CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208437Orig1s000

PRODUCT QUALITY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

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

ICC1700538 - NDA 208437 – Regulatory Device Consult

Date: August 28, 2017

To: Sadaf Nabavian (CDER/OND/ODEII/DPARP)

Through: James Lee, Branch chief (CDRH/ODE/DAGRID/RPDB)
Deepika Lakhani, Combination Products Team Lead (CDRH/ODE/DAGRID/RPDB)

From: Amy LeVelle, Biomedical Engineer (CDRH/ODE/DAGRID/RPDB)

Applicant: Sunovion Respiratory Development, Inc.

Product Name: Glycopyrrolate Inhalation Solution with eFlow Closed System Nebulizer

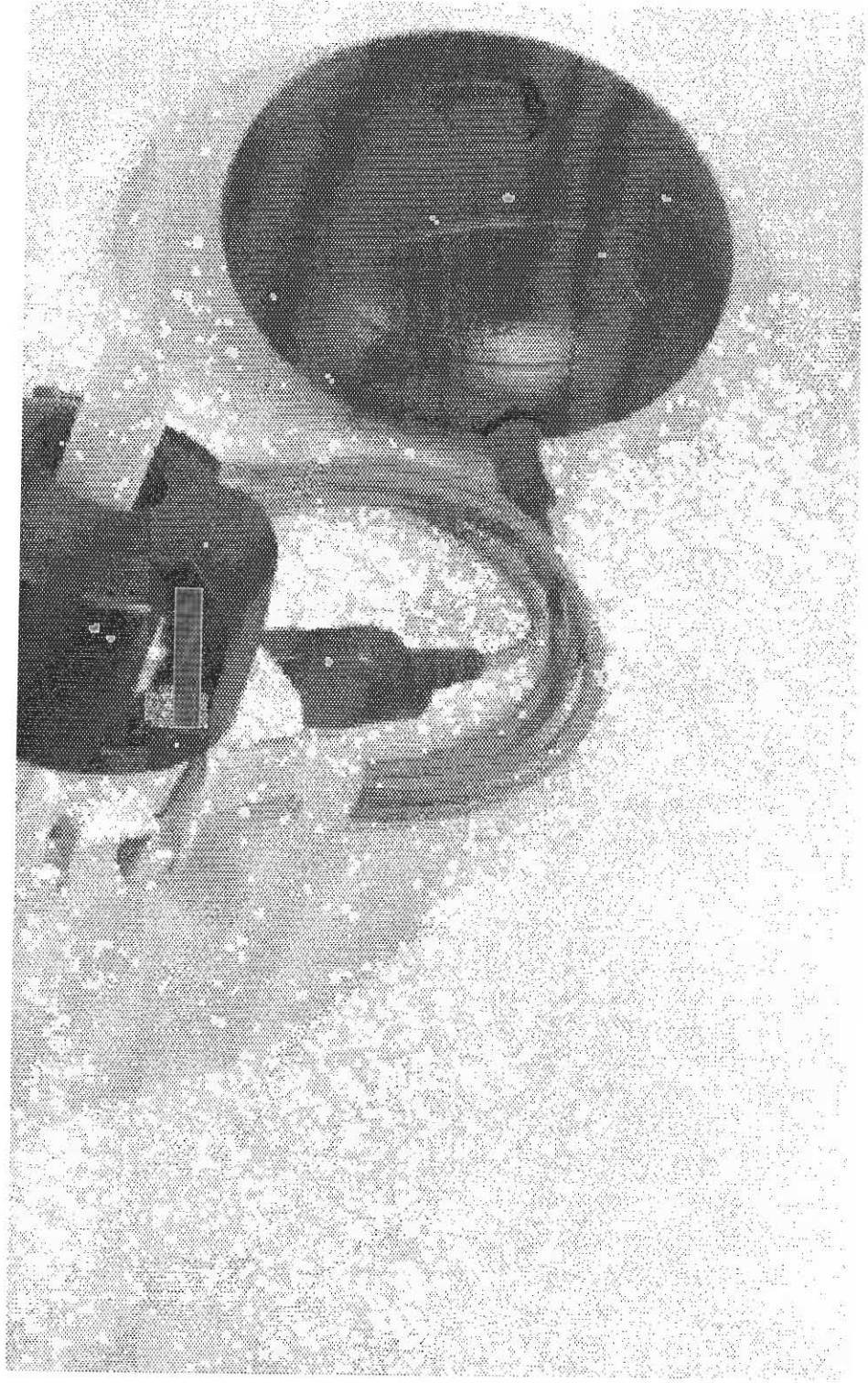
Indication: For the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.

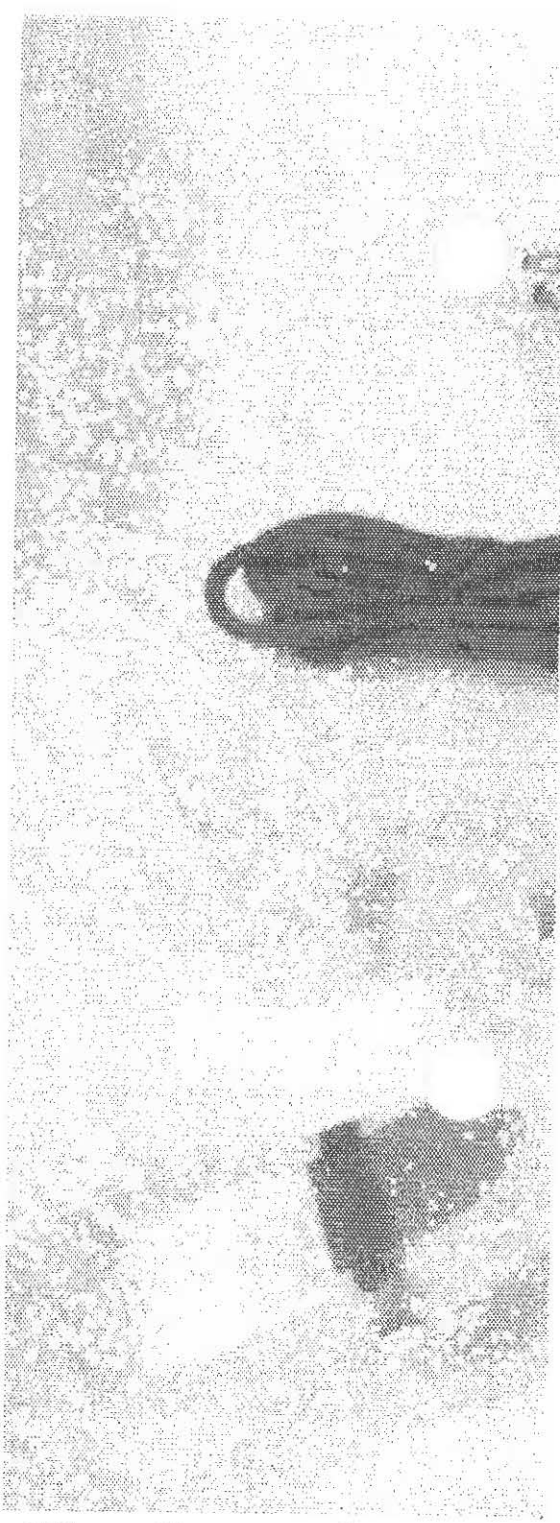
A. Executive Summary

NDA 208437 was submitted by Sunovion Respiratory Development Inc. for a formulation of inhaled Glycopyrrolate Inhalation Solution to be delivered by the eFlow Closed System Nebulizer (eFlow CS). The eFlow CS is manufactured by PARI Respiratory Equipment and was specifically designed to deliver SUN-101 (glycopyrrolate). The eFlow CS is a portable, hand-held, electronic nebulizer intended for single patient use that uses a vibrating perforated membrane to generate an inhalable aerosol. CDRH was previously consulted for the device review of the NDA. The CDRH review concluded that outstanding issues were remaining for biocompatibility and human factors.

During the original NDA review, the sponsor provided E&L testing to support the biocompatibility of their device in lieu of providing testing for genotoxicity, implantation, and systemic toxicity tests per ISO 10993. However, the new E&L testing resulted in significant degradation of the test article which invalidated their test results. Therefore, the sponsor was requested to repeat this testing using a more appropriate solvent which does not degrade the test article. In the current NDA resubmission, the sponsor has provided new E&L testing in response to the deficiency. A review of the information is provided in the memo below.

Additionally, as noted in the previous CDRH review, there was an outstanding human factors deficiency related to a use error identified which may lead to potential harm. This use error occurred when the drug vials were pierced prior to inserting the aerosol head and may cause medication to leak from the handset and patients to receive an incomplete dose of their prescribed medication. If this occurs, the patient may be unaware that they did not receive the full dose, and may continue to use the device incorrectly. The previous CDRH review recommended that additional information is provided to address how this risk has been mitigated. However, this was not sent in the Complete Response Letter and the deficiency remains outstanding. I defer to the





eFlow System System

D. Biocompatibility

The eFlow CS nebulizer contains both direct and indirect patient-contacting components. The device is a permanent exposure, external communicating device with tissue contact. The outside of the mouthpiece is a permanent exposure, surface-mucosal membrane contact component. The sponsor indicated that many of the materials are the same as in the eRapid and FDA-cleared Altera nebulizers; however, they identified there are new materials which require new biocompatibility testing. Therefore, the entire handset unit underwent biocompatibility evaluations per guidance contained in the FDA Blue Book Memoran-dum #G95-*1, Use of International Standard ISO 10993, "Biological Evaluation of Medical De-vices Part 1: Evaluation and Testing", dated May 1, 1995,* (FDA, 1995).

- In-Vitro Cytotoxicity - ISO 10993-5
- Genotoxicity - ISO 10993-3
- Implantation - ISO 10993-6
- Irritation/Intracutaneous Reactivity - ISO 10993-10
- Skin Sensitization ISO 10993-10

The sponsor also conducted testing for air quality and the results indicated there is no evidence that the device emits any particulate matter, ozone (O_3), carbon monoxide (CO), carbon dioxide (CO_2), or volatile organic compounds (VOC) in the handset air path.

Additionally, a GMP study was conducted to evaluate the level of extractable compounds from the device components that come in contact with the drug product at the time of use including the opening collar seal, blue inhalation valves, blue inhalation gasket, upper body, aerosol chamber, and the mouthpiece. The sponsor concluded that no extractables were observed from any of the device components under aqueous conditions and no leachable or elemental impurities were observed in nebulized solutions under the conditions of intended use.

A biocompatibility consult was conducted by Bifeng Qian to review the device biocompatibility information submitted. The biocompatibility reviewer concluded that additional biocompatibility testing is required, as the sponsor has not provided adequate genotoxicity, implantation, and systemic toxicity testing. The sponsor has also not provided complete test reports for their extractable and leachables (E&L) testing conducted and additional information is needed to support their biocompatibility.

In response to our December 23, 2016 letter, the sponsor submitted E&L test data for chemical characterization and toxicological risk assessment in lieu of conducting tests for genotoxicity, implantation, and systemic toxicity. However, there were significant concerns with how the E&L tests were conducted. The extraction conditions were only conducted for 2 hours which is insufficient for a permanent duration device and does not follow FDA recognized standard ISO 10993-12 for sample preparation. Therefore, E&L testing was requested through interactive review following appropriate conditions in accordance with ISO 10993-12 for both polar and nonpolar solvents. The sponsor provided new E&L testing through interactive review; however, this testing resulted in degradation of the test article which would invalidate these test results.

The sponsor has provided the additional E&L testing as requested and the resolution of this deficiency is discussed in response to deficiencies below.

E. Human Factors

Sunovion indicates they have applied human factors engineering throughout the eFlow CS development. Subjecting the nebulizer's development to extensive formative evaluations enabled Sunovion to optimize the device for its target user groups. Sunovion utilized an iterative approach, such that each study's outcome influenced future improvements of the device's design and documentation. Specifically, Sunovion based its design modifications and documentation changes on the usability study findings, the use Failure Modes and Effects Analysis (use-FMEA), and bench-top testing. These modifications were then assessed during subsequent studies.

Sunovion completed a total of ten usability studies of the eFlow CS, including nine formative studies and a subsequent summative (i.e., validation) study, which validated the nebulizer's safety and usability. The nebulizers used in the summative human factors study had the same design as the Phase 3 clinical trial and commercial devices. The sponsor concluded that these studies demonstrate that the eFlow CS nebulizer is safe to use as is and is not vulnerable to potentially harmful use errors that could lead to patient injury, serious harm, or clinically important delays in therapy or sub-optimal therapy.

A human factors consult was conducted by Shannon Hoste to review the human factors testing submitted. The HF reviewer noted that the sponsor identified use errors related to locating the aerosol head in the packaging, confusion between the handset and the easycare, difficulty with the drug vial and difficulty with the connection cords. However, it is unclear if the user is aware that they have not received a dose of medication. It was noted that the sponsor should provide additional information on the potential risks associated with this use errors identified.

In response to the March 31, 2017 request, the sponsor provided further details on the potential outcome and detectability of this issue. The sponsor concluded that one situation could potentially lead to high severity harm. This use error occurred when the drug vials were pierced prior to inserting the aerosol head and may cause medication to leak from the handset and patients to receive an incomplete dose of their prescribed medication. If this occurs, the patient may be unaware that they did not receive the full dose, and may continue to use the device incorrectly. Therefore, additional information is recommended to address how this risk was mitigated.

F. Deficiencies

The following outstanding deficiencies were identified in the previous CDRH review and the sponsor's responses are discussed below:

Biocompatibility:

1. In your response to FDA Request dated 17 March 2017, you provided two new chemical extractable and leachable (E&L) tests for the eFlow Closed System Nebulizer proposed in NDA208437. Both tests were conducted using water as the polar extraction solvent and isopropanol (IPA) as the non-polar solvent. The extraction conditions used were identified as 50°C for 72 hours or 60°C under sonication for up to 24 hours. In the test reports provided,

you stated that IPA used as the non-polar extraction solvent caused significant degradation of the test devices, under both of the two extraction conditions.

The eFlow Closed System Nebulizer proposed in NDA208437 is indicated for permanent uses. In clinical use, the device will come into direct contact with the SUN-101 (glycopyrrolate) Inhalation Solution and patient's exhaled gases. When being exposed to such clinical conditions, both polar and non-polar chemical residues may potentially leach out from the device, which may pose significant health risks to patients when inhaled.

As the IPA extraction solvent was demonstrated to be incompatible with the test device materials and caused device degradation, the test data from the IPA extracts are considered invalid. Thus your E&L testing provided is considered inadequate for the biocompatibility endpoints assessments for systemic toxicity and genotoxicity and inadequate to address the drug-device material compatibility.

To address the safety concerns for the eFlow Closed System Nebulizer, we request that you provide a revised chemical E&L testing at 50°C for 72 hours, using an appropriate non-polar extraction solvent that is compatible with the test device and does not cause the device degradation. We recommend that you use a non-polar extraction solvent or a mixed solvent system that is chemically similar in polarity to the intended medications. Alternatively, you may provide the revised chemical testing based on the intended drugs or a surrogate chemical that has chemical properties similar to the drugs proposed. If a surrogate or non-polar solvent was used, please provide your scientific rationale and justification for your choice of the surrogate or the non-polar solvent to demonstrate that the worst clinical use condition is represented. In addition, please clarify whether the surrogate or solvent used compromises the integrity of the tested device or representative component samples.

Please provide a revised toxicological risk assessment (exposure and safety assessment) for all chemical compounds identified from the revised E&L testing, including organics, inorganics, organometallics, metals, and other residues. To address a worst case safety concern, the maximum amounts of the chemicals identified per device system should be considered in the risk assessment calculation. The risk assessment calculation should also take into consideration of the inhalation exposure route, intended patient population, and a worst case scenario. For analysis of the chemical residues and the allowable limits, please refer to the published toxicological literature for the reference doses, such as the no-observed-adverse-effect-levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), and/or to the inhalation protective values from the US based health organizations or WHO. For the risk assessment calculation, you may also refer to the FDA-recognized standard ISO 10993-17:2002(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances, and the TTC approaches described in the CDER ICH M7 guidance. Please clearly identify the calculated margin of safety (MOS) value for each of the chemicals identified and describe in detail (step-by-step) how the MOS values were calculated. Please provide a clear rationale for the uncertainty values that are used in the exposure and safety assessment for each chemical residue.

Please be advised, if a safety signal (e.g. chemicals with MOS <1) is identified through your risk assessment of the chemical extractables and leachables, additional justification or biological testing may be warranted in order to address this risk.

Biocompatibility Reviewer's Comments (Bifeng Qian): *In response to the device biocompatibility deficiencies identified in the FDA Complete Response Letter to NDA 208437 dated 26 May 2017, the sponsor provided a revised chemical extractable test report and risk assessments for the chemical extractables identified. The revised study reports have been reviewed. Below, please see my additional questions and comments that are recommended to be communicated with the sponsor.*

CDRH Lead Reviewer's Comments: *The following biocompatibility deficiency was recommended to be sent to the sponsor through Interactive Review on July 13, 2017. The sponsor's response was received on August 8, 2017 (dated August 2, 2017) as discussed further in the response below.*

Interactive Review Deficiency:

1. In response to the device biocompatibility deficiencies identified in the FDA Complete Response Letter to NDA 208437 dated 26 May 2017, you provided a revised chemical extractable test report and risk assessments for the identified chemical extractables. Based on the study reports provided, we are unsure if the toxicological risks for the potential chemical residues form the eFlow Closed System Nebulizer were adequately assessed. Please address our additional questions/deficiencies below:

a) (b) (4)

- (b) (4)

b) (b) (4)

FDA does not believe that this calculated 30-day averaged daily exposure level represents the highest daily exposure level for the chemical extactables identified. During clinical uses, more chemical residues may likely leach out from the subject device and be exposed to patients during the first few days of the use as compared to the latter days. Please be remindful that the eFlow Closed System Nebulizer proposed is intended for permanent use, while some device components need to be replaced every 30 days. A repeated exposure to a higher level of the same chemicals every 30 days may pose a significant risk to patients, especially for the chemicals that have a long half-life in humans. Thus a risk assessment based on the 30-day averaged daily exposure level may likely underestimate the risks. To address the worst case safety concerns, we believe that the exposure and safety assessments should be conducted based on the highest exposure level for each of the chemical extractables identified. If the highest exposure level cannot be determined by your testing, the total detectable levels of the chemicals identified from the chemical extractable testing without being averaged should be used in the exposure and safety assessment. Please provide a revised toxicological risk assessment based on a worst case chemical exposure. Please be informed that this request is consistent for all recently cleared similar devices with the same intended use.

Sponsor's Response: Given the extractable and leachable testing data summarized above and the classification of the device as a permanent contact device, the exposure and risk assessments provided in Section 3.2.R.1.6.6 Extractables and Leachables (E&L) of the NDA resubmission considered the potential for chronic, daily exposure to the extractable compounds. For the purposes of the risk assessment for chronic exposure, it was assumed that a patient may be exposed to the cumulative amount of each extractable originating from handset components (Table 2) over a period of 30 days/60 uses.

As noted in the Information Request, a 30-day averaged daily exposure level may underestimate risks, the exposure and safety assessments were requested to be conducted based on the highest exposure level for each chemical extractable

identified. This response provides an additional safety assessment specific to this request, derived from the extraction studies conducted under exhaustive conditions at 72 hr at 50°C using a non-polar solvent.

Biocompatibility Reviewer's Comments (Bifeng Qian): *I have reviewed the sponsor's response dated August 2, 2017 and their revised toxicological risk assessment for the chemical extractables and leachables identified from the inhalation drug pathway of the eFlow Closed System Nebulizer.*

Based on the information provided, I do not see significant toxicological concerns for using the eFlow Closed System Nebulizer to deliver the SUN-101 (Glycopyrrolate) Inhalation Solution in adult patients.

Thus all biocompatibility deficiencies regarding the eFlow Closed System Nebulizer proposed in NDA208437 have been addressed. I have no further questions regarding the biocompatibility of the eFlow Closed System Nebulizer for its intended use in adult patients.

CDRH Lead Reviewer's Conclusions: Response Adequate. *The sponsor has repeated the E&L testing using appropriate solvents. Through interactive review, they have also provided additional information to support their risk assessment. I agree with the biocompatibility reviewer that the response is acceptable. There are no further outstanding biocompatibility issues remaining.*

Outstanding Human Factors:

2. You have responded to request for further information on the potential use errors identified in your human factors validation study. You have provided data indicating that use errors which lead to situations in which the system will not function will lead to a minor delay in therapy with a low potential harm. However, you have identified one situation which potentially could lead to high severity harm. In this situation, several participants experienced difficulties/errors with the use of the vials for dosing. In summary you noted:

   "Incomplete dosing may result from vials that are pierced open prior to inserting the aerosol head, but do not empty completely. The nebulizer will detect medication on the aerosol head, and the controller will not produce an error tone and an aerosol mist will be generated. The patient may, or may not, notice the shortened duration of treatment (with completion tone) or the small quantity of medication leaking from the handset. As a result of this difficulty, the patients will receive only a partial dose of their prescribed medication and a higher risk for compromised medical care."

   You have provided further details on the potential outcome and detectability of this issue, in summary you noted:

   "Continued incomplete (or under) dosing can result in compromised medical care; especially if patients are not aware they are repeatedly using the device incorrectly and not receiving the full, prescribed inhaled dose. One possible indication of incomplete dosing is

there may be a shortened duration of treatment (with completion tone). Clinically, incomplete dosing should be considered in patients experiencing unexplained increases in disease related symptomology (e.g. cough, dyspnea, and chest tightness), premature use of add-on bronchodilator therapies, increases in rescue medication use and acute exacerbations requiring antibiotics/parenteral steroids and/or hospitalization. Since these sequelae also occur with disease progression, a discussion with the patient during normal physician visits regarding device use may be important to help assess the underlying reason for changes in a patient's clinical status and evaluation of device technique."

You have not identified potential mitigations to eliminate or reduce the risk associated with this use error. Please provide your analysis of this risk. If mitigations are not being implemented, please provide rationale that possible/practicable modifications to the user interface (including the device and the labeling) would not further reduce this risk.

CDRH Lead Reviewer's Conclusions: *A response to the deficiency has never been provided for CDRH review. Therefore, the human factors concern is still outstanding from the CDRH review team. I defer to the CDER review lead as to the clinical implications of the identified risk.*

G. Recommendation

The sponsor has adequately addressed the biocompatibility deficiencies. The previously identified human factors deficiency is the only outstanding device issue which remains. I defer to the CDER review lead as to the clinical implications of the use error.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Amy K. Levelle -S 2017.08.29 16:09:58 -04'00'
Branch Chief Sign-Off	Deepika A. Lakhani -S 2017.08.29 16:22:23 -04'00'

for Dr. James Lee

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

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

NDA 208437 – Regulatory Device Consult

Date: April 24, 2017

To: Sadaf Nabavian (CDER/OND/ODEII/DPARP)
Through: James Lee, Branch chief (CDRH/ODE/DAGRID/RPDB)
From: Amy LeVelle, Biomedical Engineer (CDRH/ODE/DAGRID/RPDB)
Applicant: Sunovion Respiratory Development, Inc.
Product Name: Glycopyrrolate Inhalation Solution with eFlow Closed System Nebulizer
Indication: For the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.

A. Executive Summary

In NDA 208437, Sunovion Respiratory Development Inc. has proposed a formulation of inhaled Glycopyrrolate Inhalation Solution to be delivered by the eFlow Closed System Nebulizer (eFlow CS). The eFlow CS is manufactured by PARI Respiratory Equipment and was specifically designed to deliver SUN-101 (glycopyrrolate). The eFlow CS is a portable, hand-held, electronic nebulizer intended for single patient use that uses a vibrating perforated membrane to generate an inhalable aerosol.

The manufacturer of the eFlow CS has similar versions of the device which have been previously 510(k) cleared as an open system nebulizer not intended to be used with a specific drug formulation. While the eFlow CS 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:

Shannon Hoste (CDRH/ODE/DAGRID/HFPMET)	Human factors consultant
Sandy Weininger (CDRH/OSEL/DBP)	Electrical Safety
Bifeng Qian (CDRH/ODE/DAGRID/INCB)	Device Biocompatibility
Steven Elliott (CDRH/ODE/DAGRID/INCB)	Cleaning/Disinfection
Joseph Jorgens (CDRH/OSEL)	Software

Additional information was recommended from the sponsor regarding their device biocompatibility, cleaning, performance and human factors. This information was requested from the sponsor in a Discipline Review Letter dated 12/23/2016, with the exception of the

human factors deficiency which was sent 3/17/2017. The sponsor provided their response in a letter dated January 26, 2017. However, upon review of this information, outstanding issues were remaining for biocompatibility and cleaning.

The sponsor provided information through interactive review which adequately addressed the outstanding concerns for cleaning by removing their (b) (4) procedure. They also submitted new extractables and leachables (E&L) testing to address the outstanding biocompatibility concerns. However, the new E&L testing resulted in significant degradation of the test article for their non-polar solvent used. This degradation would invalidate these test results. E&L testing with toxicological risk assessment was conducted in lieu of genotoxicity, implantation, and systemic toxicity tests per ISO 10993. Therefore, in order to support the device biocompatibility based on the results of their E&L testing, the sponsor should repeat the testing using an appropriate nonpolar solvent which does not degrade the device material.

Additionally, the sponsor provided a response to the Human Factors deficiency on March 31, 2017. The human factors validation study identified one situation which may lead to potential high severity harm. This use error occurred when the drug vials were pierced prior to inserting the aerosol head and may cause medication to leak from the handset and patients to receive an incomplete dose of their prescribed medication. If this occurs, the patient may be unaware that they did not receive the full dose, and may continue to use the device incorrectly. Therefore, additional information is recommended to address how this risk was mitigated. However, I defer to the CDER review team as to the clinical implications of this error.

RECOMMENDATION: Outstanding deficiencies remain regarding biocompatibility and human factors which may impact safety and effective use of the device. Therefore, the device is not recommended for approval at this time from a device perspective. The recommended outstanding deficiencies to the sponsor are identified in this memo below.

B. Intended Use

The eFlow CS is intended for single patient use for the delivery of SUN-101 (glycopyrrolate) Inhalation Solution drug product by patients who self-administer treatments at home, by caregivers, and in nursing homes and hospitals by Healthcare Professionals (HCPs).

C. Device Description

Overview:

The eFlow CS is a portable, hand-held, electronic nebulizer intended for single patient use that uses a vibrating perforated membrane to generate an inhalable aerosol. The eFlow CS device including the nebulizer handset (hand-held unit, with installed aerosol head and drug vial), the connection cord, the controller, and the AC adapter, and 2 additional drug vials are shown in the figure below.

eFlow System System

The eFlow CS is a modified version of three FDA cleared PARI Respiratory Equipment (PRE) electronic nebulizers: the Altera®, the TRIO®, and the eRapid®. A comparison of key elements between these FDA cleared PRE devices and the eFlow CS are shown in Table 1 below.

Table 1: Comparison of the eFlow® CS with Other FDA Cleared PRE- Electronic Nebulizers

	eFlow® Closed System Nebulizer	Altera Nebulizer System	Trio Electronic Nebulizer System	eRapid Nebulizer System
				
510(k) Clearance date	Not applicable (part of combination product, this NDA#208437)	K100380 February 22, 2010	K033833 May 5, 2004	K112859 May 16, 2012
Use	SUN-101 only	Cayston® only NDA 050-814	General Use	General Use

Drug solution volume	1 mL	1 mL	Maximum of 4 mL	Maximum of 6 mL
Drug solution loading	Special unit-dose vial	Reservoir (for unit dose operation)	Reservoir (for unit dose operation)	Reservoir (for unit dose operation)
Aerosol technology	eFlow® Vibrating Membrane Technology			

They are single-patient use, re-usable electronic nebulizers that use a micro-perforated vibrating membrane technology to aero-solize liquid medications. They are for inhalation therapy for the home, nursing home, or hospi-tal environments. All of these devices are hand-held and portable

Unlike the other eFlow nebulizers systems, the eFlow CS uses a proprietary, pre-filled unit-dose vial of SUN-101. This unit-dose vial is required to operate the nebulizer. It re-places the medication reservoir on the other eFlow Electronic Nebulizers. The design of the eFlow CS therefore is intended to: (1) preclude the risk of using the wrong medication in the delivery device; (2) simplify the drug filling and delivery procedure, and (3) improve dose uni-formity and hygiene.

The eFlow CS, Altera, TRIO, and eRapid all use the same micro-perforated vibrating membrane technology to aerosolize the liquid medications (Figure 2). This technology uses a wafer-thin plate of stainless steel (called the "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 piezo-electric 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. Surface tension and hydrodynamic effects then cause these jets to disperse to produce a stream of precisely controlled droplets

Figure 2: Micro-Perforated Vibrating Membrane Technology for Aerosol Generation

(b) (4)

Device Components:

The eFlow CS consists of three main components: the handset unit, the controller, and the connection cord.

Handset Unit

(b) (4)

Controller

(b) (4)

Connection Cord

(b) (4)

Change History:

The investigational eFlow® system used in the development of SUN-101 underwent several changes during the course of clinical development. Table 2 provides an overview of the eFlow systems used in the specific clinical trials.

Table 2: Investigational eFlow® nebulizer system used in clinical studies

Investigational eFlow nebulizer system	Clinical Study
Open System (OS)	EP-101-01
Open System (OS)	EP-101-02
Open System (OS)	EP-101-03
Closed System 1 (CS1)	EP-101-04
Closed System 2 (CS2)	SUN101-105 (ongoing)
Closed System 2 (CS2)	SUN101-201
Closed System 2 (CS2)	SUN101-301
Closed System 2 (CS2)	SUN101-302
Closed System 2 (CS2)	SUN101-303

All the devices, except the Open System device, use a specially designed prefilled drug vial. The Open System device used a conventional blow-fill seal drug vial which required the drug to be poured into a reservoir of the device (1ml refillable reservoir). The sponsor indicated that their proposed commercial eFlow CS nebulizer system includes minor changes, previously agreed upon with the Division (**Type C Written Request 09 June 2015**), to be made to the device (CS2) after Phase 3 studies which do not affect critical aerosol path geometry, aerosol performance, or human factors.

Device Change History:

(b) (4)

Reviewer's Comments: *The differences between the previous eFlow CS2 used for Phase 3 studies and their proposed commercial eFlow CS2 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 CS2 device intended for market. This was confirmed by the sponsor in their response to our December 23, 2016 letter. Therefore, this is acceptable.

Labeling:

The drug/device combination product will be provided in two commercial configurations:

1. Starter Kit: SUN-101 drug product (30 day planned for commercial distribution. Device components would only be supplied separately twice daily supply) with a complete nebulizer kit and nebulizer accessories.
2. Refill Kit: SUN-101 drug product (30 day twice daily supply) with a handset and handset components (including aerosol head).

The Starter Kit is intended for new patients with the Refill kit to be subsequently supplied every 30 days. These two configurations are the only configurations in the case of unanticipated damage or replacement. Both commercial configurations will include the Instructions for Use (IFU). The Starter Kit will include additional instructional aids.

Proposed Aerosol Performance Specifications for eFlow CS Nebulizers Device Labeling (Instructions for Use)

The proposed aerosol performance specifications for eFlow CS Nebulizers for 25 mcg/mL SUN-101 are provided in Table 5. The aerosol data from their delivered dose by breath simulation study and the New Generation Impaction (NGI) data have been included in the IFU provided in Module 1.14:1.

Table 5: Proposed Aerosol Performance Specifications for eFlow CS Nebulizers for SUN-101 (25 mcg/mL) (Instructions for Use)

Attribute	Mean[a]	95% Confidence Range[b]
Delivered dose by breath simulation (mcg)	14.20	11.11 – 17.29
Delivered dose by breath simulation (%Label Claim)	56.80	44.45 – 69.16
MMAD[c] (μm) by NGI[d]	3.71	2.92 – 4.49
Coarse Particles (Dia. >5 μm) by NGI[d] (mcg) Coarse Particles (Dia. >5 μm) by NGI[d] in % of Delivered Dose	5.83 27.72	2.32 – 9.33 11.20 – 44.24
Fine Particles (Dia. ≤5μm) by NGI[d] (mcg) Fine Particles (Dia. ≤5μm) by NGI[d] in % of Delivered Dose	15.20 72.28	11.46 – 18.93 55.77 – 88.79

Extra-Fine Particles (Dia. <1 µm) by NGI[d] (mcg) Extra-Fine Particles (Dia. <1 µm) by NGI[d] in % of Delivered Dose	0.11 0.55	0.03 – 0.20 – 0.94
GSD[e] by NGI[d]	1.66	1.49 – 1.83

[a] n=15 devices from 3 device lots; 5 devices tested per drug product batch x 3 batches drug product
[b] 95% Confidence Range: Two-sided tolerance interval, Proportion of total population=0.95, Confidence (1- Alpha)=0.95
[c] MMAD: Mass Median Aerodynamic Diameter
[d] NGI: Next Generation Impactor
[e] GSD: Geometric Standard Deviation

D. Cleaning, Disinfection, Maintenance and Shelf Life

To maintain the performance of the nebulizer handset unit, it is recommended that the aerosol head be removed from the handset unit and the handset and aerosol head be cleaned immediately after use. If the handset unit is disinfected, only chemical disinfection is recommended. The handset unit is not sterile and is not intended to be sterilized. This is intended to be a personal use device and should not be shared with others.

(b) (4)

(b) (4)

In addition, the sponsor has conducted a simulated use study to demonstrate that the performance of the nebulizer, including delivered dose, aerodynamic particle size distribution, nebulization time, residual dose and drug vial opening torque, do not change with time over three years when used in accordance with the Instructions for Use. However, based on the complaint analysis from their clinical return study conducted, there have been numerous complaints that have been caused by inadequate cleaning. Therefore, the sponsor has determined that the aerosol head should be replaced after 30 days. They conducted additional simulated use studies following 60 days use without the additional backwashing step, as well as misuse studies with no cleaning. These studies demonstrate no significant increase in nebulization within this timeframe, and adequately support the use life of 30 days for the aerosol head.

E. Biocompatibility

The eFlow CS nebulizer contains both direct and indirect patient-contacting components. The device is a permanent exposure, external communicating device with tissue contact. The outside of the mouthpiece is a permanent exposure, surface-mucosal membrane contact component. The sponsor indicated that many of the materials are the same as in the eRapid and FDA-cleared Altera nebulizers; however, they identified there are new materials which require new biocompatibility testing. Therefore, the entire handset unit underwent biocompatibility evaluations per guidance contained in the FDA Blue Book Memoran-dum #G95-*1, Use of International Standard ISO 10993, "Biological Evaluation of Medical De-vices Part 1: Evaluation and Testing", dated May 1, 1995,* (FDA, 1995).

- In-Vitro Cytotoxicity - ISO 10993-5
- Genotoxicity - ISO 10993-3
- Implantation - ISO 10993-6
- Irritation/Intracutaneous Reactivity - ISO 10993-10
- Skin Sensitization ISO 10993-10

The sponsor also conducted testing for air quality and the results indicated there is no evidence that the device emits any particulate matter, ozone (O_3), carbon monoxide (CO), carbon dioxide (CO_2), or volatile organic compounds (VOC) in the handset air path.

Additionally, a GMP study was conducted to evaluate the level of extractable compounds from the device components that come in contact with the drug product at the time of use including the opening collar seal, blue inhalation valves, blue inhalation gasket, upper body, aerosol chamber, and the mouthpiece. The sponsor concluded that no extractables were observed from any of the device components under aqueous conditions and no leachable or elemental impurities were observed in nebulized solutions under the conditions of intended use.

Reviewer's Comment: *A biocompatibility consult was conducted by Bifeng Qian to review the device biocompatibility information submitted. The biocompatibility reviewer concluded that additional biocompatibility testing is required, as the sponsor has not provided adequate genotoxicity, implantation, and systemic toxicity testing. The sponsor has also not provided*

complete test reports for their extractable and leachables (E&L) testing conducted and additional information is needed to support their biocompatibility.

In response to our December 23, 2016 letter, the sponsor submitted E&L test data for chemical characterization and toxicological risk assessment in lieu of conducting tests for genotoxicity, implantation, and systemic toxicity. However, there were significant concerns with how the E&L tests were conducted. The extraction conditions were only conducted for 2 hours which is insufficient for a permanent duration device and does not follow FDA recognized standard ISO 10993-12 for sample preparation. Therefore, E&L testing was requested through interactive review following appropriate conditions in accordance with ISO 10993-12 for both polar and nonpolar solvents. The sponsor provided new E&L testing through interactive review; however, this testing resulted in degradation of the test article which would invalidate these test results.

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.

The controller's incorporated software performs the following three functions in continuous loops. These are the same as in the FDA-cleared Altera, TRIO, and eRapid controllers:

- Checking the supply voltage
- Measuring current consumption for correct connection to the aerosol head
- Checking whether or not liquid is present on the membrane of the aerosol head

The values detected are then compared with the predefined values. If out-of-range parameters are detected, the controller issues a combination of alerts by visual and audible feedback, and shuts itself off automatically.

The software is device-specific, i.e., it is not "off-the shelf". It is not dependent on any external devices and does not perform any patient data monitoring, assessment or interpretation. Further, no date information is recorded or assessed.

From the user perspective, once set up, the operation is simple. A single button turns the device on. Then the device turns itself off when it no longer detects liquid medication in the vial, if any other out-of-range parameter is detected or after 15 minutes.

1. Level of Concern: Acceptable

In the Appendix entitled Software in the Document entitled Level of Concern, the firm provided the correct determination of the Level of Concern and included their supporting rationale: MODERATE.

2. Software Description: Acceptable

In the Appendix entitled Software in Section 7.2 entitled Software Description, the firm provided an acceptable overview of the device features that are controlled by software, and a description of the

intended operational environment, which included information on the programming language and the hardware platform. The firm states there is no Off-The-Shelf software.

3. **Device (including software) Hazard Analysis: Acceptable**
In the Appendix entitled Software in the Document entitled Level of Concern, the firm provided an acceptable description of the hazards (including clinical hazards) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

4. **Software Requirements Specifications (SRS): Acceptable**
In the Appendix entitled Software in the Document entitled Software Requirements Specification (SRS) the firm provided an acceptable copy of their software requirements specification document, which documented the functional, performance, interface, design and development requirements.

5. **Architecture Design Chart: Acceptable**
In the Appendix entitled Software in the Document entitled Architecture Design Chart, the firm provided an acceptable detailed depiction of functional units and software modules, which included state diagrams as well as flow charts.

6. **Software Design Specification (SDS): Acceptable**
In the Appendix entitled Software in the Document entitled Software Design Specification, the firm provided an acceptable design specification document, which describes how the requirements in the Software Requirements Specifications (SRS) are implemented.

7. **Traceability: Acceptable**
In the Appendix entitled Software in the Document entitled Traceability Matrix the firm provided an acceptable traceability matrix, which provides traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing.

8. **Software Development Environment Description: Acceptable**
In the Appendix entitled Software in the Document entitled Software Development Environment Description, the firm provided an acceptable description of the software development environment, which included a summary of the software life cycle development plan, an annotated list of the control/baseline documents generated during the development process, and a summary of the configuration management and maintenance activities.

9. **Verification and Validation Documentation: Acceptable**
In the Appendix entitled Software in the Document entitled Verification and Validation, the firm provided an acceptable description of the validation and verification activities at the unit, integration, and system level and the results of these activities.

10. **Revision Level History: Acceptable**
In the Appendix entitled Software in Section 7.10 entitled Revision Level History, the firm provided an acceptable revision history log documenting all major changes to the software during its development cycle and the release version numbers.

11. **Unresolved Anomalies (bugs): Acceptable**
In the Appendix entitled Software in Section 7.11 entitled Unresolved Anomalies, the firm stated that there are no unresolved anomalies. This is acceptable.

Reviewer's Comment: *The software reviewer provided the following conclusion: "The firm has provided acceptable documentation demonstrating that they have developed the software for this device under an appropriate software development program; that they have performed a hazard*

analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way. It is recommended that from a software standpoint this submission be approved."

G. **EMC and Electrical Safety**

As certified by a Nationally Recognized Testing Laboratory (NRTL), the eFlow CS conforms to the applicable requirements of Medical Electrical Equipment:

• Medical Electrical Equipment Part 1: General requirements for basic safety and essential performance, IEC 60601-1:2005 (Third Edition) + CORR. 1:2006 + CORR. 2:2007 + A1:2012 (or IEC 60601-1: 2012 reprint)

• Medical Electrical Equipment - Part 1-2: General requirements for basic safety and essen-tial performance - Collateral Standard: Electromagnetic Disturbances - Requirements And Tests (home, hospital, vehicle, and airplane), IEC 60601-1-2 (Edition 4.0) 2014-02 Additionally, the controller has met all IEC 60601-1-2 Edition 4.0; 2014-02 test levels with respect to electromagnetic immunity for equipment and systems that are not life supporting.

• Medical Electrical Equipment, General requirements for safety - Collateral Standard: Us-ability, Part 1-6, IEC 60601-1-6:2010 (Third Edition) + A1:2013 for use in conjunction with IEC 62366:2007 (First Edition) + A1:2014 and IEC 60601-1:2005 (Third Edition) + Corr.1 (2006) + Corr.2 (2007) + A1: 2012 or equivalent consolidated version IEC 60601-1:2012 (Edition 3.1)

• Medical Electrical Equipment, Part 1-11: General requirements for basic safety and es-sential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment, IEC 60601-1-11:2015 (Second Edition) for use in conjunction with IEC 60601-1:2012 (Third Edition) + A1:2012 (Second Edition): 2015-01

Reviewer's Comment: *The electrical safety reviewer recommended that the device is found safe from an electrical safety perspective. The sponsor has also conducted EMC testing in accordance with FDA recognized standards appropriate for a device intended for home use environment. The sponsor further indicates although the device is not intended to be used while traveling in vehicles and airplanes, testing for compliance with EMC for vehicles and airplanes was also conducted. This is acceptable.*

H. **Device Performance**

In vitro Aerosol Characterization of eFlow CS Nebulizers with SUN-101

Aerosol performance of the eFlow CS nebulizers was characterized using thirty devices from multiple device lots and six lots of SUN-101 (three 25 mcg/mL lots and three 50 mcg/mL lots). The devices were selected such that the aerosol heads included the entire range of in-process mass median diameter (MMD) specification. Aerodynamic particle size distribution of the aero-

sol was determined by Next Generation Pharmaceutical Impactor (NGI) and delivered dose was determined by breathing simulation (DD/BS), both tested in accordance with USP<1601>. In addition, delivered dose under constant flow (DD/CF) was also assessed.

A summary of the in-vitro aerosol performance characteristics of the eFlow CS devices tested with SUN-101 25 mcg/mL and 50 mcg/mL strengths are shown in Table 3. The mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine particle fraction (FPF) and DD/CF (% LC) are independent of the concentration strength. The FPF increased in proportion to the SUN-101 product strength. The DD/BS (%LC) is slightly higher for the 50 mcg/mL strength compared to the 25 mcg/mL strength. The mean nebulization time was approximately 2 minutes (data not shown).

(b) (4)

Environmental Conditions Testing

Tests to validate the environmental operating conditions of the eFlow CS nebulizer have been conducted. One device was used as EUTs (Equipment Under Test), and 0.9% NaCl solution was used for the nebulization. A climate cabinet was used for inducing the temperature and humidity variations. During the testing it was observed that the EUTs were operating at all tested conditions.

Device Robustness Study
Sunovion conducted a series of device robustness studies to assess the mechanical robustness of the eFlow CS nebulizers which included mechanical shock and free fall of the handset unit. The studies were conducted in accordance with the Product Free Fall Drop test described in IEC 60601-1 and the Mechanical Shock test described in IEC 60601-1-11.

None of the devices tested sustained damage when exposed to mechanical shock. Free fall drops did not sustain damage when dropped from the upright and inverted position but had sustained broken clasps when dropped with the clasp side facing down. Although the handset with the broken clasp was inoperable, the aerosol head was not affected after all mechanical and free drop exposures and was shown to work as intended in another handset base. While optimization of the clasp might improve the robustness of the eFlow CS handset units, it has been noted that the number of complaints due to broken clasps from the SUN-101 Phase 3 clinical studies have been low. Out of over 2800 devices deployed, 13 devices were confirmed to have broken plastics, which equates to a failure rate of <0.5% (3.2.R.1.9.9.2.2.1 Complaint Devices). On the basis of the device robustness studies and the number of returned Phase 3 clinical devices with broken plastic parts, the risk of having the device damaged during regular use is considered low and Sunovion determined that modification to the handset unit/handset components is not required.

Clinical return study (Complaint Analysis)
Table 34 provides an overview of the complaint data from the Phase 3 Studies (SUN101-301,SUN101-302, or SUN101-303).

Table 34: Clinical Return Report: Summary of Overall Complaints (Confirmed and Unconfirmed)

Study No.	No. of Devices[a] with Complaints n/N (%)	No. Subjects with Complaints n/N (%)
SUN101-301	78/723 (11%)	75/653 (11%)
SUN101-302	62/706 (9%)	56/640(9%)
SUN101-303	303/1495 (20%)	223/620 (36%)
Total	443/2924 (15%)	354/1913 (19%)

[a] Device(s): represent a complete device system or a device component (e.g., aerosol head)

The sponsor reports that of the 354 subjects who reported a device complaint in the Phase 3 studies:

- No subjects reported a medical device-related adverse event that caused or may have caused or contributed to a death or serious injury.
- No subjects reported an Adverse Event (AE) where the device was considered to have caused the event.
- No subjects reported a Human Factors/Use complaint where the user reported operating the device incorrectly or an issue understanding the IFU.
- 7 (0.4%) subjects in the Phase 3 studies reported a complaint associated with subject perception/dissatisfaction with the device.

Of the 269 confirmed complaints, the majority were associated with the aerosol head (Table 35), based on results of failure determination/root cause assessment.

Table 35: Summary of Device Complaint Assessment

Device Flow[a]	Number of Devices[b]			
	301	302	303	Total
Devices used in Phase 3 studies	723	706	1495	**2924**
Devices with reported complaints	**78**	**62**	**303**	**443**
Devices where complaint was resolved and continued use	5	6	4	15
Devices assessed by PRE for complaint confirmation	63	43	240	346
Devices pending analysis[c]	0	3	10	13
Devices where investigation was not possible or warranted[d]	8	10	45	63
Devices found to be working as received (fully functional)	**18**	**10**	**49**	**77**
Devices where complaint was confirmed	**45**	**33**	**191**	**269**
AC Adapter Related	0	0	0	0
Controller Related[e]	0	0	1	1
Connection Cord Related	0	0	1	1
Handset Related[f]	2	2	9	13
Aerosol Head Related[g]	39	30	180	249
Delaminated aerosol heads	8	11	48	67
Clogged aerosol heads	12	4	26	42
Aerosol heads having liquid ingress	9	8	30	47
Aerosol heads with electrical failures	0	2	13	15
Aerosol heads combination failures	9	3	52	64
Unclear aerosol head root causes	1	2	11	14

[a] *See Figure 18 for flow of device complaint assessments*
[b] *Device(s): represent a complete device system or a device component (e.g., aerosol head)*
[c] *Failure mode determinations and testing are ongoing; final results will be on file at Sunovion.*
[d] *Investigations were not possible or warranted when a device for which a complaint was reported was never returned for evaluation.*
[e] *Controller worked on AC power only. Battery fuse was blown.*
[f] *The clasp used to attach the top and bottom of the handset together was broken.*
[g] *Detailed information on these aerosol head root cause assessments and observations are provided in Table 36*

Sunovion conducted several additional laboratory and clinical assessments to better understand the device failures and develop a strategy to mitigate device complaints during commercialization. The following assessments were performed:

• Laboratory Assessments
  – Laboratory Stress Testing Study (Section 9.9.2.5.1): Conducted to simulate conditions where subjects would neither clean nor remove the aerosol head from the device for up to 60 days.
  – 60-day Simulated Use Study (Section 9.9.2.5.2): Conducted to test the cleaning method utilized in the Phase 3 studies on devices for 60 days of simulated use after being stored for 3 years.
  – 60 day Simulated Use Study (Section 9.9.2.5.3): Conducted to test the cleaning method described in the proposed IFU on devices for 60 days of simulated use.
  – Delaminated Aerosol Heads: Leachables Assessment (Section 9.9.2.5.4): Conducted to determine if leachables were found in the aerosol mist following use with delaminated aerosol heads.
  – Elemental Impurity Analysis (Section 9.9.2.5.5): Conducted to analyze the aerosol mist from devices where brownish spots (corrosion) were observed.

•Clinical Assessments
  – Nebulization Times in Phase 3 Clinical Studies (Section 9.9.2.5.6): Provided additional clarity around the "nebulization time too long" reported complaint in the Phase 3 clinical studies.
  – Proactive Aerosol Head Replacement Strategy in Study SUN101-303 (Section 9.9.2.5.7): Implemented to mitigate device complaints in this study.

To simulate severe misuse, the aerosol head was left in the handset after each dose (i.e., no removal of the aerosol head from the handset and no cleaning or drying of aerosol head or handset, and no backwashing with the easycare unit). The devices were tested over a period of 60 days in use with 120 doses delivered without cleaning between doses and with no weekly backwashing or disinfection. The nebulization times, the time from visual appearance of the aerosol mist to the end-of dosing audible signal, were recorded with each dose throughout the study.

Under the simulated laboratory conditions, the nebulization times gradually increased over time. However, after 45 days of severe misuse, the nebulization times were all under 5 minutes. In the last 10 days of severe misuse, the nebulization times markedly increased but were all under 15 minutes (automatic shut off time). Nebulization time was recorded as start time to end time of visual appearance of aerosol mist for each run.

After 30 days of severe misuse, 2/6 aerosol heads demonstrated signs of delamination and after 60 days, 5/6 aerosol heads demonstrated signs of delamination. Visual examination of all six of these aerosol heads showed signs of corrosion/brownish spots after 30 days of severe misuse. These results demonstrated that the lack of cleaning or improper cleaning contribute to the aerosol head root cause assessment of delamination after severe misuse and provide a laboratory method for replicating prolonged nebulization time, delamination, and brownish spots.

A second 60-day simulated use study was conducted on five eFlow CS2 devices to verify the cleaning procedure in the proposed IFU but without weekly backwashing with the easycare unit. These test devices had limited previous use as demonstration devices in the Phase 3 clinical studies.

SUN-101 25 mcg/mL was used as the test solution. A total of 120 nebulization cycles were tested on each handset (2 doses per day × two times per day × 60 days of use). Handset unit cleaning was performed after each use and disinfection with Control III was conducted after every 14 uses (equivalent to weekly use). The handset units were tested for aerodynamic particle size distribution by the Next Generation Pharmaceutical Impactor (NGI) and delivered dose under a constant flow rate after the 60-day simulation study. However, all five handset units tested show no appreciable overall change in the nebulization times through the study.

Reviewer's Comment: *The complaints were related primarily to malfunctions of the aerosol head, related to delamination, clogging, and liquid ingress. This resulted in a prolonged nebulization time, but does not appear to impact the aerosol performance. The root cause analysis provided by the sponsor concludes this was a result of inadequate cleaning. As a result, the sponsor has modified their device so the aerosol head will be replaced after 30 days and a weekly backwashing step is no longer needed. The sponsor conducted additional 60 day simulated use studies in order to validate the use life without the additional backwashing step, as well as with misuse in which no cleaning is performed. These studies demonstrate that there is not a significant increase in nebulization time and is acceptable to support the claimed use life of 30 days.*

I. Human Factors

Sunovion indicates they have applied human factors engineering throughout the eFlow CS development. Subjecting the nebulizer's development to extensive formative evaluations enabled Sunovion to optimize the device for its target user groups. Sunovion utilized an iterative approach, such that each study's outcome influenced future improvements of the device's design and documentation. Specifically, Sunovion based its design modifications and documentation changes on the usability study findings, the use Failure Modes and Effects Analysis (use-FMEA), and bench-top testing. These modifications were then assessed during subsequent studies.

Sunovion completed a total of ten usability studies of the eFlow CS, including nine formative studies and a subsequent summative (i.e., validation) study, which validated the nebulizer's safety and usability. The nebulizers used in the summative human factors study had the same design as the Phase 3 clinical trial and commercial devices. The sponsor concluded that these studies demonstrate that the eFlow CS nebulizer is safe to use as is and is not vulnerable to potentially harmful use errors that could lead to patient injury, serious harm, or clinically important delays in therapy or sub-optimal therapy.

Reviewer's Comment: *A human factors consult was conducted by Shannon Hoste to review the human factors testing submitted. The HF reviewer noted that the sponsor identified use errors related to locating the aerosol head in the packaging, confusion between the handset and the easycare, difficulty with the drug vial and difficulty with the connection cords. However, it is unclear if the user is aware that they have not received a dose of medication. It was noted that the sponsor should provide additional information on the potential risks associated with this use errors identified.*

In response to the March 31, 2017 request, the sponsor provided further details on the potential outcome and detectability of this issue. The sponsor concluded that one situation could potentially lead to high severity harm. This use error occurred when the drug vials were pierced

prior to inserting the aerosol head and may cause medication to leak from the handset and patients to receive an incomplete dose of their prescribed medication. If this occurs, the patient may be unaware that they did not receive the full dose, and may continue to use the device incorrectly. Therefore, additional information is recommended to address how this risk was mitigated.

J. Deficiencies

Biocompatibility:

1. Please clarify if the intended patient population will be limited only to adults. Specifically, please confirm that the eFlow Closed System Nebulizer will not be used in any patients with body weight < 10 kg.

> **Reviewer's Comment: Response Adequate.**
> *This clarification question was not conveyed to the sponsor. Confirmed by the CDER lead review team, this combination product will be only used in adults, which is not intended for neonates or infants*

2. You stated: "*The investigational eFlow® system used in the development of SUN-101 underwent several changes during the course of clinical development. The proposed commercial eFlow CS nebulizer system includes minor changes, to be made to the device (CS2) after Phase 3 studies*". Please confirm that the test device used in the biocompatibility testing, chemical extractable and leachable testing, and air quality assessment, which was identified as PARI nebulizer (3a), was identical to the final eFlow Closed System Nebulizer intended for marketing. Please provide a statement using the language as recommended below, to document how the test device model (PARI nebulizer, 3a) compares to the final device model of the commercial eFlow CS nebulizer system.

> ***Comparison to test article:*** "The test article is identical to the medical device in its final finished form in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents)."

If the PARI nebulizer (3a) tested was not representative of the final finished commercial eFlow CS nebulizer, testing using the final product intended for marketing is considered necessary. For details regarding how to perform appropriate biocompatibility assessments, please refer to the FDA Guidance Document: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (Document issued on: June 16, 2016), which can be obtained at the link below:

http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

Sponsor's Response:

- The test article PARI 3a nebulizer used in the biocompatibility testing as referenced in the NAMSA reports for Cytotoxicity, Genotoxicity, Irritation/ Intracutaneous, and Sensitization, and the test article nebulizer used in chemical extractable and leachable

testing, and the air quality assessment is identical to the medical device (eFlow Closed System nebulizer) in its final finished form in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents).

- In the Muscle Implantation testing, the test article was identical to the medical device in its final finished form in formulation, processing, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents) with the exception that the device was sterilized prior to implantation. Please refer to Section 5.2 of this response where the rationale for and impact of sterilization prior to implantation testing is further discussed.

Reviewer's Comment: Response Adequate. *The biocompatibility reviewer indicates "the response is deemed adequate to clarify the test devices used in the biocompatibility testing, chemical extractable and leachable testing, and air quality assessments, in relation to the final finished eFlow CS nebulizer intended for marketing." This is acceptable.*

3. In NDA208437, you only provided one *in vitro* genotoxicity testing, the bacterial reverse mutation test. This is considered inadequate to address the genotoxicity concerns. Because no single test can detect all genotoxins known to be associated with cancer risk, to evaluate genotoxicity of medical devices, FDA generally recommends two *in vitro* and one *in vivo* genotoxicity tests. To address the genotoxicity concerns for the eFlow Closed System Nebulizer, please provide additional genotoxicity testing as follows:

   I. An *in vitro* mammalian genotoxicity assay. A choice of one of the following is recommended:
      a) Mouse lymphoma gene mutation assay (OECD 476), which is preferred since it detects the broadest set of genotoxic mechanisms associated with carcinogenic activity;
      b) *In vitro* chromosomal aberration (CA) assay (OECD 473); or
      c) *In vitro* micronucleus assay (OECD 487).

   II. An *in vivo* cytogenetics assay. A choice of one of the following is recommended:
      a) Bone marrow micronucleus (MN) Assay (OECD 474);
      b) Bone marrow chromosomal aberration (CA) assay (OECD 475); or
      c) Peripheral blood MN assay

Sponsor's Response:

- The potential safety concerns associated with genotoxicity of the eFlow CS nebulizer device have been adequately addressed and in accordance with FDA comment #5 for chemical extractable and leachable testing and risk assessment, additional genotoxicty testing is not necessary.

Reviewer's Comment: Response Inadequate. *The E&L testing and associated risk assessments were not conducted appropriately. Therefore, the response was considered inadequate to address genotoxicity.*

4. The 2-week muscle implantation study provided contains the following issues. Please address.

    a) The eFlow Closed System Nebulizer proposed in NDA208437 is intended for permanent use. However, the study provided was based only on an implantation period of 2-weeks, which is inadequate to address the long-term safety concerns. Please provide a long-term implantation study based on ISO 10993-6:2007/(R)2010 Biological evaluation of medical devices - Part 6:Tests for local effects after Implantation. The implantation period shall be determined based on the worst clinical exposure condition or be continued until or beyond a steady state has been reached with respect to the biological response. For non-degradable and non-resorbable materials, the long-term responses are normally assessed in tests exceeding 12 weeks.

    b) You stated that the test device was sterilized by steam. However, the subject device system intended for marketing will be provided non-sterile. As sterilization may change the material property of the device and subsequently invalidate the biocompatibility test results, it is our expectation that all biocompatibility endpoints assessments should be performed based on the final finished subject device, or representative samples from the final product, or materials processed in the same manner as the final product (including sterilization). To justify the test device, please provide solid scientific evidence to explain how you believe that the sterilization procedures used would not affect the material property of the device. Alternatively, please provide a revised test report based on the final finished, non-sterilized subject device system.

Sponsor's Response:

- There was no safety signal of concern attributable to the eFlow CS nebulizer device identified through the extractable and leachable testing, the toxicology assessment, and the overall risk assessment. Based on the absence of leachables and extractables identified under aqueous extraction conditions, in accordance with FDA comment #5 additional implantation testing is not necessary for this device.

- Additionally, the results of the 2 week muscle implantation study did not identify any risks; i.e., concluded that the macroscopic reaction was not significant for each test article as compared to the negative control articles.

Reviewer's Comment: Response Inadequate. *The E&L testing and associated risk assessments were not conducted appropriately. Therefore, the response was considered inadequate to address the biocompatibility endpoint for implantation.*

5. In NDA208437 you did not provided any endpoints assessments for the short- and long-term systemic toxicity. To address the safety concerns, please provide the systemic toxicity testing based on ISO 10993-11:2006/(R)2010 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity.

Sponsor's Response: There was no safety signal of concern attributable to the SUN-101 eFlow CS device identified through the extractable and leachable testing, the toxicology assessment, and the overall risk assessment. Therefore, in accordance with FDA

comment #5, additional testing for systemic toxicity is not necessary for this device.

Reviewer's Comment: Response Inadequate. *The E&L testing and associated risk assessments were not conducted appropriately. Therefore, the response was considered inadequate to address the biocompatibility endpoint for systemic toxicity.*

6. You stated that you conducted a chemical extractable and leachable testing for the eFlow CS nebulizer system. However in NDA208437, you did not provide the test report for review. To support the biocompatibility of the eFlow CS nebulizer system and its compatibility with the intended SUN-101 (Glycopyrrolate) Inhalation Solution, please provide a complete test report for chemical analysis of the extractables and leachables, dated and signed by the testing laboratory. The test report should include a clear description for the test device, sample preparation, analytical methods and instrumental limits used, and chromatograms to assess the residues.

   Please be advised that the chemical analytical testing should be conducted based on a worst case scenario. For example, the test samples should be appropriately prepared; the extraction condition should represent a worst chemical leaching and exposure condition for the devices proposed. We recommend that you follow the FDA-recognized standard ISO 10993-12:2007 Biological evaluation of medical devices - Part 12: Sample preparation and reference materials and use an exhaustive extraction method or equivalent (e.g. 50°C for 72 hours) and appropriate polar and non-polar solvents for preparation of the test samples. The extraction solvents used should be adequate for a worst case extraction of both polar and non-polar chemical residues, be compatible with the test devices and do not cause device degradation.

   Please provide a comprehensive risk assessment (exposure and safety assessment) for all residues identified, including the organic, inorganic, organometallics, metals, and other residues. For analysis of the leachable and extractable residues and the allowable limits, please refer to the published toxicological literature. Please include all your calculations in the risk assessment, such as the calculations for the margin of safety (MOS), the body weight for adults and pediatrics, the reference doses/LOAELs/NOAELs, the limit of detections (LODs), the limit of quantifications (LOQs), the exposure assessment, etc. In addition, please provide a clear rationale for the uncertainty values that are used in the safety assessment for each residue.

   FDA agrees that chemical extractable and leachable testing plus a risk assessment, when conducted appropriately, may address the safety concerns for systemic toxicity and genotoxicity. If sufficient information can be provided through appropriate chemical extractable and leachable testing and risk assessment, additional testing for systemic toxicity, genotoxicity, and implantation may be no longer necessary for the patient gas pathway contacting devices. In this case, you may disregard the Deficiencies #3-5 above. However if insufficient information is obtained and/or a safety signal is identified through the extractable and leachable testing and the risk assessment, additional testing for systemic toxicity, genotoxicity, and implantation may still be warranted in order to address the risks. In this case, Deficiencies #3-5 as identified above should be addressed.

   Sponsor's Response:

   - Chemical extractable and leachable testing as well as a comprehensive risk

assessment (exposure and safety assessment) has been conducted. Specific information and details regarding the extractable and leachable studies, toxicological assessment, and overall risk assessment are provided in Section 2 of this response. Detailed summaries are included in 3.2.R.1.6.6 Extractables and Leachables. As requested the signed test reports are listed in Table 2 and are included in the NDA Section 3.2.R.1.6.6. The overall risk assessment has been updated to address these analyses; however the conclusions have not been changed. As stated in Section 2.1.3, there was no safety signal of concern attributable to the eFlow CS nebulizer device identified through the extractable and leachable testing, the toxicology assessment, and the overall risk assessment. Therefore, in accordance with the FDA comments, additional testing for genotoxicity, implantation, and systemic toxicity are not necessary for this device.

Reviewer's Comment: Response Inadequate. *The E&L testing and associated risk assessments were not conducted appropriately. Additional E&L testing following appropriate test conditions is recommended.*

7. To evaluate the quality of air delivered through the eFlow CS nebulizer, you provided testing of volatile organic compounds (VOCs), fine particles (particulate matters, $PM_{2.5}$), and other inorganic compounds (ozone, CO_2, and CO). However, based on your information provided in the test reports, we are unclear if your air quality assessments are adequate. To demonstrate that the output gas from the subject nebulizer system is not adulterated with VOCs, particulate matters, and hazardous inorganic compounds, please clarify/address the following:

   a) Please confirm that the air quality assessments were conducted based on the output air samples delivered through the entire eFlow CS nebulizer system.

   Sponsor's Response:
   - Sunovion confirms that the samples tested were from air that passed through the entire eFlow CS nebulizer system as stated in the submitted study reports listed in Table 4 (see 3.2.R.1.6.5 Air Path Testing).

   Reviewer's Comment: Response Adequate. *This response is deemed adequate.*

   b) Please describe in depth how the VOCs, particulate matters, and other inorganic compounds (ozone, CO_2, and CO) were extracted. Please justify that the extraction conditions used (e.g. the extraction time, temperature, flow rate, etc.) represented a worst clinical use condition for analysis of adulterated airs.

   Sponsor's Response:
   - The eFlow Closed System nebulizer was assembled as described in the IFU using the AC adapter as the power source and the sampling cartridge was attached to the mouthpiece. Samples tested were from air that passed through the entire eFlow CS nebulizer system and out of the mouthpiece into the sampling cartridge affixed to the mouthpiece. The nebulizer system was on during the entire sampling process. The extraction conditions for the studies

are described in the reports. The extraction conditions represent worst case conditions because:

- Continuous flow ensured consistency and precision; furthermore continuous flow simulates a more challenging constant inhalation as opposed to the actual inhalation/exhalation cycle.
- The sampling flow rate ensured the minimum flow needed by the collection device to capture the analyte while ensuring the flow was slow enough to prevent dilution of the analyte.
- The extraction time was chosen to meet the detection limit of the test.

Reviewer's Comment: Response Adequate. *The sponsor provided justification of the VOC testing conditions. Although the sponsor used lower flow rates than may be used clinically, Dr. Qian and I agreed that the overall concern is low. Additionally, as all components of the nebulizer are also within the humidified gas pathway, these additional biocompatibility endpoints must be met.*

c) Based on your test report, the VOC analysis was conducted based on air samples delivered through the device for 15 min. However, the eFlow Closed System Nebulizer is intended for continuous, permanent use. You did not justify how the short extraction time of 15 min is considered adequate for extraction and analysis of all VOC compounds that may potentially leach from the subject device system. Please provide solid scientific evidence to justify the extraction time of 15 min. Alternatively, please provide a revised VOC test report based on a worst case extraction and analysis of the VOCs.

If VOCs are identified in the output air samples, the emissions should be eliminated if possible. If emissions of the VOCs cannot be eliminated, the emissions should be explained and shown to have no adverse effects. A toxicological risk assessment should be provided for all identified VOCs based on the intended patient population, inhalation exposure route, and a worst case scenario.

Sponsor's Response:

- The 15-minute VOC sample time was selected based on previous experience with other nebulizer submissions reviewed and cleared by FDA and the detection limit of the assay. As stated in this FDA comment, and as an alternative, VOC testing was repeated with a 24-hour sample time which is intended to increase the levels of VOC.
- As stated above (Section 1.1), it is important to clarify that while the device is intended for long term use for the maintenance treatment of patients with COPD, exposure to the device is limited to intermittent twice daily use for 2-3 minutes each time the drug is administered. Therefore, the device is not in continuous use but rather, patient exposure to the device is limited to a cumulative duration of approximately 6 minutes per day. Furthermore, during commercialization, the handset will be replaced every 30 days. Thus, the handset will be replaced after 2.8 hours of exposure; therefore, the 24-hour sample time used for this VOC testing exceeds handset monthly use by 8 fold.

- The 24-hour VOC analysis met the acceptance criteria and there was no statistically significant difference between source air and air that passed through the nebulizer. The VOC protocol and analysis for the 24-hour extraction is provided in Protocol 16-0063 Final Report Volatile Organic Compounds (VOC) Analysis of the eFlow CS nebulizer.

Reviewer's Comment: Response Adequate. *The output air samples for the repeated VOC testing were collected at the intended flow rate of 28L/min for 24 hrs. The VOCs detected in the ambient air controls and in the output airs delivered through the eFlow Closed System Nebulizer appears to be comparable. The repeated VOC testing is deemed acceptable.*

Performance:

8. You have made modifications to your device intended for commercial marketing compared with the CS2 investigational device, including to the enclosure, circuit board, and software. These differences may not impact aerosol performance, but could impact other aspects of the performance, related to the software verification & validation, electrical safety, electromagnetic compatibility, and mechanical safety. Pleased confirm these performance tests have been conducted on your final eFlow CS device intended for commercial marketing. If not, please provide testing on the final device. Alternatively, please provide justification for why any modifications between the commercial eFlow CS and device tested could not impact the resulting data.

   Sponsor's Response: The minor modifications, as detailed in 3.2.R.1.3 Device Change History, Table 13, were implemented prior to final testing. All performance tests submitted in the original NDA, including those related to the software verification & validation, electrical safety, electromagnetic compatibility, and mechanical safety were conducted on the final eFlow CS device intended for commercial marketing. The test article is identical to the medical device in its final finished form in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents).

Reviewer's Comment: Response Adequate. *The sponsor clarified testing was conducted on the final device. This is acceptable.*

Human Factors:

9. In your Human Factors Report data submitted you have identified several use errors and difficulties. These include: locating the aerosol head in the packaging, confusion between the handset and the easycare, difficulty with the drug vial and difficulty with the connection cords. You have indicated that each of these will result in the device being unable to deliver medication. It is unclear if in each of these scenarios the user is aware that they have not received a dose of medication. Additionally it was demonstrated in your testing that a participant believed that the AC adaptor connected to the controller connection cord port. Further information was not provided on the potential risks associated with this connection error. The Agency asks for an analysis of any potential risks for errors which could lead to severe harm, noting that for combination products, harm is defined to include compromised

medical care. Please provide further details on the potential outcomes of the use errors identified and identify if further design changes are needed to mitigate these risks.

Sponsor response 31 March 2017:
Sunovion recognizes that some of the use errors and difficulties which occurred during the SUN-101 eFlow® nebulizer summative study could represent a potential for harm to patients based on compromised medical care.

Table 1 summarizes the use errors and difficulties potentially associated with compromised medical care which were cited in this information request. These use errors and difficulties were analyzed in the context of compromised medical care and organized into the following resultant categories: no dose being delivered, delayed therapy, or incomplete dosing (under dose).

All use errors/close calls/difficulties that may lead to compromised medical care which occurred during the summative study are listed in the Summative Study Report, Appendix A: Events with Limited Potential for Harm or Negative Effect on Prescribed Therapy (pages 35-64) and are identified by the same categories of potential compromised medical care, i.e., due to no dose (being delivered), delayed therapy, and under dose (incomplete dosing). Therefore, the residual risk analyses provided herein is complete.

Detailed residual risk analysis for the use error/difficulty and corresponding categories listed in Table 1 is provided in the subsequent sections. Additionally the analysis provides clarity on whether the patient was aware of whether or not they had received their dose.

Table 1: Use Errors or Difficulties with Potential Compromised Medical Care

Use Errors/ Difficulties	Resulting Harms	Participants[a]	Was the participant aware that they did not receive a dose of medication?	References
Locating aerosol head in the packaging	Delayed therapy	P2, P5, H7 (Difficulty)	Yes (P2, P5, H7)	SUN-101 Summative Test Report (pages 56-58)
Difficulty with the drug vial	No dose being delivered, delayed therapy, incomplete dose (under dose)	P13, C2, CT5, CT7 (Difficulty)	No (C2, CT5, CT7) Yes (PT13)	SUN-101 Summative Test Report (pages 39-42)
		P10[b] (Use error)	Yes	SUN-101 Summative Test Report (pages 27-28) and HFE Report Section 6.4.2.2 (pages 62-65)
Difficulty with the connection cords	Delayed therapy	C9 (Difficulty)	No	SUN-101 Summative Test Report (pages 50-52)
		PT12[b] (Use error)	No	SUN-101 Summative Test Report (pages 29-30) and HFE Report Section 6.4.2.3 (pages 65-68)

[a] P – COPD patient who did not receive training on device prior to test session; PT – COPD patient who received training on device prior to test session; C – Caregiver who did not receive training on device prior to test session; CT – Caregiver who received training on device prior to test session; H – Healthcare professional who did not receive training on device prior to test session; HT – Healthcare professional who received training on device prior to test session

[b] Task failure due to participant requiring test administrator assistance. Residual Risk Analysis for this use error has been included in the HFE report.

Difficulty locating aerosol head in the packaging

...Three participants (P2, P5, and H7) had difficulty locating the aerosol head in the

nebulizer box in the summative study (Table 1). As a result, after the first 25 test sessions, the aerosol head package was relocated to lying flat on top of the eFlow bag such that it was more visible when users viewed the box's components and less vulnerable to being hidden from view by other components (Summative Test Report, Test plan deviations (page 17)). This change in the aerosol head's presentation proved to be effective since no other participant in the remainder of the summative study (66 test sessions) had difficulty locating the aerosol head....

Difficulty with the drug vial resulting in an underdose
...Incomplete dosing may result from vials that are pierced open prior to inserting the aerosol head, but do not empty completely. The nebulizer will detect medication on the aerosol head, and the controller will not produce an error tone and an aerosol mist will be generated. The patient may, or may not, notice the shortened duration of treatment (with completion tone) or the small quantity of medication leaking from the handset. As a result of this difficulty, the patients will receive only a partial dose of their prescribed medication and a higher risk for compromised medical care...

Difficulty with the connection cords
...There is an acceptably low residual risk associated with inserting a connection cord incorrectly (i.e., into the AC adapter port of the controller or into handset upside down). The erroneous physical action itself poses no risk of personal injury or device damage. However, patients will not be able to proceed with a treatment until they recognize the difficulty and correct it. As such, the compromised medical care caused by this difficulty is related to a delay in therapy...

Reviewer's Comment: Response Inadequate. *Based on their analysis, incomplete dose is the highest risk as it may not be detected by the user. The sponsor has not provided adequate information for how this risk was mitigated. The Human factors reviewer recommended additional information is requested from the sponsor.* ***See Outstanding Deficiency #2 at the bottom of this memo.***

Cleaning:

10. The cleaning validation report did not include visual confirmation of cleaning in the acceptance criteria. Visual cleanliness is routinely used by device users to as a cleaning endpoint and should be included in cleaning validations along with quantitative cleaning assessment criteria. To address this concern, please confirm that all devices used in the cleaning validation were determined to be visually clean in addition to the quantitative criteria. Additionally, it is recommended that labeling be revised to explicitly state that device should be inspected, following cleaning, and the cleaning process be repeated if the device is not visually clean.

Sponsors response: A visual confirmation of cleaning was performed, and was one of the acceptance criteria for cleaning validation. The visual confirmation is documented in text form at the top on p.8 in the Final Report (GLP Protocol 0079v000) and reads as follows:

(b) (4)
[redacted]."

The cleaning validation also included the quantitative requirement that residual protein and carbohydrate had to be below (b) (4), respectively.

The previously submitted IFU (Section F. Cleaning Your DEVICE) included a warning box after step F9 that instructs patients:

> *"...If the parts still appear dirty after cleaning, then soak the disassembled parts for an additional 5 minutes."*

Based on the FDA comment, the labeling statement regarding visual inspection after cleaning was also specified as a separate step in the revised IFU, to instruct patients to inspect the cleanliness of the device and further cleaning the device if the components are not visibly clean to reinforce the instruction (see labeling history, Table 2).

Reviewer's Comment: Response Adequate. *The cleaning consultant indicates that the response addresses the concern that the devices be demonstrated visibly clean and that the labeling be revised to ensure visual inspection of cleanliness following reprocessing. This is acceptable.*

11. The exact composition of the test soil used in the cleaning validation could not be located. This information is needed for review of the cleaning validation protocol. To address this concern, please provide or identify the location in the submission that state the specific amounts of the soil components used in the stated test soil. Please justify the test soil as an appropriate worst case for the subject device.

Sponsors response:
The exact composition of the test soil formulation used in the cleaning validation is provided in Table 5 and Table 6. The test soil formulation, Augmented Artificial Saliva, was used in the cleaning validation to simulate an appropriate worst case for the eFlow CS device. The Augmented Artificial Saliva was prepared using (b) (4) (Table 6). This artificial saliva described in Ionta FQ, et al. *In vitro assessment of artificial saliva formulations on initial enamel erosion remineralization*, Journal of Dentistry (2014) was (b) (4).

The test soil is considered worst case for the eFlow CS device because it mimics saliva after a protein-rich, carbohydrate meal, which was dried on the device prior to testing. In contrast, the device IFU requires the user to rinse and wash the device immediately after use, before the device dries.

Table 5: Test Soil Formulation (Augmented Artificial Saliva)

Ingredient	Amount
(b) (4)	

Table 6: Artificial Saliva Formulation

Ingredient	Amount
(b) (4)	

Reviewer's Comment: Response Adequate. *The cleaning consultant indicates that provided response is adequate and includes a rationale for the test soil as an appropriate worst case for the use of the device. The provided rationale is stated to simulate saliva after a meal. This appears to be a probable contamination condition for the subject device. The fortification of soil with additional heme, protein and carbohydrate markers does not have a known deleterious effect on soil challenge. This is acceptable.*

12. (b) (4)

Sponsors response:

(b) (4)

(b) (4)

[redacted]

Corresponding changes were made to related labeling documents. The labeling history summarizes all proposed labeling revisions to the following labeling documents:

☐ Package insert (patient instructions): provided in track change (word and pdf) and clean (word and pdf)

☐ IFU
☐ Quick Reference Guide
☐ Video Script

Reviewer's Comment: Response Inadequate. (b) (4)

[redacted]

Interactive Review Deficiencies

The following deficiencies were sent to the sponsor on March 23, 2017 regarding the outstanding issues with the device extractable and leachable testing, and device disinfection:

1. In response to the FDA Request dated 23 December 2016, you provided a chemical extractable and leachable test report and a risk assessment report for the chemicals identified. You stated that the extractable study was performed based on ISO 10993-12:2007 Biological evaluation of medical devices - Part 12, using an accelerated extraction condition and two different solvents, water and isopropanol. However, your extraction condition used (60°C with agitation by sonication for 2 hours) showed a significant deviation from the referenced test standard ISO 10993-12:2007. Please be remindful that the eFlow Closed System Nebulizer proposed in NDA208437 is intended for patients with chronic obstructive pulmonary disease (COPD). Although you claimed that each medication treatment will only take 2-3 minutes and that the handset unit will be replaced every 30 days, patients under the COPD medical conditions may repeatedly use the eFlow Closed System Nebulizer and its replacements. Due to considerations of the potential for cumulative use and exposure to the device and its replacements, FDA considers that the eFlow Closed System Nebulizer is a permanent contact device.

Your extraction condition used (60°C, 2 hours) did not represent a worst chemical leaching and exposure condition for the eFlow Closed System Nebulizer, which are therefore not acceptable by the FDA. Due to inappropriate/inadequate preparation and analysis of the test samples, the chemical extractable and leachable testing and associated risk assessment provided is deemed inadequate to address the safety concerns for the chemical residues from the eFlow Closed System Nebulizer.

Please provide a revised chemical extractable and leachable test report based on a worst case extraction and analysis of the chemical residues. As we have previously recommended, please follow the FDA-recognized standard ISO 10993-12:2007 Biological evaluation of medical devices - Part 12: Sample preparation and reference materials and use an exhaustive extraction method at 50°C or at a worst clinical relevant temperature, for preparation of the test samples. The extraction solvents used should be adequate for a worst case extraction of both polar and non-polar chemical residues, be compatible with the test devices and do not cause device degradation. The analytical instruments and test methodologies used should be adequate for detection and analysis of various types of chemical residues, including the organics, inorganics, organometallics, metals, and other residues.

Please provide a comprehensive risk assessment (exposure and safety assessment) for all chemical extractables and leachables identified, based on the inhalation exposure route, intended patient population, and a worst case scenario. Please specify the concentrations per device for each of the chemical residues identified, including organics, inorganics, organometallics, metals, and other residues. For analysis of the chemical residues and the allowable limits, please refer to the published toxicological literature, the inhalation protective values from the US based health organizations or WHO, the FDA-recognized standard ISO 10993-17:2002(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances, and/or the TTC approaches described in the CDER ICH M7 guidance. Please describe in detail how your risk assessment calculations are made, such as the calculations for the margin of safety (MOS), the body weight, the reference doses/LOAELs/NOAELs, the limit of detections (LODs), the limit of quantifications (LOQs), the acute and chronic exposure assessments, etc. The body weight and daily inhalation rate (m^3/day) used in the risk assessment calculations shall be appropriately justified, based on a worst case scenario and the published US NHANES and EPA values. In addition, please provide a clear rationale for the uncertainty values that are used in the safety assessment for each residue.

Reviewer's Comment: Response Inadequate. *The sponsor provided new E&L testing using extraction conditions following ISO 10993-12 at 50C for 72 hours and at 60C for 24 hours with agitation. Water was used as a polar solvent and isopropanol (IPA) was used as a nonpolar solvent. However, the test article resulted in significant degradation when IPA was used as a solvent which would invalidate these test results. The sponsor should address this and conduct new testing using an appropriate solvent.* ***See Outstanding Deficiency #1 below.***

2. (b) (4) 

K. Outstanding Deficiencies

The following deficiencies are recommended to the sponsor:

Biocompatibility:

1. In your response to FDA Request dated 17 March 2017, you provided two new chemical extractable and leachable (E&L) tests for the eFlow Closed System Nebulizer proposed in NDA208437. Both tests were conducted using water as the polar extraction solvent and isopropanol (IPA) as the non-polar solvent. The extraction conditions used were identified as 50°C for 72 hours or 60°C under sonication for up to 24 hours. In the test reports provided, you stated that IPA used as the non-polar extraction solvent caused significant degradation of the test devices, under both of the two extraction conditions.

   The eFlow Closed System Nebulizer proposed in NDA208437 is indicated for permanent uses. In clinical use, the device will come into direct contact with the SUN-101 (glycopyrrolate) Inhalation Solution and patient's exhaled gases. When being exposed to such clinical conditions, both polar and non-polar chemical residues may potentially leach out from the device, which may pose significant health risks to patients when inhaled.

   As the IPA extraction solvent was demonstrated to be incompatible with the test device materials and caused device degradation, the test data from the IPA extracts are considered invalid. Thus your E&L testing provided is considered inadequate for the biocompatibility endpoints assessments for systemic toxicity and genotoxicity and inadequate to address the drug-device material compatibility.

   To address the safety concerns for the eFlow Closed System Nebulizer, we request that you provide a revised chemical E&L testing at 50°C for 72 hours, using an appropriate non-polar extraction solvent that is compatible with the test device and does not cause the device

degradation. We recommend that you use a non-polar extraction solvent or a mixed solvent system that is chemically similar in polarity to the intended medications. Alternatively, you may provide the revised chemical testing based on the intended drugs or a surrogate chemical that has chemical properties similar to the drugs proposed. If a surrogate or non-polar solvent was used, please provide your scientific rationale and justification for your choice of the surrogate or the non-polar solvent to demonstrate that the worst clinical use condition is represented. In addition, please clarify whether the surrogate or solvent used compromises the integrity of the tested device or representative component samples.

Please provide a revised toxicological risk assessment (exposure and safety assessment) for all chemical compounds identified from the revised E&L testing, including organics, inorganics, organometallics, metals, and other residues. To address a worst case safety concern, the maximum amounts of the chemicals identified per device system should be considered in the risk assessment calculation. The risk assessment calculation should also take into consideration of the inhalation exposure route, intended patient population, and a worst case scenario. For analysis of the chemical residues and the allowable limits, please refer to the published toxicological literature for the reference doses, such as the no-observed-adverse-effect-levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), and/or to the inhalation protective values from the US based health organizations or WHO. For the risk assessment calculation, you may also refer to the FDA-recognized standard ISO 10993-17:2002(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances, and the TTC approaches described in the CDER ICH M7 guidance. Please clearly identify the calculated margin of safety (MOS) value for each of the chemicals identified and describe in detail (step-by-step) how the MOS values were calculated. Please provide a clear rationale for the uncertainty values that are used in the exposure and safety assessment for each chemical residue.

Please be advised, if a safety signal (e.g. chemicals with MOS <1) is identified through your risk assessment of the chemical extractables and leachables, additional justification or biological testing may be warranted in order to address this risk.

Human Factors:

2. You have responded to request for further information on the potential use errors identified in your human factors validation study. You have provided data indicating that use errors which lead to situations in which the system will not function will lead to a minor delay in therapy with a low potential harm. However, you have identified one situation which potentially could lead to high severity harm. In this situation, several participants experienced difficulties/errors with the use of the vials for dosing. In summary you noted:

   "Incomplete dosing may result from vials that are pierced open prior to inserting the aerosol head, but do not empty completely. The nebulizer will detect medication on the aerosol head, and the controller will not produce an error tone and an aerosol mist will be generated. The patient may, or may not, notice the shortened duration of treatment (with completion tone) or the small quantity of medication leaking from the handset. As a result of this difficulty, the patients will receive only a partial dose of their prescribed medication and a higher risk for compromised medical care."

You have provided further details on the potential outcome and detectability of this issue, in summary you noted:

"Continued incomplete (or under) dosing can result in compromised medical care; especially if patients are not aware they are repeatedly using the device incorrectly and not receiving the full, prescribed inhaled dose. One possible indication of incomplete dosing is there may be a shortened duration of treatment (with completion tone). Clinically, incomplete dosing should be considered in patients experiencing unexplained increases in disease related symptomology (e.g. cough, dyspnea, and chest tightness), premature use of add-on bronchodilator therapies, increases in rescue medication use and acute exacerbations requiring antibiotics/parenteral steroids and/or hospitalization. Since these sequelae also occur with disease progression, a discussion with the patient during normal physician visits regarding device use may be important to help assess the underlying reason for changes in a patient's clinical status and evaluation of device technique."

You have not identified potential mitigations to eliminate or reduce the risk associated with this use error. Please provide your analysis of this risk. If mitigations are not being implemented, please provide rationale that possible/practicable modifications to the user interface (including the device and the labeling) would not further reduce this risk.

L. Recommendation

The outstanding deficiencies identified above should be addressed regarding biocompatibility and human factors. Therefore, the device is not recommended for approval at this time from a device perspective.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Amy K. Levelle -S Digitally signed by Amy K. Levelle -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy K. Levelle -S, 0.9.2342.19200300.100.1.1=2000378253 Date: 2017.04.24 18:06:46 -04'00'
Branch Chief Sign-Off	James J. Lee -A Digitally signed by James J. Lee -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=James J. Lee -A, 0.9.2342.19200300.100.1.1=2000954859 Date: 2017.04.25 09:50:34 -04'00'

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

/s/

SADAF NABAVIAN
05/16/2017

Recommendation: Approval

NDA 208437
Review #1

Drug Name/Dosage Form	Glycopyrrolate inhalation solution
Strength	25 mcg/mL
Route of Administration	Oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Sunovion Respiratory Development, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*29-JUL-2017*	*All*
Amendment	*16-NOV-2016*	*Drug product*
Amendment	*12-DEC-2016*	*Microbiology/process*
Amendment	*06-JAN-2017*	*Drug product*
Amendment	*11-JAN-2017*	*Drug product*
Amendment	*13-JAN-2017*	*Microbiology/process*
Amendment	*16-MAR-2017*	*Microbiology/process*
Amendment	*23-MAR-2017*	*Facilities*
Amendment	*29-MAR-2017*	*Facilities*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	NDBII/DNDAPI
Drug Product	Xiaobin Shen	NDPBIV/DNDPII
Process	Yuesheng Ye	PABVIII/DPAIII
Microbiology	Julie Nemecek	MABIII/DMA
Facility	Rose Xu	IABII/DIA
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Florence Aisida	RBPMBI/DRBPMI
Application Technical Lead	Craig M. Bertha	NDPBIV/DNDPII
Laboratory (OTR)	N/A	

Environmental Analysis (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)						Sufficient information provided in NDA
						Sufficient information provided in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110663	Sunovion's IND for glycopyrrolate inhalation solution

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, process, microbiology, and facilities teams outlined in the review below, an overall recommendation of **approval** is to be forwarded to the clinical Division (DPARP).

II. Summary of Quality Assessments

A. Product Overview

The current application seeks approval for an inhalation solution drug product that is part of a combination product (drug/device). The drug product is proposed to be co-packaged with the device. Glycopyrrolate is an anticholinergic compound and the drug product is intended to be indicated for the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD).

Proposed Indication(s) including Intended Patient Population	COPD
Duration of Treatment	Chronic
Maximum Daily Dose	25 mcg BID
Alternative Methods of Administration	Glycopyrrolate is also given by injection pre-operative to surgery to reduce salivary, tracheobronchial, and pharyngeal secretions and for treatment of peptic ulcer; oral tablets are also used to treat peptic ulcer disease

B. Quality Assessment Overview

The information for the drug substance is mainly provided by reference to two drug master files (DMF (b) (4)), both of which have been reviewed and have been found to be sufficient to support this application.

The drug product is a buffered and pH-adjusted sterile solution. The active glycopyrrolate is very soluble in the buffer. All the excipients are commonly used for inhalation/injection products and at levels within that of the already approved products. The drug product is sterilized (b) (4) The drug product is well controlled for an inhalation solution. Extractables and

leachables have been studied and the levels of leachables are found to be below the safety concern threshold. Under the consistent drug product solution pH and ambient temperature, the active degrades over time in a predictable pattern and an expiration dating period of 24 months is supported.

The drug substance is manufactured at two facilities by two separate firms and both were deemed acceptable based on their inspectional history and manufacturing capability. The drug product manufacturer, (b) (4) is a contract manufacturer and the associated facility was found to be acceptable based on its PAI coverage.

Note that regarding the device manufacturing, CDRH/OC also recommends approval of the application based on the information provided in the submission and the inspectional history.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

90 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

MICROBIOLOGY

Product Background: -

NDA: 208437

Drug Product Name / Strength: SUN-101 (Glycopyrrolate Inhalation Solution, formally known as EP-101); 25µg/mL

Route of Administration: Sterile solution for inhalation

Applicant Name: Sunovion Respiratory Development, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Summary: Recommended for Approval.

List Submissions being reviewed: 7/29/2016, 10/24/2016, 12/12/2016, 1/13/2017, and 3/16/2017.

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: N/A

Remarks Section: The 10/24/2016 submission contains the current version of the package insert.

An IR was conveyed to the applicant on 11/22/2016. The applicant responded to the IR on 12/12/2016. A second IR was conveyed to the applicant on December 13, 2016. The applicant responded to the IR on 1/13/2017. A third IR was conveyed to the applicant on March 9, 2017. The applicant responded to the IR on 3/16/2017. The responses are incorporated following the agency comment in relevant sections of this review.

S Drug Substance

The drug substance is not the focus of this review as the drug product is sterilized (b) (4).

P.1 Description of the Composition of the Drug Product

- Description of drug product – Colorless, transparent solution (3.2.P.5.1 Specifications, page 1 of 4).

- Drug product composition –

  (3.2.P.1 Description and Composition of the Drug Product, page 1 of 1)

Ingredient	Content per mL of drug product	Content per mL of placebo
Glycopyrrolate	25 µg	N/A
Citric acid monohydrate	(b) (4)	
Sodium chloride		
Sodium hydroxide	Adjust to pH 4.0	Adjust to pH 4.0
Hydrochloric acid	(b) (4)	
Water for injection	q.s. to 1 mL	q.s. to 1 mL

  A placebo solution is supplied with each unit dose vial of the drug product. The placebo will be used for demonstration of the associated nebulizer device and is not intended for inhalation or therapeutic use. The placebo contains all of the above components minus the drug substance (Placebo-Inhalation Solution, 3.2.P.1. Description and Composition of the Drug Product.pdf, page 1 of 1).

- Description of container closure system –
  (3.2.P.7 Container Closure System, page 2-5 of 7; Sterility Assurance Validation Report, page 19 of 475)

  Vials are formed from a low density polyethylene (b) (4) . The 1 mL vials are filled, formed, and sealed using a (b) (4) . The vials are single-dose.

  The vials are designed to be used with the eFlow Closed System nebulizer. The vial is inserted into the medication cap of the nebulizer. When the cap is closed, the vial is pierced and solution drains into the device and onto a vibrating membrane for nebulization. The applicant states that the nebulizer is not sterile and is not intended to be sterilized. The nebulizer is for single patient use and cleaning instructions are provided (3.2.R.1.1 Executive Summary, page 15 of 23; 3.2.R.1.5 Cleaning-Disinfection-Maintenance-ShelfLife.pdf, page 4 of 76).

Acceptable

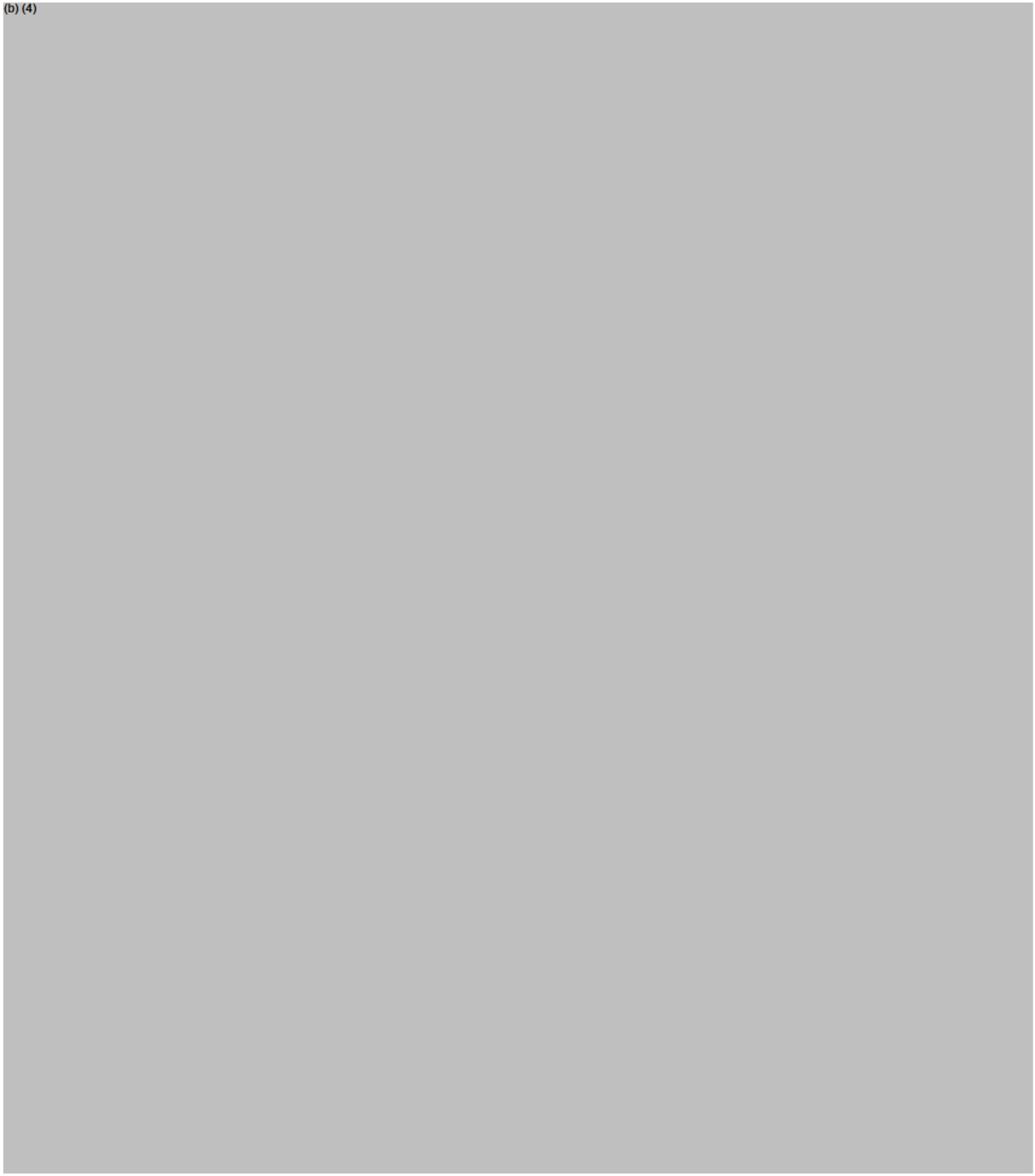
Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility. The nebulizer is beyond the scope of this product quality microbiology review.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(3.2.P.3.4 Control of Critical Steps, pages 2-5 of 7; 3.2.R.4 Draft Commercial Master Batch Record, page 8 of 45).

(b) (4)



(b) (4)

Acceptable

Reviewer's Assessment: Container-closure integrity testing is performed on 100% of manufactured vials during commercial production and any leaking vials rejected. The applicant's verification of container closure integrity is consistent with regulatory expectations for a sterile pharmaceutical product.

Antimicrobial Effectiveness Testing

Not applicable.

Acceptable

Reviewer's Assessment: The subject drug product is packaged in a single-dose vial; antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

(3.2.P.3.1 Manufacturer(s), page 1 of 3)

Drug product manufacturing:

- (b) (4)
-

Release and stability testing:

- (b) (4)

(b) (4)

-
-

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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

2.A. Package Insert

- Storage: 20-25 °C in the protective foil pouch.
- The unit-dose vials are used immediately after opening and are discarded after use. The drug product is not diluted or reconstituted.

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

Post-Approval Commitments: Not applicable.

Lifecycle Management Considerations: Not applicable.

List of Deficiencies: Not applicable.

Primary Microbiology Reviewer Name and Date: Julie Nemecek, Ph.D., 3/26/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Dupeh Palmer 3/26/2017. **"I concur".**

Dupeh Palmer-Ochieng

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Date: 3/08/2017 02:21:02PM
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Julie Nemecek

Digitally signed by Julie Nemecek
Date: 3/27/2017 09:53:46AM
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Attachment – Final Risk Assessment

DP attribute/ CQA[1]	Factors that can impact the CQA	O[2]	S[2, 3]	D[2]	FMECA RPN #	Comment & considerations
Glycopyrrolate assay/impurities	• incorrect amount of API formulated (incorrect concentration) • high impurity levels in input API • high level of degradation of API as formulated • non-uniform fill volume • leak in protective packaging leading to evaporation	3	3	1	9	(b) (4) [redacted]

[1] Applicant defines critical attributes as per table 16 in P.2 (device is to be evaluated by CDRH)
[2] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[3] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs

(b) (4) [redacted]

pH	• changes in levels of acidic or basic impurities in formulation components (API, excipients)	2	3	1	6	(b) (4)
Sterility/Endo-toxins[5]						
Osmolality	• incorrect amount of sodium chloride added • leachables from LDPE alter osmolality of solution	2	3	1	6	
Particulate matter	• particulate matter introduced during manufacturing	3	3	2	18	
Leachables	• volatile components from proposed commercial foil (b) (4) ((b) (4) permeate LDPE vial	2	3	3	18	

[5] Evaluation to be done by the microbiology team

	• compounds in vial LDPE (b) (4) leach directly into formulation					(b) (4)

Craig Bertha, ATL

Craig
Bertha

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