. Additionally, we determined there are distinct users between Arikayce and other drugs that utilize the Pari eFlow nebulizer due to the level of care users are likely to receive. Thus, due to the new critical task and distinct users, we determined that a HF validation study is required to determine whether the user interface supports the safe and effective use of Arikayce.

Additionally, the Agency previously provided HF comments during the Type C Meeting on June 23, 20172 and July 3, 2014 meeting.3


2 Type C Meeting Minutes for Arikayce. Silver Spring (MD): FDA, CDER, OAP, DAIP (US); 2017 July 18. IND 108674.

3 Preliminary Meeting Comments for Arikayce. Silver Spring (MD): FDA, CDER, OAP, DAIP (US); 2014 June 30. IND 108674.
2 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Background Information</td>
<td>B</td>
</tr>
<tr>
<td>Previous HF Reviews (DMEPA and CDRH)</td>
<td></td>
</tr>
<tr>
<td>Human Factors Validation Study Report</td>
<td>C</td>
</tr>
<tr>
<td>Information Requests Issued During the Review</td>
<td>D-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>E</td>
</tr>
</tbody>
</table>

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED
The sections below provide a summary of the study design, errors/close calls/use difficulties observed and our analysis to determine whether the results support the safe and effective use of the proposed product.

We also consulted CDRH Human Factors team to review the study report. The CDRH HF team identified additional deficiencies\(^4\). We met with the CDRH HF team on June 11, 2018, June 29, 2018, and July 10, 2018 to discuss the deficiencies and come to an agreement on the recommendations to the Applicant. After our discussion on these dates, CDRH deferred to DMEPA to make the necessary and appropriate final determination given the public health considerations for the proposed product.

3.1 SUMMARY OF STUDY DESIGN
According to the Applicant, the objective of the HF validation study was to confirm that nebulizer use is not vulnerable to use errors that could lead to patient harm and to confirm that the Instructions for Use (IFU), Quick Start Guide (QSG), and instructional video are clear and effective and that they guide safe and effective nebulizer use. The HF validation study included 92 participants who are representative of the following 3 distinct user groups:

1. Patients, including NTM patients or individuals with an underlying respiratory condition (e.g., asthma, Chronic Obstructive Pulmonary Disease [COPD], bronchiectasis) who represent NTM patients (16 trained, 15 untrained)

2. Lay caregivers who might assist patients in administering Arikayce with the nebulizer (15 trained, 16 untrained)

3. Healthcare professionals (HCPs) who train patients and lay caregivers on proper nebulizer use (15 trained, 15 untrained)

Half the participants received training, which included a one hour session for patients and lay caregivers and 30 minutes for HCPs. The training sessions were representative of training the Applicant expects to provide in actual use and consisted of one-on-one training with a trainer (medical professional). The trainer consistently provided participants with hands-on training involving the nebulizer and its packaging, placebo-filled vials, the IFU, and the instructional video. Participants received training one overnight prior to the test session to allow for training decay.

After the participant performed all evaluation activities and provided his/her impression of each evaluation activity, the test administrator conducted a final, post-test interview. The interview included open-ended questions and focused on identifying the root causes of any errors, close calls, and use difficulties. Then, the test administrator asked open-ended questions to collect participants’ subjective feedback about their interactions with the product and associated instructional and training materials.

**3.2 RESULTS AND ANALYSIS**

Table 2 describes the study results for the new critical task of replacing the aerosol head every 7 days, the Applicant’s analyses of the results, and DMEPA’s analyses and recommendations.
<table>
<thead>
<tr>
<th>Critical Task</th>
<th>Number of Use Errors and Description of Use Errors</th>
<th>Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties</th>
<th>Participant’s Subjective Feedback on Use Errors, Close Calls, and Use Difficulties</th>
<th>Applicant’s Root Cause Analysis</th>
<th>DMEPA’s Analysis and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replace aerosol head after 7 days</td>
<td>n=51</td>
<td>Close calls n=6: Initially did not replace the aerosol head with a new one before setting up the nebulizer for the second week of simulated treatment during Use Scenario 2</td>
<td>-Present important instructions, such as those related to the Blue Valve orientation and replacing the aerosol head, in a larger text size and a bold style, presumably so users notice such information among other smaller, un-bolded font. -Add another panel of instructions for changing the aerosol head.</td>
<td>Use Errors: n=12: Did not see a new aerosol head among their supplies. They did not open the ARIKAYCE® box to retrieve a new vial, because the task prompt instructed users to stop before adding medication. However, these participants all speculated that if they had opened the box, they would have seen the new aerosol head in Week 2’s box, and therefore would have been reminded to replace the aerosol head. n=10: attributed the error to test artifact and explained that they forgot to simulate that it was the second week of treatment and/or that they had used the aerosol head seven times n=5: focused more on assembling the Handset correctly than on replacing the aerosol head</td>
<td>The use errors and close calls attributed to the user interface may be further mitigated with design modifications to the carton and labeling revisions. The Applicant did not implement any mitigation strategies based on the use errors and close calls. Our concern is that failure to replace the aerosol head weekly may result in a longer nebulization time and possible worsening of the underlying lung condition because users may not use the product for the full time to nebulize the drug. Thus, based on the root cause analysis, we recommend the Applicant consider a design modification to shorten the flaps of the weekly carton to improve visibility of the</td>
</tr>
</tbody>
</table>
Notably, this participant could not articulate why an additional panel of instructions related to changing the aerosol head would be valuable.

- Increase the conspicuity of IFU page 2’s instruction to replace the aerosol head after seven days (i.e., 13th bullet-pointed warning) by presenting the warning in bold.

n=4: overlooked the instruction on the ARIKAYCE® box to replace the aerosol head. Some of these participants further explained that the individual weekly box’s lid and/or flaps cover the instruction and/or replacement aerosol head.

n=4: concluded that the ARIKAYCE® box only contained vials of medication because the box is labeled ARIKAYCE®™. As such, they were not aware that the box also contained new aerosol heads.

n=4: overlooked the instruction in the IFU to replace the aerosol head, due in part to the inconspicuous and buried, (i.e., after presentation in the IFU or their limited review of the IFU).

n=3: attributed their error to blunder and explained that during the use scenario they incorrectly recalled the task prompt, such that they thought it said to imagine it was the second day rather than the second week of treatment.

n=2: concluded that they did not need to replace the aerosol head because electrical aerosol head so that the flaps do not cover the aerosol head or instruction to replace the aerosol head. Additionally, based on the root cause analysis and participants’ subjective feedback, we recommend revisions to the carton labeling (See Table 4 Carton Labeling-Weekly Sleeve #1) and IFU (See Table 4 IFU #1) to address these use errors and close calls. At this time, we do not need additional HF validation to support these revisions.
components do not typically require frequent, (i.e., after seven uses) replacement, and they thought that the aerosol head looked like an electrical component

n=2: concluded that their simulated patient had already replaced the aerosol head before coming back to their office in the use scenario

n=1: thought the aerosol head seemed like an expensive component, so he attempted to use it as long as possible to save costs

n=1: was unaware at the time that ARIKAYCE® is used daily. As such, she thought that the aerosol head had only been used once rather than seven times

n=1: focused more on ensuring that he cleaned and disinfected the aerosol head correctly than he did on replacing the aerosol head

n=1: attributed his error to feeling rushed and anxious during his test session
n=1: explained that he thought that users needed to clean and disinfect the aerosol Head after seven uses rather than replace the aerosol head

n=1: attributed her error to the fact that she had not actually completed each day’s treatment from the first week, (i.e., due to the simulated nature of the scenario), and therefore, did not have an opportunity to physically discard the original aerosol head after the seventh day. As such, she had to rely on her memory to do so, and ultimately could not remember to replace the component.

n=1: explained that he was not focused on replacing the aerosol head because he stored the device fully-assembled, and as such, did not see the aerosol head while setting up for the first simulated treatment of the second week

n=1: thought that the test administrator presented her with ready-to-use components, including a brand new, clean, and disinfected aerosol head
n=1: reported that she forgot to replace the aerosol head due to the tedious steps associated with using the device (e.g., cleaning and disinfection)

n=3: unable to articulate a root cause for their error

n=2: Due to time constraints, the test administrator did not debrief on the participant’s reported root cause

Close Calls:
n=3: initially assembled the Handset with the existing aerosol head, (i.e., the component from the first week of simulated treatment), but they ultimately remembered to replace it with a new one when they opened the second week’s medication box and noticed it contained the replacement aerosol head. One participant furthermore initially explained during the task that the entire Handset needed to be replaced, before ultimately determining that only the aerosol head needed replacement. During the post-test interview, two participants further explained that having the original Handset components on the table distracted them, which contributed to
their close call. The other participant attributed her close call to the fact that seven days had not passed.

n=1: initially explained during the task that she did not need to replace the aerosol Head because she concluded that one day, rather than one week had passed, due to the fact that she had only administered a single simulated treatment. She explained that she ultimately remembered to replace the aerosol head with a new one when she saw the replacement component in the second week’s medication box.

n=1: initially attempted to replace the Medication Cap, rather than the aerosol head. After opening the replacement Handset bag and retrieving the new Medication Cap, she called the helpline to determine whether she needed to clean and disinfect the Medication Cap, after she could not locate such information in the IFU. While on the phone with the helpline representative, she opened the second week’s medication box and noticed the replacement aerosol head within it, which ultimately led her to replace the correct
component. During the post-test interview, she explained that she initially misidentified the Medication Cap as the aerosol head because she thought the Medication Cap appeared similar to a shower head and because the aerosol head did not match her expectation, based upon its name (i.e., it did not look like a “head” to her).

n=1: initially assembled the device with the original aerosol head, but she could not attach the Connection Cord seemingly due to a defective Handset component. As a means of troubleshooting, the participant then opened the replacement Handset component bag, retrieved the components, and then realized that she also needed to replace the aerosol head. During the post-test interview, she explained that she did not initially pay attention to replacing the aerosol head because the simulated patient had just returned to her office with each of the device components, (i.e., she concluded that the system could readily be used). She added that addressing the defective component led her to recognize her mistake.
<table>
<thead>
<tr>
<th><strong>Interpret IFU to determine to replace aerosol head weekly</strong></th>
<th><strong>n=29: did not determine to replace the aerosol head once weekly while interpreting the IFU excerpt in Knowledge task 2</strong></th>
<th><strong>n=12: focused on information regarding clogging of the aerosol head when interpreting the IFU excerpt on page 2. Some participants explained that they could readily find information on replacing the aerosol head throughout the instructional materials, but could not similarly find other information related to clogging. One participant added that he expected information related to clogging to be most critical because such clogging could prevent medication administration</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>n=5: focused more on content related to cleaning and disinfection in the knowledge task IFU excerpt, in part because details related to cleaning and disinfection comprised most of the passage</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>n=4: considered the need to replace the aerosol head regularly to be commonly understood and, therefore, unnecessary to mention</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>n=4: explained that the information did not stand out to them among the other information in the knowledge task IFU excerpt, (e.g., because it does not have</strong></td>
</tr>
</tbody>
</table>
its own bullet point), and because the IFU did not emphasize it

n=2: explained that they focused on how to prevent aerosol mist reduction due to their perception of the importance of correctly administering the treatment or because of the frequency with which they observe diminished capacity of nebulizers in practice

n=1: explained that she forgot to mention replacing the aerosol head because she focused on other IFU content related to becoming ill, which frightened her

n=1: explained she attempted to summarize the IFU excerpt, rather than entirely restate it
Cleaning and Disinfecting Tasks

The cleaning and disinfecting tasks for Lamira are the same as those for another approved Pari eFlow nebulizer. We consider cleaning and disinfecting tasks to be critical tasks because failure to follow the cleaning and disinfecting procedure may result in a temporary worsening of the underlying lung infection. There were several use errors, close calls, and difficulties surrounding the cleaning and disinfecting procedure. We expect that users will become more familiar with the proper cleaning and disinfecting tasks with repeated use of the nebulizer. However, we acknowledge that Applicant did not provide additional data to support that use errors will diminish with repeated use. The participants’ subjective feedback and root cause analysis indicates that some of the use errors, close calls, and difficulties may be attributed to the labels and labeling. Thus, we recommend revisions to the labels and labeling to mitigate the risk for these errors (See Table 4). At this time, we do not need additional HF validation to support the label and labeling revisions.

Assembly Tasks

The assembly tasks for the handset and nebulizer are the same as those for another approved Pari eFlow nebulizer. There were several use errors, close calls, and difficulties surrounding the assembly procedure. We note that failure to correctly assemble the handset and nebulizer may result in an underdose, missed dose, or a delay in therapy. However, because treatment with Arikayce should be continued of negative sputum cultures while on therapy, a one-time occurrence of an underdose, missed dose, or a delay in therapy will not result in permanent harm to users. In addition, with repeated use of the nebulizer, we expect that users will become more familiar with the proper assembly of the handset and nebulizer. However, we acknowledge that Applicant did not provide additional data to support that use errors will diminish with repeated use. The participants’ subjective feedback and root cause analysis indicates that some of the use errors, close calls, and difficulties may be attributed to the labels and labeling. Thus, we recommend revisions to the labels and labeling to mitigate the risk for these errors (See Table 4). At this time, we do not need additional HF validation to support the label and labeling revisions.

3.3. LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted packaging, labels, and labeling our rationale for concern, and the proposed recommendation to minimize the risk for medication error.
4. CONCLUSION
We acknowledge errors related to the combination product, and that residual risks still exist based on the results of the HF validation study. However, we recognize that this application is a priority review to provide needed therapy in an unmet population. Thus, given the public health considerations, we find the residual risk acceptable given the following recommendations in Table 4 be instituted by the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant so that our recommendations are implemented prior to approval of this NDA. Lastly, we provide Prescribing Information (PI) recommendations in Table 3 below for the Division.
Table 3: Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)

<table>
<thead>
<tr>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDENTIFIED ISSUE</td>
</tr>
<tr>
<td><strong>Highlights of Prescribing Information</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

| **Full Prescribing Information** | | |
| 1 | The strength of the vial (590 mg/8.4 mL) is missing from the Dosage and Administration Section | The missing strength in the Dosage and Administration section could lead to confusion | Revise the following statement from, \(^{(b)}{}^{(4)}\), to, “The recommended dose of ARIKAYCE (amikacin liposome inhalation suspension) in adults is the once daily inhalation of the contents of one 590 mg/8.4 mL ARIKAYCE vial using the Lamira Nebulizer System.” |
| 2 | The strength of the vial (590 mg/8.4 mL) is missing from the How Supplied Section | The missing strength in the How Supplied section could lead to confusion | Add the strength (590 mg/8.4 mL) to the How Supplied section |
| 3 | Preparation instructions for Arikayce are in Section 16, How Supplied Section | Information in this section is intended for healthcare practitioners, whereas preparation instructions are intended for patients and caregivers. Thus, the preparation instructions in this section take away from the readability of important product information and contribute to clutter. | Consider removing the paragraph (b) (4) |

| 4 | Inconsistent text formatting for Lamira in the Patient Instructions for Use section | Inconsistent text formatting for Lamira and Arikayce may result in confusion between the device and medication name. One participant in the HF validation study determined that the handset (rather than the medication) should not be frozen prior to use. Based on the URRRA, inhalation of cold medication could result in temporary worsening of the underlying lung disease. | Revise the text formatting of “LAMIRA” in Step 2 under Taking Arikayce section from uppercase to title case for consistency with the presentation of Lamira throughout the rest of the IFU and to minimize confusion with the medication (ARIKAYCE) that is presented in uppercase letters throughout the IFU, (for example, “Press and hold down on the On/Off button for a few seconds to turn the Lamira on.”) |

**Comments for Insmed**

We found the results of your human factors (HF) validation study acceptable. Our evaluation of the proposed packaging, labels and labeling identified areas of vulnerability that may lead to medication errors. Additionally, we provided a recommendation below for the user interface. We provided recommendations in the table below and we recommend that you implement these recommendations.
<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instructions for Use (IFU)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1. Instructions to replace aerosol head are not prominent | Several participants in the HF validation study provided subjective feedback that instructions to replace the aerosol head are not prominent. Failure to replace the aerosol head weekly may result in increased nebulization time and potentially worsening of the underlying lung disease | Use color, bold font, boxing, or some other means to increase the prominence of the following statements:  
• in the 12th bullet under Warning on page 2 of the IFU, “Replace the aerosol head with a new one after 7 uses”  
• in Step C1 on page 3 of the IFU, “4 Lamira aerosol heads (1 aerosol head to be used for 7 days and then replaced)” |
<p>| 2. Dosing regimen is not prominent | 10 participants in the HF validation study did not determine the correct dosage regimen when referring to the IFU because they overlooked the information in the IFU | Use color, bold font, boxing, or some other means to increase the prominence of the following statement in Step C1, “28 once-daily vials of ARIKAYCE (1 vial to be used each day for 28 days)” |</p>
<table>
<thead>
<tr>
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<th></th>
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</thead>
</table>
| **3.** | As previously communicated on October 17, 2017 during our review of the HF validation study protocol, information on the time it takes Arikayce to warm to room temperature is not included | One participant in the HF validation study did not identify that Arikayce should only be used at room temperature. Based on the URRA, inhalation of cold medication could result in temporary worsening of the underlying lung disease. | Revise the following statement on page 8 of the IFU from, “

> to include the amount of time it takes Arikayce to warm to room temperature based on your internal testing.

**4.** Inconsistent text formatting for Lamira | Inconsistent text formatting for Lamira and Arikayce may result in confusion between the device and medication name. One participant in the HF validation study determined that the handset (rather than the medication) should not be frozen prior to use. Based on the URRA, inhalation of cold medication could result in temporary worsening |

Revise the text formatting of Lamira in the following statement from uppercase to title case for consistency with the presentation of Lamira throughout the rest of the IFU and to minimize confusion with the medication (ARIKAYCE) that is presented in uppercase letters throughout the IFU, “Your ARIKAYCE should be at room temperature before use to make sure that your LAMIRA operates properly.” |
<p>| | | |</p>
<table>
<thead>
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<th></th>
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</thead>
<tbody>
<tr>
<td>5.</td>
<td>Graphic depicting orientation of blue valve flaps is small</td>
<td>One participant in the HF validation study explained that she did not notice the blue valve’s raised/depressed graphics in Figure E-4 due to the graphic’s small size. Based on the URR, failure to insert the blue valve correctly could increase the likelihood of temporary persistence of MAC lung infection. Increase the size of the graphic in Figure E-4a to better depict the correct orientation of the blue valve’s flaps.</td>
</tr>
<tr>
<td></td>
<td>“Section G Maintaining Your Lamira,” “Section H Cleaning Your Lamira,” and “Section I Disinfecting Your Lamira” are located at the end of the IFU</td>
<td>Several participants in the HF validation study provided subjective feedback to relocate cleaning and disinfecting instructions closer to the beginning of the IFU so that users are more likely to notice and implement. Revise the order of the following: “Section G Maintaining Your Lamira,” “Section H Cleaning Your Lamira,” and “Section I Disinfecting Your Lamira” so that they immediately follow “Section D Using Batteries or the A/C Power Supply” to increase the prominence of the cleaning and disinfecting instructions and so that the tasks follow sequential order.</td>
</tr>
<tr>
<td></td>
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<tr>
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</tr>
<tr>
<td>7.</td>
<td>Inside cover page of IFU does not include warning statement to clean and disinfect</td>
<td>One participant in the HF validation study provided subjective feedback to add instructions for users to clean and disinfect before use. Add the following Warning statement in Section G Maintaining Your Lamira also to the inside of the cover page of the IFU to increase the prominence of the cleaning and disinfecting instructions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Warning" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>To reduce the risk of infection, illness, or injury from contamination or improper use, it is important to complete the following 2 steps:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Rinse and clean the Handset right after each use. (See Section H) Do not wash the Controller, Connection Cord, or A/C Power Supply. Use clear liquid soap made for washing dishes to clean the Handset. Do not use liquid dish soaps that are white or antibacterial liquid dish soaps because these may contain additives harmful to the Aerosol Head.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Disinfect the Handset and Aerosol Head every day (see Section I)</td>
</tr>
<tr>
<td>8.</td>
<td>Graphic depicting hand washing is missing. There is inconsistency in the instruction between the QSG and IFU.</td>
<td>75 participants in the HF validation study did not wash their hands prior to assembling the nebulizer. One participant provided subjective feedback to include a handwashing graphic in the IFU. Failure to wash hands may result in infection. Inconsistency of the instruction and figure between the QSG and IFU may result in confusion. Revise IFU Step E2, “Wash your hands with soap and water, and dry them well” for consistency with the QSG. Add the handwashing graphic from Step B1 in the QSG to Step E2 in the IFU.</td>
</tr>
</tbody>
</table>
9. Graphic depicting shaking vial is inconsistent between IFU and QSG

36 participants did not shake the Arikayce vial for 10-15 seconds in the HF validation study. Several participants provided subjective feedback that they did not realize the arrows in Figure F-1 are intended to instruct users to shake the vial or that sideways depiction of the vial was confusing. Failure to shake the vial may result in prolonged nebulization time. Inconsistency between the IFU and QSG may result in confusion.

Revise the graphic in Step F1 of the IFU to the graphic in Step C1 in the QSG.

10. Instruction in Step F-10 is error-prone

1 participant in the HF validation study only rinsed the aerosol head instead of following the entire cleaning and disinfecting procedure because...

Revise the following instruction in Step F-10 from, (b) (4) to, “Follow the instructions in Steps H6 through H9 below and replace the aerosol head with a new one”
Step F-10 directs the user to follow Step H-6 instead of all steps related to cleaning and disinfecting the aerosol head.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>11.</td>
<td>“Handset Maintenance Summary Table” in Section G does not indicate to clean and disinfect components prior to first use</td>
</tr>
<tr>
<td></td>
<td>One participant in the HF validation study did not clean or disinfect the new aerosol head because the Handset Maintenance Summary Table did not specify that users should complete all cleaning and disinfection steps prior to first use. Rather, the “When” column describes performing maintenance steps after each use, after cleaning, or every day. Failure to follow the cleaning and disinfecting steps may result in infection.</td>
</tr>
<tr>
<td></td>
<td>Revise the “When” column in the Handset Maintenance Summary Table to add “Prior to first use” for each instruction</td>
</tr>
</tbody>
</table>

Reference ID: 4293589
12. The frequency for cleaning the controller and connection cord is missing from Section H Step H11

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device components not labeled in Figure (Section B, Step 2):</td>
<td>One participant in the HF validation study required assistance to locate the aerosol head among the other device components. Based on the URRA, failure to insert the aerosol head correctly could increase the likelihood of temporary persistence of MAC lung infection.</td>
<td>Label the aerosol head and blue valve in the figure to increase clarity</td>
</tr>
<tr>
<td>Device assembly not comprehensively depicted in Figure (Section B, Step 5):</td>
<td>One participant in the HF validation study required assistance to attach the connection cord to</td>
<td>Revise the figure to depict assembly to this point by depicting the blue valve and mouthpiece to improve clarity</td>
</tr>
</tbody>
</table>
Specifically, the figure excludes the mouthpiece and blue valve that would be assembled at this point. The handset. Based on the URRA, failure to attach the connection cord to the handset correctly could increase the likelihood of temporary persistence of MAC lung infection.

3. Cleaning and disinfecting instructions are located on the back panel
2 participants in the HF validation study indicated that they did not disinfect the handset after use because they did not notice the instructions because they are located on the back panel

   Relocate the cleaning and disinfecting instructions from the back panel to the front panel so they are visible along with the other instructions

4. Revise the statement “Additional information, including a video, is available at www.arikeyce.com. The additional information has not been evaluated or approved by the FDA.”

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container Labels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4293589
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>There is inadequate space between the numerical strength and unit of measure.</td>
<td>Inclusion of a space between the numeral and the unit of measurement in the strength statement improves readability.</td>
</tr>
<tr>
<td>2.</td>
<td>The net quantity statement is missing.</td>
<td>The missing net quantity statement may lead to confusion.</td>
</tr>
<tr>
<td>3.</td>
<td>The package type term is missing.</td>
<td>The package type term is needed to identify how the medication should be safely handled and used. (^6)</td>
</tr>
<tr>
<td>4.</td>
<td>Manufacturer name and logo competes in prominence with more important information on the</td>
<td>The prominence of the manufacturer name and logo on the principal display panel takes readers’ attention away from important</td>
</tr>
</tbody>
</table>


principal display panel | information such as the established name, strength, and route of administration.

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. See Container Labels #1</td>
<td>See Container Labels #1</td>
<td>See Container Labels #1</td>
</tr>
<tr>
<td>2. See Container Labels #2</td>
<td>See Container Labels #2</td>
<td>See Container Labels #2</td>
</tr>
<tr>
<td>3. See Container Labels #3</td>
<td>See Container Labels #3</td>
<td>See Container Labels #3</td>
</tr>
<tr>
<td>4. There is a space on the top panel for the pharmacy to apply a use by dating sticker; however, it is not clear where/how the pharmacy will obtain the use by dating sticker</td>
<td>Confusion may result if the “discard after” date once the product is removed from refrigeration is missing</td>
<td>Replace the statement, “Pharmacy: Write Discard After Date 6 weeks from dispensing here: Discard After <em><strong><strong>/</strong></strong></em>/<em><strong><strong>” with, “Pharmacy: Write Discard After Date 6 weeks from dispensing here: Discard After <em><strong><strong>/</strong></strong></em>/</strong></strong></em>” to allow space for the pharmacy to write the discard after date</td>
</tr>
</tbody>
</table>

**Carton Labeling-Weekly Sleeves**

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carton does not state that it includes a replacement aerosol head</td>
<td>4 participants in the HF validation study did not replace the aerosol head because they were not aware that the box also contained new aerosol heads</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>2.</td>
<td>See Container Labels #1</td>
<td>See Container Labels #1</td>
</tr>
<tr>
<td>3.</td>
<td>See Container Labels #2</td>
<td>See Container Labels #2</td>
</tr>
<tr>
<td>4.</td>
<td>The statements, “Week 1,” “Week 2,” “Week 3,” and “Week 4” compete in prominence with the proprietary and established names on the principal display panel</td>
<td>The prominence of the weekly statements on the principal display panel takes readers’ attention away from important information such as the proprietary and established names</td>
</tr>
<tr>
<td>5.</td>
<td>See Container Labels #3</td>
<td>See Container Labels #3</td>
</tr>
<tr>
<td>6.</td>
<td>Manufacturer name and logo competes in prominence with more important</td>
<td>The prominence of the manufacturer name and logo on the principal display panel takes readers’</td>
</tr>
<tr>
<td>IDENTIFIED ISSUE</td>
<td>RATIONALE FOR CONCERN</td>
<td>RECOMMENDATION</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1. We acknowledge your rationale for</td>
<td>(b) (4)</td>
<td>Remove the (b) (4)</td>
</tr>
<tr>
<td>(b) (4) However, as previously communicated on October 17, 2017 during our review</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Back panel states, “Store at room temperature up to 25°C (77°F) until the [ ] Date indicated on the outer carton.”

The term, [ ] Date may lead to confusion. We recommend “Discard After” because it is an affirmative statement and has been shown to result in the desired action.

Revise the statement from, “Store at room temperature up to 25°C (77°F) until the Date indicated on the outer carton.” to, “Store at room temperature up to 25°C (77°F) until the Discard After Date indicated on the outer carton.”
of the HF validation study protocol, this labeling strategy is error-prone

<table>
<thead>
<tr>
<th>Aerosol Head Carton Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDENTIFIED ISSUE</strong></td>
</tr>
<tr>
<td>1. The statement, “Clean and disinfect before first use” is on the back panel</td>
</tr>
</tbody>
</table>
2. As previously communicated on October 17, 2017 during our review of the HF validation study protocol, the statement, “Do not touch the center silver part of the aerosol head” is missing from the principal display panel. There were several use errors observed in the HF validation study where participants touched the center silver part of the aerosol head either while cleaning or assembling the device.

Add the statement, “Do not touch the center silver part of the aerosol head” to the principal display panel.

### Handset Packaging Outer Labeling

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The statement, “Clean and disinfect before first use” lacks prominence</td>
<td>There were several use errors observed in the HF validation study where participants did not clean and/or disinfect</td>
<td>Revise the statement, “Clean and disinfect before first use” to, “Clean and disinfect before first use and daily thereafter.” Increase the prominence of this statement with the use of bold font, color, boxing, or some other means.</td>
</tr>
</tbody>
</table>

Reference ID: 4293589
Several participants explained that they concluded that the packaged handset components would already be clean and disinfected, due to their brand-new, unopened nature. Additionally, the statement does not instruct users to clean and disinfect daily thereafter. Failure to clean and disinfect the handset may result in infection.

### Design of Packaging for Weekly Carton

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE AND RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The results of the HF validation study show that 51 participants failed to replace the aerosol head after 7 uses and 29 participants did not interpret the IFU correctly in the knowledge assessment. Our concern is that failure to replace the aerosol head weekly may result in a longer nebulization time and possible worsening infection.</td>
<td>Consider a design modification to shorten the flaps of the weekly carton to improve visibility of the aerosol head so that the flaps do not cover the aerosol head or instruction to replace the aerosol head.</td>
</tr>
</tbody>
</table>
of the underlying lung condition. The use of errors and close calls attributed to the user interface may be further mitigated with design modifications to the carton.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Arikayce that Insmed, Inc. submitted on March 28, 2018.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Therapeutic Drug Class or New Drug Class</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient (Drug or Biologic)</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td><strong>Intended Users</strong></td>
</tr>
<tr>
<td><strong>Intended Use Environment</strong></td>
</tr>
</tbody>
</table>
APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods
On April 23, 2018, we searched the L:drive and AIMS using the terms, Arikayce and 108674 (IND associated with this NDA) to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results
Our search identified 2 previous reviews\(^7\),\(^8\), and we confirmed that our recommendations were implemented or considered.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\cdsesub1\evsprod\nda207356\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ntm-infection\5354-other-stud-rep\human-factors\nebulizer-engineering-report.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW - N/A

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis,\(^9\) along with postmarket medication error data, we reviewed the following Arikayce labels and labeling submitted by Insmed, Inc on March 28, 2018.

- Container label
- Carton labeling
- Device labels and labeling
- Instructions for Use (IFU)-accessible in EDR via:
  \cdsesub1\evsprod\nda207356\0001\m1\us\ifu-launch.pdf
- Quick Start Guide (QSG)-accessible in EDR via:
  \cdsesub1\evsprod\nda207356\0001\m1\us\qrg.pdf
- Prescribing Information (PI)-accessible in EDR via:


\(^8\) Type C Meeting Minutes for Arikayce. Silver Spring (MD): FDA, CDER, OAP, DAIP (US); 2017 July 18. IND 108674.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES H SCHLICK
07/20/2018

OTTO L TOWNSEND on behalf of MILLIE B SHAH
07/20/2018

OTTO L TOWNSEND
07/20/2018

QUYNHNHU T NGUYEN
07/23/2018
1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Griffith and Winthrop) were selected for inspections for three protocols (INS-212, INS-312, and TR02-112) that were submitted to support this application. Both clinical sites enrolled a relatively higher number of subjects in all three studies. The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the requested indication under this NDA.

The final classification for the inspection of Dr. Griffith’s clinical site is No Action Indicated (NAI). The preliminary classification for the inspection of Dr. Winthrop’s clinical site is Voluntary Action Indicated (VAI) due to minor protocol violations. Preliminary classification is based on communications with the ORA investigator. Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a letter is issued to the inspected entity.
2. BACKGROUND

ARIKAYCE (amikacin liposome inhalation suspension) is a unique liposomal suspension of amikacin (an aminoglycoside antibiotic) formulated for oral inhalation using an eFlow® Nebulizer System that is provided as a Lamira™ nebulizer handset along with the eFlow control Unit. The sponsor submitted a 505(b)(2) Accelerated Approval application under Subpart H seeking marketing authorization for this drug-device combination product. The proposed indication for amikacin liposome inhalation suspension (ALIS) is for the treatment of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as a part of a combination antibiotic regimen for adult patients. This new formulation and route of administration is intended to achieve greater local concentrations of amikacin in the lung, while minimizing systemic concentrations.

ARIKAYCE was granted Orphan Drug designation March 25, 2013 for liposomal amikacin for infections caused by nontuberculous mycobacterial, Fast Track and Breakthrough Therapy designations (granted June 28, 2013 and June 16, 2014, respectively) and the designation as a Qualified Infectious Disease Product (QIDP) granted on June 28, 2013.

The sponsor conducted one Phase 3 clinical study (Protocol INS-212), a safety extension study (Protocol INS-312), and a Phase 2 study (Protocol TR02-112) to support the proposed indication.

Protocol INS-212

Protocol Titles: A Randomized, Open-Label, Multicenter Study of Liposomal Amikacin for Inhalation (LAI) in Adult Subjects with Nontuberculous Mycobacterial (NTM) Lung Infections Caused by Mycobacterium avium Complex (MAC) That Are Refractory to Treatment.

This is a Phase 3, multicenter, randomized, open-label study of ALIS in adult subjects with NTM lung infections caused by MAC that were refractory to treatment. The study is currently ongoing and the initial report in the NDA submission includes final data for the initial analysis as of the data through the cutoff date of 07 July 2017, the date when the last subject completed their Month 6 visit.

The primary objective of study was to evaluate the efficacy of ALIS (590 mg) administered once daily (QD), when added to a multidrug regimen (MDR), for achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 compared to an MDR alone. The date of conversion was defined as the date of the first of 3 negative monthly cultures.

The primary efficacy endpoint was the proportion of subjects achieving culture conversion by Month 6. Other secondary endpoints included 6-minute walk test (6MWT) and St. George’s Respiratory Questionnaire (SGRQ).

The main inclusion criteria of the study included male or female subjects, aged 18 years or older (20 years of age or older in Japan); diagnosed with MAC NTM lung infection with evidence of underlying lung disease such as nodular bronchiectasis and/or fibrocavitary disease by chest radiography or chest computed tomography (CT); had positive sputum culture for MAC while being treated with an MDR (at least 2 antibiotics) for a minimum duration of 6 consecutive months [MDR treatment must be
either ongoing or have been stopped no more than 12 months before Screening (exceptions to treatment with an MDR for 6 consecutive months included treatment with doses or frequencies below those recommended by guidelines and/or short interruptions of therapy, both occurring due to safety/tolerability issues); had a MAC lung infection documented by at least 2 positive cultures (MAC or mixed infection with MAC as the dominant species), consisting of at least 1 positive culture obtained within 6 months prior to Screening and 1 positive culture at Screening (cultures to be at least 1 month apart); and had a MAC-positive sputum at Screening.

The study subjects were randomized in a 2:1 ratio to ALIS 590 mg administered QD + MDR or MDR alone for a minimum of 8 months. Subjects were stratified by smoking status (current smoker or not) and prior MDR (on treatment or off treatment for at least 3 months) at Screening. At Month 8 (-28 to +7 days), after all sputum culture results were known, up to and including Month 6, subjects were assessed as converters or non-converters. A converter was defined as a subject who had 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study. Non-converters were discontinued from the study at Month 8. Converters who completed a total of 12 months of treatment (end of treatment [EOT]) returned after the EOT visit for 28 days, 3, 6, and 12 months off-treatment follow-up visits. The 12 months off-treatment follow-up visit was the end of study visit.

The study randomized 336 subjects from 127 sites in 18 countries and enrolled the first patient on May 27, 2015 and the last patient completed Month 6 visit on July 7, 2017. The study is ongoing.

Protocol INS-312

Protocol Titles: An Open-Label Safety Extension Study to a Multicenter Study of Liposomal Amikacin for Inhalation (LAI) in Adult Patients with Nontuberculous Mycobacterial (NTM) Lung Infections Caused by Mycobacterium avium Complex (MAC) That Are Refractory to Treatment.

This is an ongoing open-label safety extension study to assess safety and tolerability of ALIS 590 mg QD added to a multidrug regimen (MDR) in subjects with NTM lung infections due to MAC who were refractory to therapy and failed to convert in Study INS-212.

The primary objective is to evaluate the long-term safety and tolerability of Amikacin Liposome Inhalation Suspension (ALIS; 590 mg) administered daily (QD) for up to 12 months in subjects who were refractory to standard multidrug treatment and failed to convert in Study INS-212.

The primary endpoint is the frequency of treatment emergent adverse events (TEAEs), TEAEs leading to withdrawal from study, treatment-emergent serious adverse events (SAEs), adverse events (AEs) of special interest, clinically significant abnormal laboratory test results, and vital signs measurements. The secondary endpoints include proportion of subjects achieving culture conversion (3 consecutive negative sputum cultures with no relapse or recurrence) by Month 6 and proportion of subjects achieving culture conversion by Month 12/EOT.

Subjects participating in Study INS-212 who had not achieved the Study INS-212 protocol definition of culture conversion (3 consecutive monthly negative sputum cultures) or who had experienced a relapse or recurrence (agar positive or more than 2 consecutive broth positive results after culture
conversion had occurred) by Month 6, as determined by their sputum culture results from Day 1 through Month 6 and confirmed at their scheduled Month 8 visit, were eligible to participate in Study INS-312.

All subjects in this safety extension study were to continue the multidrug antimycobacterial regimen that they were receiving during Study INS-212 and were to also receive ALIS 590 mg QD for up to 12 months. The subjects will remain in the study for up to a total of 13 months (up to 12 months on-treatment plus 1 month off ALIS treatment for safety follow-up).

The study enrolled 133 subjects and enrolled the first patient on February 5, 2016 and the last patient completed Month 6 visit in Study INS-212 on July 7, 2017. The study is ongoing.

**Protocol TR02-112**

Protocol Titles: A Randomized, Double-blind, Placebo-controlled Study of Liposomal Amikacin for Inhalation (LAI) in Patients with Recalcitrant Nontuberculous Mycobacterial Lung Disease.

This was a Phase 2, randomized, placebo-controlled, double-blind study of efficacy, safety, and tolerability of once daily (QD) dosing of LAI 590 mg versus placebo for 84 days in subjects with treatment-refractory nontuberculous mycobacteria (NTM) lung infection on a stable multidrug regimen.

The primary objective of this study was to evaluate the safety, tolerability, and efficacy of LAI in patients with treatment-refractory NTM lung infection.

The primary efficacy endpoint was the change from baseline on the full semi-quantitative scale (SQS) for mycobacterial culture at Day 84. The safety assessment included frequency and severity of treatment-emergent adverse events, including serious adverse events, adverse events resulting in discontinuation, and change from baseline in clinical laboratory tests.

The main inclusion criteria of the study included subjects with 18 to 85 years of age; history of chronic infection defined as at least 2 documented positive cultures in the prior 2 years; of which at least 1 was obtained in the 6 months before screening with either MAC or M. abscesses or mixed infection with both species; receiving ATS/IDSA guidelines-based treatment regimen defined as: adherent to a multidrug regimen for at least 6 months before screening with persistently positive mycobacterial cultures; ability to produce at least 3.0 mL of sputum or be willing to undergo an induction that produced at least 3.0 mL of sputum for mycobacteriology.

The study randomized 90 subjects and enrolled the first patient on April 19, 2012 and the last patient completed the last visit on June 18, 2015.
3. RESULTS (by site):

<table>
<thead>
<tr>
<th>Name of CI, Address</th>
<th>Protocol #, Site #, and # of Enrolled Subjects</th>
<th>Inspection Date</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>David E. Griffith, M.D. &lt;br&gt;The University of Texas Health Science at Tyler &lt;br&gt;11937 US Highway 271 &lt;br&gt;Tyler, Texas 75708</td>
<td>Protocol INS-212 Site 114 Enrolled Subjects=22 &lt;br&gt;Protocol INS-312 Site 0114 Enrolled Subjects=15 &lt;br&gt;Protocol TR02-112 Site 2359 Enrolled Subjects=16</td>
<td>June 5-12, 2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Kevin L. Winthrop, M.D. &lt;br&gt;Oregon Health and Science University &lt;br&gt;3181 SW Sam Jackson Park Road, GH104 &lt;br&gt;Portland, Oregon 97239</td>
<td>Protocol INS-212 Site 107 Enrolled Subjects=21 &lt;br&gt;Protocol INS-312 Site 0107 Enrolled Subjects=10 &lt;br&gt;Protocol TR02-112 Site 2365 Enrolled Subjects=14</td>
<td>June 5-14, 2018</td>
<td>*VAI</td>
</tr>
</tbody>
</table>

Key to Compliance Classifications
NAI (No Action Indicated) = No deviation from regulations.
VAI (Voluntary Action Indicated) = Deviation(s) from regulations.
OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1. David E. Griffith, M.D. (Protocol INS-212, Site 114; Protocol INS-312, Site 0114; and Protocol TR02-112, Site 2359; Tyler, Texas)

For Protocol INS-212, the site screened 37 subjects and enrolled 22 subjects. Among the 22 enrolled subjects, 16 subjects completed the study; three subjects are in follow-up; and three subjects discontinued the study (Subject 1 died of acute chronic respiratory failure, not related per investigator; Subject 2 and 3 were due to subject withdrawal). An audit of all 22 enrolled subjects’ records was conducted.
For Protocol INS-312, the site has enrolled 15 subjects at the time of inspection. Among the 15 enrolled subjects, 10 subjects completed the study; three subjects are still on treatment; one subject is in follow-up; and one subject discontinued the study (Subject (2) died of chronic obstructive pulmonary disease). The discontinuation data listing provided in the NDA were verified by review of source documents. An audit of all 15 enrolled subjects’ records was conducted.

For Protocol TR02-112, the site screened 20 subjects and enrolled 16 subjects. Among the 16 enrolled subjects, 15 subjects were randomized and completed the study. One subject discontinued the study due to adverse event (Subject (1) was discontinued due to protocol violation for development of an exclusion criterion). An audit of all 16 enrolled subjects’ records was conducted.

The inspection evaluated the following documents: informed consent, inclusion/exclusion criteria, protocol deviations, randomization and blinding, adverse events, verification of efficacy endpoints, IRB correspondence and study approvals, sponsor correspondence, electronic case report forms, source records, and drug accountability records. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No significant observations were noted and a Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear reliable in support of this specific indication.

2. Kevin L. Winthrop, M.D. (Protocol INS-212, Site 107; Protocol INS-312, Site 0107; Protocol TR02-112, Site 2365; Portland, Oregon)

For Protocol INS-212, the site screened 37 subjects and enrolled 21 subjects. Among the 21 enrolled subjects, 15 subjects completed the study and six subjects discontinued the study (Subject (6) was due to MAC NTM infection exacerbation; Subject (7) was due to hoarseness; Subject (8) was due to use of rescue medication; Subject (9) was due to non-compliance with study drug; and Subjects (10) and (11) died of SAEs, unspecified, at follow-up period). An audit of all 21 enrolled subjects’ records was conducted.

For Protocol INS-312, the site enrolled 10 subjects. Among the 10 enrolled subjects, 9 subjects completed the study and one subject (Subject (12) discontinued study treatment due to hypersensitivity pneumonitis but continued study visits. An audit of all 10 enrolled subjects’ records was conducted.

For Protocol TR02-112, the site screened 24 subjects and enrolled 14 subjects. Among the 14 enrolled subjects, 13 subjects completed the study and one subject (Subject (13) discontinued due to subject withdrawal and died of SAE (unspecified) post withdrawal. An audit of all 14 enrolled subjects’ records was conducted.
The inspection evaluated the following documents: source records, screening and enrollment logs, eligibility criteria, randomization and blinding procedure, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

An FDA 483, Inspectional Observations, was issued to the site for the following protocol violations:

1. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests.

   Specifically, for protocol TR02-112, Subject had a CT scan and audiology testing performed on 9/9/13 prior to signing the Informed Consent Form on 9/12/13.

2. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

   Specifically,
   1) For protocol TR02-112, two cartons of the study drug were dispensed to incorrect subjects. Subject was assigned carton T3692, but received carton T3629 and dosed with one vial. Subject was assigned carton T3629, but received carton T3692. Subject did not dose with any vials from T3692.

   2) For Protocol INS-212: Subject had a serious adverse event of pneumonia that was not reported within 24 hours as required by the protocol. Site was aware on 9/28/2015 but did not report until 10/7/2015.

3. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation and informed consent.

   Specifically, for protocol INS-212, the original informed consent form signed by subject was lost. The subject was re-consented on 11/3/2016 after the screening visit had been conducted

OSI Reviewer’s comments:

For dispensing errors identified in Study TR02-112, Subject was randomized to placebo group but received a single dose of Arikace treatment (carton T3629). Subject was randomized to the Arikace group and did not dosed with placebo vials (carton T3692). These are listed as protocol deviations in the clinical study report submitted to this NDA. The site notified the sponsor and IRB after identified the errors and corrective actions were taken. At the time that the error occurred the research pharmacy implemented a check by a 2nd pharmacist. Since this
issue occurred the research pharmacy now receives orders through the electronic medical records system and dispenses study drug using the vestigo system. The other above protocol violations were also reported in the clinical study reports in the NDA submission by the sponsor. These protocol violations appear unlikely to have significant impact on the primary efficacy endpoint and safety results of the study.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. Data submitted by this clinical site appear acceptable in support of this application.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Division Director/ Sumathi Nambiar
Review Division /Clinical Team Leader/ Peter Kim
Review Division/Medical Officer/ Hiwot Hiruy
Review Division /Project Manager/ Deborah Wang
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP Reviewer/Min Lu
OSI/ GCP Program Analyst/Yolanda Patague
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MIN LU
07/20/2018

KASSA AYALEW
07/20/2018
Human Factors (HF) Review

Consult Number: CON1810551
Document Number: ICC1800293; NDA 207356
Applicant: ARIKAYCE® (Amikacin liposome inhalation suspension)
Trade Name: Insmed Inc

Consult Type: Human factors
Requester: Deepika Lakhani
depiaka.lakhani@fda.hhs.gov
Requester Home: CDRH\ODE\DCD\CDDB
Requester Consultant: Hanniebey D. Wiyor
Division: CDRH\ODE\DAGRID\HFPMET

Date Requested: April 25, 2018
Due Date: May 21, 2018

Requestor Instructions: Dear Hanniebey, Please assign/review HF consult request from DMEPA for this NDA. Thanks, deepika

Indication for Use: Treatment of Nontuberculous Mycobacterial (NTM) lung disease caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen for adult patients

Key considerations for conducting a HF review: NDA – Does the supporting documentation demonstrate that the subject device UI supports safe & effective use?

I. Date consult sent: May 23, 2018,
II. Resent: June 20, 2018

HF Recommendation: Please communicate the four (4) deficiencies below to the sponsor.
II. HF Review:
HF Consult Response to communicate to sponsor

Deficiency 1
You report a total of 1,049 use errors, 12 instances of test administrator assistance, 53 close calls, and 70 difficulties with varied potential for serious harms during the summative Human factors validation testing of the subject device and the associated IFU and QRG (Nebulizer-engineering-report, Section 8: HUMAN FACTORS VALIDATION TESTING DETAILS, Pg. 96-209 and Nebulizer-summative-test-report). Consequently, you revised the device user documentations i.e., IFU, QRG, instructional materials as summarized in Table 2. IFU, QRG, and Packaging Modifications Post-Summative Testing, Pg. 7-12 (Nebulizer-engineering-report, Section 1.3 Enhancements). However, you did not provide a Human factors validating testing data, analysis and conclusion to support that effectiveness of proposed risk mitigation controls as user documentations revisions. To validate the effectiveness of your device user documentations, please provide a supplementary human factors validation testing involving the recruitment of test participants from the previous summative testing. In addition to collecting both performance and subjective data, be very specific in eliciting participant’s responses regarding their feedback on changes being made and how it affects the safe use of the device (See deficiency 3 below)

Deficiency 2a
A reviewed of ufmea-analysis identified user tasks for maintenance, cleaning, disinfection and replacement of the subject device aerosol head as non critical with associated severity of negligible (6) to temporary uncritical conditions (13). (i.e., Tasks ID Number 5.1 to 5.6). However, the accompanying ARIKAYCE® IFU WARNING statements states that failure or improper or lack of adherence to maintenance, cleaning, disinfection and replacement of the aerosol head may lead to infection, illness, or injury from contamination (i.e., Sections G (Maintaining Your Lamira, Pg. 11), H (Cleaning Your Lamira, Pg. 12-14), and I Disinfecting Your Lamira, Pg. 15 of IFU). As defined in 2016 CDRH Human factors guidance, critical tasks are user tasks which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined as degree of physical injury or loss of life, compromised medical care etc. Thus, for the safe-use of the subject device, please reconduct a use-related risk assessment to identify critical user tasks associated with the device-user documentations’ WARNING, PRECAUTION, NOTES statements for maintenance, cleaning, disinfection, and replacement for the aerosol heads. And, accordingly revise these tasks as critical user tasks with a high severity in the ufmea-analysis document
Deficiency 2b
Specific to aerosol head knowledge tasks assessments for cleaning and disinfections, the Human factors validation results revealed a plethora of committed use errors with potential for serious harm such as 54 instances of knowledge tasks failures (Table 10, Page 104) and between 25% to 80% successful task performance in Tables11 (Pg. 106-113), 12 (Pg. 114-115), and 13 (Pg.116-117). As an illustration below:

Clean the nebulizer (Pg.106)
Rinse Aerosol Head for at least 10 seconds on each side (14% pass rate)

Disinfect the nebulizer (Pg. 107)
Simulate boiling the Handset parts, including the Aerosol Head, in a clean pot of distilled water for a full 5 minutes (47% pass rate)

Although the Agency notes that the harm associated with aerosol head user tasks as serious in deficiency 2a above, you did not describe the possible harm that could result had these events occurred during actual use of the subject device. Please explain the potential harm that could result from lack of adherence to the aerosol head WARNING statements and describe risk mitigations control being considered. Provide results of supplementary Human factors validation testing, results, analysis, and conclusion to support aerosol head use safety against contamination. (Note, this can be combined with deficiency 1)

Deficiency 3
You obtained post subjective responses based on six (6) questions (Section 8.2.4.4 Participants' subjective assessment, Pg. 118). However, this approached fails to capture test participant’s experiences regarding their use-difficulties, hesitations, confusions, close calls, failures, etc. during human factors task/use scenario performance. Subjective data provides test participants the opportunity to comment on what they experience including “mental” close calls where they are confused, almost do the wrong thing and then realize how to do it right but this confusion is not observable to the test administrator. Please perform a comprehensive reanalysis of subjective data to include participant’s responses to use-difficulties, hesitations, confusions, close calls, failures. It is important to consider this data in deficiency 1 above. This information is necessary to the Agency to conduct premarket evaluation of the subject device.
III. Reviewer Notes

Device Description
Nebulizer
The nebulizer is a multi-part, multi-use device intended for the daily inhalation administration of ARIKAYCE®. The originator FDA-approved devices are the drug specific Altera® nebulizer system and the generic use eRapid and Trio nebulizer systems, which were developed by PARI Respiratory Equipment.

The only differences between the nebulizer and the currently-marketed eFlow nebulizer are (1) an increased medication reservoir fill volume, and (2) slightly changed geometry of the laser-drilled holes in the aerosol head membranes. PARI made these modifications for Insmed to accommodate the larger volume of drug and the corresponding longer nebulization time compared to drugs currently used with the eFlow nebulizer.

Nebulizer as it appears assembled
2.7. **Method of Operation**

Step 1. The controller can be powered by batteries or an A/C adapter. The batteries need to be inserted into the controller or the A/C adapter needs to be plugged into the controller.
Step 2. Assemble the nebulizer by placing the blue (inhalation) valve (3) flat against the rim of the aerosol chamber (4). Insert the aerosol head (5) into the medication reservoir.

Step 3. Then, close the nebulizer and attach the mouthpiece (6a) with the blue expiratory flap (6b) facing upward. Press the blue expiratory flap into the slot (6c).
Step 4. Attach the Connection Cord

Step 5. Connect the Connection Cord to the Controller

Step 6. Fill the medication reservoir then attach the cap and turn the cap clockwise.

Step 7. To start inhaling, press the ON/OFF button on the controller to start the aerosol production then insert the Mouthpiece by placing it on top of your
bottom lip and tongue. Close your lips around the Mouthpiece then take slow, deep breaths then breathe normally in and out through the Mouthpiece until your treatment is complete.

Step 8. Continue inhaling and exhaling slowly and deeply though the mouthpiece while the mouthpiece remains in the mouth until the nebulization is finished and the controller automatically shuts off.

Step 9. The device will shut off when the ON/OFF button is pressed again, or when there is no medication left in the reservoir that is in contact with the aerosol head or when the handset becomes disconnected from the controller.

During inhalation, air enters the system through the sides of the handset base (A in Figure 15, left) and then through the inhalation valve of the aerosol chamber. The aerosol chamber is aerodynamically designed for optimum aerosol output. The inhaled air is drawn into the aerosol chamber where it moves the aerosolized medication through the mouthpiece and into the patient’s respiratory tract. During inhalation, the exhalation valve on the mouthpiece is closed (B in Figure 15, left), which minimizes aerosol dilution. During exhalation, the inhalation valve closes and the exhalation valve inside the aerosol chamber opens, driving the expired air out of the mouthpiece (Figure 15, right). The exhalation valve is located between the patient and the aerosol chamber to minimize the amount of unused medication leaving the nebulizer.

Figure 15  Inhalation vapor path

2.8. Functional Specifications

Both the ALIS eFlow and the Altera are drug-specific electronic nebulizers that share almost identical specifications except the Altera aerosol performance is tailored for that specific drug (Cayston), while the ALIS eFlow is tailored for the delivery of ALIS. Table 2 compares the FDA-cleared Altera with the ALIS eFlow.
IV. HF Activities
Regulatory/Interaction History
Original Submission

HF Validation Study Results

8.2.3.4 Data analysis
After conducting the test sessions, consolidated and analyzed the use scenario performance data with a focus on critical tasks, which are defined as user tasks that, if performed incorrectly or not performed at all, would or could cause serious harm or compromised medical care to the patient or user.

8.2.4 Overall performance summary

8.2.4.1 Overview of findings
The subsections below describe participants' overall performance throughout their interaction with the nebulizer, the IFU, and the QRQ. summarizes both the overall use scenario and knowledge task performance (see Overall use scenario and knowledge task performance summary) as well as detailed information regarding participants' step-by-step task performance (see Task performance summaries).

Overall, observed a total of 1,049 use errors, 12 instances of test administrator assistance, 63 close calls, and 70 difficulties during the usability test. (See Event categorization for detailed event definitions.)
Reviewer Analysis/Comments:
No data was provided to support the risk mitigation controls implemented. A supplementary HF validation testing is requested to support the effectiveness of proposed risk mitigations.
Subjective Data

Review Analysis/Comments:
Incomplete subjective data.
Request to perform a comprehensive reanalysis of subjective data to include participant’s responses use-difficulties, hesitations, confusions, close calls, failures

V. Consult Request
Human factors review

VI. Materials Reviewed
- hf-ifu
- hf-qrg
VII. End of Review

Hanniebey D. Wiyor -S
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMEET C JOSHI
06/26/2018
Signing off on behalf of CDRH for the electronic archive.