CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208437Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110663

MEETING MINUTES

Sunovion Respiratory Development, Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Attention: Renee M. Carroll, MS, RAC
Sr. Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SUN-101 (glycopyrrolate) inhalation solution.

We also refer to the meeting between representatives of your firm and the FDA on April 12, 2016. The purpose of the meeting was to discuss the clinical studies completed to support the NDA and device performance.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 12, 2016 2:00 – 3:30 PM
Meeting Location:	White Oak Building 22, Conference Room: 1315
Application Number:	IND 110663
Product Name:	SUN-101, glycopyrrolate inhalation solution with eFlow CS nebulizer
Indication:	Chronic obstructive pulmonary disease (COPD)
Sponsor/Applicant Name:	Sunovion Respiratory Development, Inc. (Sunovion)
Meeting Chair:	Dr. Badrul Chowdhury, Director
Meeting Recorder:	Christine Ford, Regulatory Project Manager

FDA ATTENDEES:

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Banu Karimi-Shah, MD, Clinical Team Leader, DPARP
Erika Torjusen, MD, Clinical Reviewer, DPARP
Marcie Wood, PhD, Supervisory Pharmacologist, DPARP
Christine Ford, MS, RPh, Regulatory Project Manager, DPARP
Anshu Marathe, PhD, Team Leader, Division of Clinical Pharmacology II
Yunzhao Ren, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II
Lan Zeng, PhD, Biometrics Reviewer, Division of Biometrics II
Craig Bertha, PhD, CMC Lead, Division of New Drug Quality Assessment (DNDQA) III
Xiaobin Shen, PhD, CMC Reviewer, DNDQA III
Mishale Mistry, PharmD, MPH, Team Leader (Acting), Division of Medication Error Prevention and Analysis (DMEPA)
Lissa Owens, PharmD, Safety Evaluator, DMEPA
Michael Sinks, PharmD, Safety Regulatory Project Manager, Office of Surveillance & Epidemiology (OSE)

Deepika Arora Lakhani, PhD, Team Lead – Combination Products, Respiratory & Pulmonary Devices Branch, CDRH

Patricia Love, MD, Deputy Director, Office of Combination Products (OCP)
Melissa Burns, Engineer, Sr. Program Management Officer, OCP

SPONSOR ATTENDEES:

Andrea Bauer, PhD, RAC	Senior Director, Formulation Development
Phil Bonasia, PhD	Head, Chemistry Manufacturing and Controls North America
Sara Burke	Associate Director, Product Development
Renee Carroll, MS, RAC	Senior Director, Global Regulatory Affairs
Raymond Claus, MS	Director, Biostatistics
Thomas Goodin, PhD	Senior Director, Clinical Development
Antony Loebel, MD	Executive VP, Group Head Global Clinical Development & Chief
Chris Ott, PhD	Director, Quality Assurance
Robyn Parker, MS	Associate Director, Regulatory Affairs
Stephen Pham, PhD	Formulation and Device Consultant
James Rawls, PharmD	Head, Global Regulatory Affairs
John Salveta, MS	Director, Global Regulatory Affairs
Robert Tosiello, PhD	Executive Director, Biostatistics
Alistair Wheeler, MD	Head, Clinical Research Respiratory

Background:

Sunovion has been developing SUN-101 for oral inhalation using the eFlow Closed System (CS) nebulizer for twice daily treatment of bronchoconstriction in patients with COPD and requested a pre-NDA meeting to discuss the clinical studies completed to support the NDA and device performance. They plan to co-package the drug product with the nebulizer, proposing two commercial configurations, 1) a starter kit and 2) a refill kit. The briefing package was received March 11, 2016.

After review of the briefing package, FDA sent preliminary responses to Sunovion's questions on April 11, 2016. In an email dated April 12, 2016, Sunovion specified the following areas for further discussion at the meeting: responses to questions 4.2.1; 4.1; 4.6(i); Additional comments – Biocompatibility; and OSI requests.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics* and FDA's responses (meeting preliminary comments) in normal font. Summary of meeting discussions, <u>if any</u>, are found in **bold normal font** following the specific area of discussion. The NDA submission is planned for late July 2016.

QUESTIONS AND RESPONSES

Question 4.1
Does the Division agree that the two 12 week pivotal efficacy and safety studies and 48 week long term safety study will provide substantial evidence of efficacy and safety for SUN-101 in support of an NDA submission?

FDA response:
Pending review of the data, we agree.

Additional Clinical Comment:
We note that you have captured SGRQ data as part of your phase 3 studies. We consider SGRQ to be a clinically meaningful endpoint; information regarding SGRQ will be included in Section 14 of the product label regardless of the results. We refer you to the package inserts of the recently approved Seebri Neohaler to provide guidance as to our approach to the reporting of SGRQ in product labels. Note that the information presented in the product labels reports the results of SGRQ as a responder analysis (defining a responder as one who achieves the accepted MCID for the instrument of -4). Your NDA submission should include a responder analysis of the SGRQ data.

Discussion:
Sunovion asked whether information regarding both doses would be included in the USPI since there was statistical separation of doses from placebo as well as acceptable safety profiles.

FDA responded that dose-ranging information would be included in the product label, but historically, only one dose is approved for this class of medications. Based on topline data submitted in the briefing document, the 2 doses performed similarly with no apparent differences in efficacy. Given the known cardiovascular safety signal associated with antimuscarinic medications, a careful assessment of the risk-benefit profile must be considered for each dose. Seebri Neohaler was offered as an example, in which higher doses were found to have adverse cardiovascular events; FDA referred the Sponsor to publicly available NDA reviews for further details. Taking these points into consideration, a proposal for approval of 2 doses would have to be strongly justified. FDA recommended that the sponsor propose only one dose for registration.

Regarding the SGRQ analysis comments provided in the meeting preliminary comments, FDA inquired about the results since they were not included in the meeting package.

Sunovion noted that while the analyses have not been corrected for multiple comparisons, the SGRQ responder analysis was statistically significant for both doses in both studies. Sunovion asked if the USPI would include SGRQ data for both doses and if SGRQ data would be included if the data trended in the wrong direction (against the drug).

FDA stated that the USPI would likely include SGRQ information only for the approved dose; however, final determination would be made based on full review of the data.

Question 4.1.6
Does the Division agree with the proposal to provide the clinical study report for Study SUN101-105 without integrated analyses in the 120 day safety update of the planned NDA?

FDA response:
Your proposal is reasonable.

Question 4.2.1
Given the clinical (Section 4.1) and device performance (Section 4.2.1) results, does the Division agree that the device has demonstrated suitable performance for its intended purpose in a commercial setting?

FDA response:
Overall the proposed data supports the functionality of the device for the intended use. Note that we have not reviewed any biocompatibility data for this device. General feedback relating to biocompatibility is provided under additional comments.

Discussion:
Since biocompatibility data was not presented in the briefing document, FDA stated that they are providing information about what will need to be submitted in the NDA, including the intended patient population and how the proposed device is categorized, i.e., identical to previously cleared device or biocompatibility testing conducted.

Does the Division have comments regarding the commercial 30 day replacement strategy?

FDA response:
The strategy appears reasonable. Please also validate the cleaning instructions with respect to its effectiveness on device performance under simulated use studies.

Discussion:
FDA stated that data for simulated use over 1 year should be included. Since cleaning of the device appears to impacts its performance, information about how the patient used it over 30 days as well as the condition of returned devices should also be included.

In response to Sunovion's inquiry, FDA replied that the presentation of the complaint data in the briefing document would be acceptable for the NDA.

Does the Division agree with the proposed presentation and location of the device performance information in Section 3.2.R.1.9 Device Performance?

FDA response:
We agree this is an acceptable location.

In addition, we refer you to the FDA guidance for other information on the use of the Reviewers guide for identifying the location of device information using the eCTD format. See page 1, 13-15, and 17 in the eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications"* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf.

Question 4.3
Does the Division agree with Sunovion's conclusions above regarding the cGMP requirements under 21 CFR 4 for Sunovion, the registered device manufacturer and the two (drug and co-packaging) contract manufacturers based on the proposed commercial co-packaged configurations?

FDA response:
The approach regarding which facilities are subject to which CGMP requirements under 21 CFR part 4 appears to be acceptable. The NDA should include information to support compliance with the applicable requirements; e.g., of 21 CFR 820. See "Combination Product CGMP Compliance Additional Comments" section below.

Question 4.4
Does the Division concur with the proposed registration and listing plans for Sunovion, the registered device manufacturer, and its contract manufacturers based on the proposed commercial co-packaged configurations?

FDA response:
The device constituent part manufacturer should register and list under the device requirements. If the device manufacturer is already registered, the NDA device constituent part can be added as a listing. To register or add a listing for the device constituent part of a combination product under an NDA, please contact reglist@cdrh.fda.gov. Industry users cannot currently add a listing for a device constituent part of a combination product under an NDA due to software limitations in the Device Registration Listing Module of the FDA Unified Registration and Listing System. The other registration and listing proposals appear acceptable.

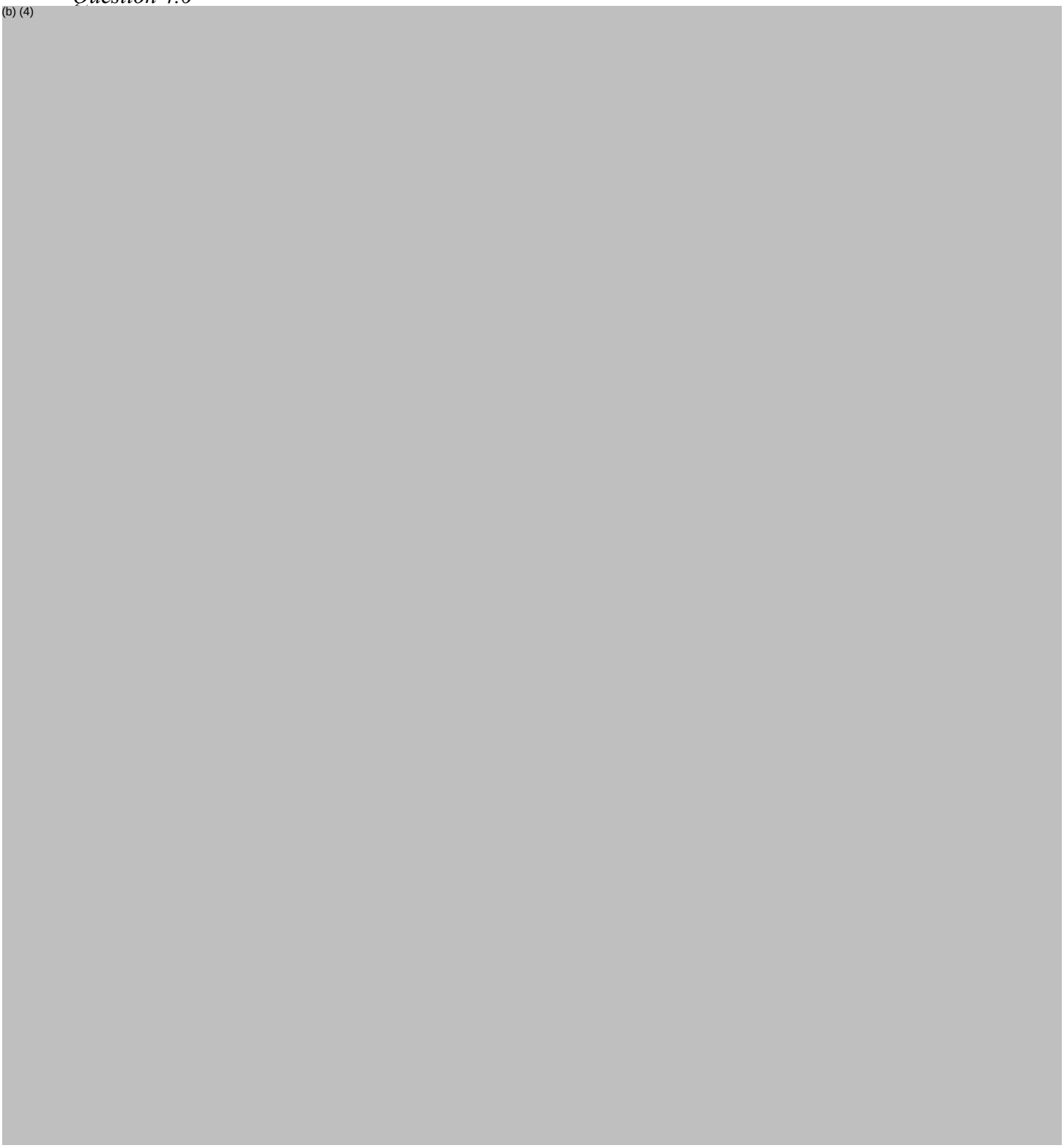
Question 4.5
Does the Division agree with the proposed Device Comparability Protocol?

FDA response:
You have not provided details of exact changes that may be underway for the device post-NDA approval. Your proposed changes appear too broad for an agreement at this

stage. It is premature to review the comparability protocol without understanding the exact nature of changes that will be made to the device.

Question 4.6

(b) (4)



(b) (4)

i) Does the Division have any additional feedback on Sunovion's proposed configurations and/or labeling considerations?

FDA response:
We recommend that each low density polyethylene (LDPE) vial is individually wrapped, with the proprietary name appearing on the foil package/overwrap.

Discussion:

(b) (4)

Additional Comments:

I. Biocompatibility:

Please provide a complete summary of all materials that may come into contact with the patient's skin or the patient's airway. We consider the components which contact the humidified gas path of the patient (i.e., delivery tubing, inside of patient interface) external communicating components with tissue contact.

If *identical* materials are used as your own previously cleared device with the same type and duration of patient contact, you may identify the predicate device in lieu of performing biocompatibility testing. We recommend the following statement for biocompatibility certification of previously used materials:

"The [polymer/metal/ceramic/composite name] [component name] of the [subject device name] is identical to the [component name] of the [predicate device name] as it was approved in [PMA/510k/IDE number, approval date] in formulation, processing, and sterilization, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.)."

If biocompatibility testing is conducted, we recommend that you provide reports on testing that was conducted in accordance with FDA General Program Memorandum #G95-1:

(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080742.htm).

The test strategy should be based on the type and duration of patient contact. To characterize the biocompatibility of your device, you should provide a comprehensive summary of all components and accessories that may come into direct contact with the patients or that may be exposed via indirect contact. For each contacting component or accessory within the respiratory gas pathway, you should also identify the ceramics, polymers, plasticizers, additives, cross-linkers, metals/metal alloys, colorants and pigments, and inks used in device manufacture. Qualitative information on processing additives (e.g., mold-release agents) should also be provided. In discussing the type of patient contact and the duration of use, you should take into consideration the potential for repeated exposures, which may have a longer cumulative duration of use. Biocompatibility testing of the device components should be conducted in accordance with ISO 10993 series of standards.

For externally communicating devices with prolonged contact (24 hours – 30 days) with circulating blood, we generally recommend that the biocompatibility testing include cytotoxicity (per ISO 10993-5), sensitization, and irritation or intracutaneous reactivity (per ISO 10993-10), sub-chronic systemic toxicity (per ISO 10993-11), hemocompatibility (per ISO 10993-4) and genotoxicity (per ISO 10993-3). Please characterize the "extractables" and leachables" (E&L) of the device components in contact with the respiratory gas pathway. Additionally, you should provide test results on the particulate matter and volatile organic compound (VOC) content to verify that there are unacceptable levels of hazardous contaminants in the user air stream under conditions of intended use.

A. When reporting the results of E&L testing, we are especially interested in the description of the test article (e.g., common name and model number); the extraction conditions utilized (e.g., the polarity of test extractants), time and temperature conditions for extraction; the limit of detection for analyses; test controls (e.g., reference standards), if used; and limitations of the analysis.

    1. Your test report should include qualitative and quantitative estimates of the specific residuals, based on worst case exposure conditions that are likely to demonstrate residue related contamination of the gas pathway. You should provide a complete study report with the chromatographic profiles and appropriate scientific justification for the extraction and worst case conditions used. We recommend that you use ANSI/AAMI BE83:2006/(R)2011 for performing a chemical characterization of the leachables and extractables.

    2. We generally recommend that you conduct E&L testing with at least one polar solvent, and one non-polar solvent. Per ISO 10993-12, it is important to select extraction solvents and conditions that are at least as aggressive as real world use conditions.

    3. Based on the results obtained from the leachables and extractables study, you should provide a risk assessment of the residuals to address patient safety concerns using user population, route of administration and allowable limits for residual exposures as criteria for analysis. A risk assessment typically includes

- Summary of toxicity information, based on a literature review (e.g., cell or animal model, route of exposure, doses tested, summary results, and literature citations);
- The NOAEL (No observed adverse effect level), if available, and supporting information (animal model, route of exposure, doses tested, summary results and citations);
- The LOAEL (low observed adverse effect level), if available;
- A summary of other toxicity information from the literature.

For determining allowable limits, please refer to ISO 10993-17.

B. Provide a quantitative physicochemical characterization of the emissions of airborne particulates (e.g., using National Institute for Occupational Safety and Health Method No. 0500) and VOCs (e.g., using U.S. EPA Compendium Method TO-15, "Determination of Volatile Organic Compounds (VOCs) In Air…") under simulated use conditions. Results should be used to determine whether particulate matter or VOC levels are above or below recommended exposure limits. As with our recommendations on extractables and leachables, you should conduct an exposure risk assessment. For comparison, we recommend that you also sample ambient air. Prior to testing, you may also want to provide an estimation of the duration of sampling required given the detection limits of the test apparatus, and then extrapolate the results to user exposure under worst case scenario conditions (e.g., highest frequency and longest duration of product use per product labeling).

II. Combination Product CGMP Compliance:

For a combination product facility that will manufacture under the 21 CFR 210/211-based operating system, the following reflects the information you should have available upon inspection to demonstrate compliance with each of the listed requirements. Additionally, in the NDA include a summary of the information with the submission to facilitate review.

A. Management Responsibility, 21 CFR 820.20

1. You should have a description of the management executive who is responsible for establishing your policy and objectives for quality and ensuring that the quality policy is understood, implemented, and maintained at all levels of the organization.
2. You should have a description of the organizational structure established and maintained to ensure that the combination product is designed and produced according to the quality policy. The description should identify the responsibilities, authorities, and interrelations of the personnel who manage, perform, and assess the work affecting quality, ensure the adequate resources to do the work.
3. You should have a description of who reviews the suitability and effectiveness of the quality at defined intervals to ensure that the quality system satisfies the requirements of the established quality policy and objectives.

4. You should establish a quality plan which defines the quality practices, resources, and activities relevant to the combination products design and manufacture, along with the appropriate quality system procedures and instructions.

B. Design Controls, 21 CFR 820.30

1. You should provide an explanation of where in your design and development process the combination product became subject to design control program.
2. You should provide the design and development plan(s), or a summary of the plan(s), for the combination product under review. Your design and development plan(s) or summary should describe or reference, and assign responsibility (e.g., which persons or operational unit(s) are responsible for oversight of these design elements) for the implementation of:

   - Design Inputs
   - Design Outputs
   - Design Review
   - Design Verification
   - Design Validation
   - Design Changes

   Your plan or summary should describe how you made decisions regarding the device constituent part of your combination product, such as:

   - How did you decide to use the particular device constituent in your combination product and how did your drug development program (see for example, application of ICH Q8 principles) identify that this device and its critical quality attributes (flow rate, droplet size, etc.) were appropriate for the end user (i.e., met the quality target product profile)?
   - What risk management activities did you conduct as part of this assessment (see for example, ICH Q9 or ISO 14971)?
   - Which stakeholders within or outside of your firm did you consult to ensure that the design of the product was appropriate for the end user(s)?
   - How did you determine that the design outputs for the combination product (e.g., specifications) ensure that the product meets requirements identified for the end user? This is typically addressed by design verification and validation activities. For your product, these activities may include bench tests, clinical experience, or other user experience.
   - How did you make decisions about whether to implement changes to the device constituent part during product development and how were these changes documented, reviewed, and approved?
   - What procedures are in place to ensure conduct of design reviews, and appropriate review and approval as changes are made and design and development evolves?

3. You should document the design control activities in the Design History File (DHF) and submit the location of the DHF to the Agency.

C. Purchasing Controls 21 CFR 820.50

You should document the oversight of the supplier(s) of the device constituent part. You should demonstrate that you have:

- a formal program by which you identify appropriate supplier(s) to provide the device constituent part,
- a formal mechanism to communicate changes between your firm and the supplier (both changes initiated by the supplier or changes initiated by your firm.

If you have a quality agreement that addresses these issues, you should confirm that you maintain the records pursuant to the agreement at the facility that receives the device constituent.

D. Corrective and Preventive Action 21 CFR 820.100

You should have a description of how issues including non-conformances and manufacturing problems regarding the combination product, including each constituent part, are incorporated and considered by corrective and preventive action system.

Discussion:

Sunovion asked if FDA had any general guidance for smooth filing and review of the NDA.

FDA stated that there is extensive knowledge already available about the drug and disease; uniqueness of this application is in the device. Any additional efforts should be placed on meeting the regulatory requirements for the device, as noted in the "Additional Comments" section above.

FDA noted that the device uses a vibrating mesh membrane and that they had not expected to see clogging occurring with the drug product. Although having a replacement strategy is good planning, the sponsor should continue to investigate the root cause of the clogging.

Sunovion noted availability of cleaning validation data with protein and carbohydrate markers from simulated use studies.

FDA responded that submission of cleaning validation data may not be necessary, but sponsor should provide information whether clogging occurs even with 30-day replacement of the aerosol head and handset - which may be exhibited as increased nebulization time.

Additionally, location of device information (e.g., design control, manual) in the eCTD can be specified in the reviewer guide, and hyperlinks can be provided to aid review.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance

is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

Discussion:

For subsections I.3 and II below, Sunovion asked if the requested information can be submitted with responses to the 74-day letter since there are approximately 90 clinical sites.

FDA replied that OSI will be consulted and response provided as post-meeting clarification in the minutes of this meeting.

FDA post-meeting clarification:
Although the application should be complete at submission, it may be acceptable to provide the requested information in OSI subsections I.3 and II, within a reasonable timeframe after issuance of the 74-day letter.

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

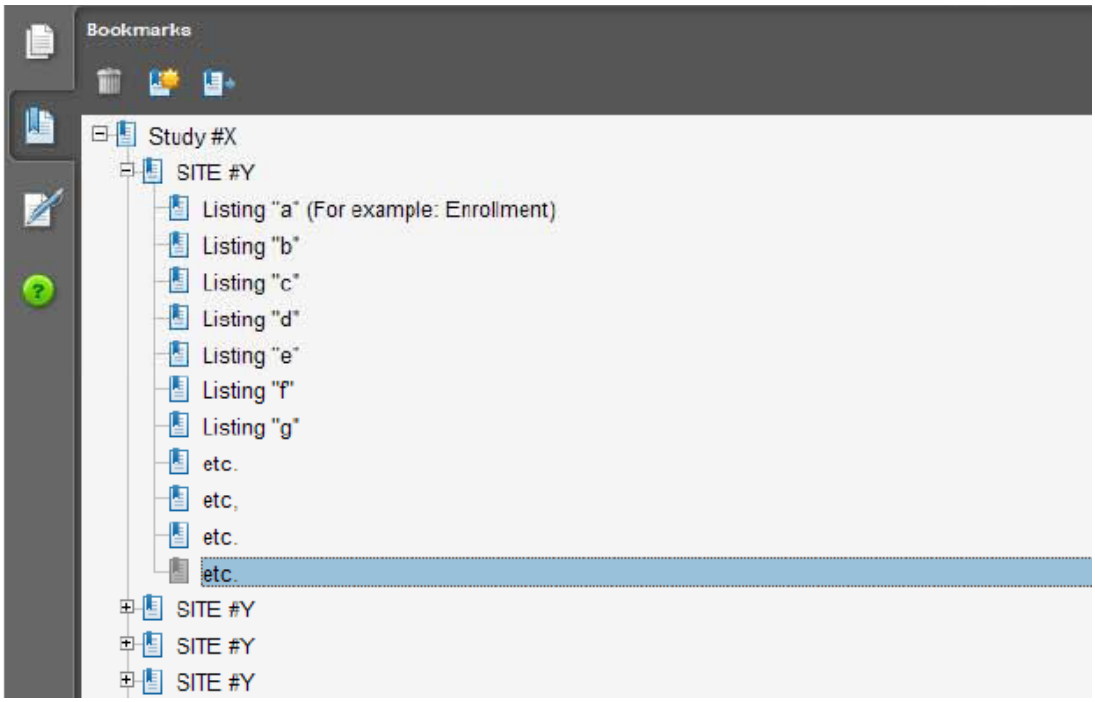
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION:

See post-meeting clarification provided in the body of the minutes.

ATTACHMENTS AND HANDOUTS:

None.

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

/s/

CHRISTINE H CHUNG
05/11/2016
Christine Ford (formerly Chung)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110663

MEETING MINUTES

Sunovion Respiratory Development, Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Attention: Helen Milton, Ph.D.
Sr. Director, Regulatory Affairs

Dear Dr. Milton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glycopyrrolate inhalation solution (GIS).

We also refer to the meeting between representatives of your firm and the FDA on September 17, 2013. The purpose of the meeting was to discuss the development program completed to support the NDA for use of GIS delivered by the eFlow nebulizer for the maintenance treatment of patients with COPD.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2 (EOP2)

Meeting Date and Time: September 18, 2013
Meeting Location: White Oak Building 22, Conference Room: 1415

Application Number: IND 110663
Product Name: glycopyrrolate inhalation solution (GIS) [SUN-101]
Indication: Chronic obstuctive pulmonary disease (COPD)
Sponsor/Applicant Name: Sunovion Respiratory Development, Inc. (Sunovion)

Meeting Chair: Badrul A. Chowdhury, Director
Meeting Recorder: Christine Chung, Regulatory Project Manager

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, M.D., Deputy Director, DPARP
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP
Kimberly Witzmann, M.D., Clinical Reviewer, DPARP
Marcie Wood, Ph.D., Supervisory Pharmacologist, DPARP
Christine Chung, R.Ph., Program Coordinator, DPARP
Craig Bertha, Ph.D., CMC Lead (Acting), Division of New Drug Quality Assessment (DNDQA) III
Xiaobin Shen, Ph.D., Product Quality Reviewer, DNDQA III
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCPII)
Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer, DCPII
Joan Buenconsejo, Ph.D., Biometrics Team Leader, Division of Biometrics II (DBII) Analysis (DMEPA), Office of Surveillance & Epidemiology (OSE)
Lissa Owens, Pharm.D., Safety Evaluator, DMEPA
Quynh Nhu Nguyen, Human Factors Protocol Reviewer, Division of Anesthesiology, General hospital, Respiratory, Infection control, and Dental devices (DAGID), CDRH
Sugato De, Respiratory Devices Branch, CDRH
Bindi Nikhar, M.D., Acting Clinical Advisor, Office of Combination Products
Anya Harry, M.D., Acting Chief, Medical Officer, Respiratory Devices Branch, CDRH

SPONSOR ATTENDEES

Stewart Mueller, MS, MBA	Senior Vice President, Global Regulatory Affairs and Quality Assurance
Helen Milton, PhD	Senior Director, Regulatory Affairs
Renee M Carroll, MS, RAC	Senior Director, Regulatory Affairs
Fred Grossman, DO	Senior Vice President, Clinical Development and Medical Affairs
Alistair Wheeler, MD, MFPM	Vice President, Clinical Development and Medical Affairs
Michael Edwards, PhD	Associate Director, Clinical Development and Medical Affairs
Gary Maier, PhD	Vice President, Clinical Pharmacology
Robert Tosiello, MS	Executive Director, Biostatistics
Raymond Claus, MS	Director, Biostatistics
Ahmet Tutuncu, MD, PhD	Clinical Consultant, Sunovion Respiratory Development Inc.
John Salveta, MS	Director, Regulatory Affairs
Andrea Bauer, PhD RAC	Senior Director, Formulation Development
Siriporn Toongsuwan, PhD	Associate Director, Formulation Development
Chris Ott, PhD	Director, Quality Assurance
Colleen Synan, MS, DABT	Principal Scientist, Toxicology
James F. Donohue MD	Consultant, University of North Carolina

BACKGROUND:

Sunovion is developing glycopyrrolate, a long-acting muscarinic antagonist (LAMA) bronchodilator, as inhalation solution for delivery using PARI's eFlow nebulizer (closed system, portable, electronic). Proposed indication for GIS is for long term, twice daily maintenance treatment of bronchoconstriction in patients with COPD. Sunovion requested this EOP2 meeting to discuss the development program completed and to reach agreement with FDA on the proposed phase 3 development plan to support the NDA. The briefing package for this meeting was received August 8, 2013.

After review of the meeting package, FDA provided meeting preliminary comments to the sponsor's questions via a letter on September 16, 2013.

Sunovion emailed slides and specified areas for further discussion regarding FDA Introductory comments 1, 2, 3, and 5, as well as responses for Questions 2, 8, and 9. Time permitting, Sunovion also requested to discuss FDA responses to Clinical Development Questions 5 and 6, and Chemistry, Manufacturing, and Controls (CMC) Question 7, only the last paragraph regarding the timing of summative usability studies. Slides emailed by Sunovion before the meeting on September 17, 2013, are included as an attachment at the end of the minutes.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics* and FDA's responses (meeting preliminary comments) in normal font. Summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

QUESTIONS AND PRELIMINARY RESPONSES

FDA Introductory Comments:
We have reviewed your briefing package in preparation for the EOP2 meeting scheduled for September 17, 2013, and have the following preliminary comments:

1. It is premature to discuss your phase 3 program for SUN-101 as a treatment for reversible airflow obstruction as you have not adequately characterized the dose-response for SUN-101 to the extent needed to select a dose(s) for phase 3 trials. While the Golden-1 study effectively demonstrated that SUN-101 is a twice daily inhaled antimuscarinic agent, the Golden-2 study, in which patients with COPD were dosed twice daily, does not support the selection of any particular dose(s) studied. Specifically, Figure 6 on page 38 of the briefing document demonstrates substantial drug activity for even the 2 lowest doses, 12.5 and 25 mcg twice daily. In particular, the 25 mcg twice daily dose performed very similarly to your proposed 100 mcg twice daily dose. The finding that doses 4 or more times lower than your proposed dose of 100 mcg twice daily perform similarly to the 100 mcg dose is highly suggestive that the proposed 100 mcg dose is too high. In addition, the death of a 52 year-old man with COPD who received the same daily dose of SUN-101 as you propose (200 mcg total daily dose) from a myocardial infarction is also highly suggestive that the 100 mcg twice daily dose is not only too high but potentially dangerous. As a result of the findings described above, you will need to conduct at least one additional dose selection study.

When designing the study, keep in mind that because of the potential cardiovascular risk for inhaled antimuscarinic agents, we expect adequate characterization of the low end of the dose-response curve, including identification of a dose which could be viewed as likely ineffective. As such, we highly recommend you include a dose or doses less than 12.5 mcg twice daily, which was the lowest dose studied in Golden-2. Also, consistent with the strong recommendation we conveyed to you at the Pre-IND meeting held on March 2, 2011, in written responses provided on June 20, 2012, and during the teleconference with you on September 17, 2012, we continue to believe you should carry more than one SUN-101 dose forward into phase 3 trials.

Discussion:

With regard to dose-exploration, FDA stated the following:

- **In general, we look for a separation of doses and try to identify a dose that clearly is not effective. We want to have a dose at the lower end of the dose-response curve to serve as a benchmark from which to judge the added effect of higher doses. For example, in your Golden-1 and -2 studies, it appears there is still substantial activity of the 12.5mcg dose, and the 25mcg seems better than the 50mcg dose, which suggests a plateau has been reached; higher doses may provide no additional efficacy, but will be concerning for safety, especially in the context of known LAMA safety issues.**
- **We are therefore looking for a dose-finding study, similar to your Golden-1, which would evaluate your lowest feasible dose (perhaps 6.25mcg), with doses up to 2- to 4-fold higher, and a LAMA benchmark (such as tiotropium) for 7 days; we would expect one dose to drop out, and it would be reasonable to assume no effect at that dose.**
- **We recommend your dose-finding study(ies) include as many doses as you feel necessary to clearly define a clearly ineffective dose, that they have a homogeneous patient population, and a larger N than in previous studies to reduce variability (noise).**
- **Using trough FEV1 as an endpoint is not unreasonable, but looking at AUC_{0-12} data is also important for optimal dose identification.**
- **We strongly recommend that you take 2 doses forward into Phase 3.**
- **While use of the 100mcg dose will not lead to a clinical hold, we believe this dose is too high and doubt that it would be an acceptable dose to take into Phase 3.**
- **Once dose-finding data have been obtained, sponsor should request a Type C meeting before moving into Phase 3.**

With regard to the discussion of the patient in Golden-1 who died:

We considered the 100mcg dose of your drug to likely be too high, even before consideration of the reported death. However, in the context of ongoing concerns about LAMA cardiovascular safety issues, it cannot be disregarded as an outlier event in a patient with preexisting cardiovascular disease; this patient

is characteristic of your proposed treatment population of older, sicker patients with COPD who would more likely prefer nebulized therapy.

2. A more general consideration for your SUN-101 development program is the size of the safety data base. While the size of your proposed safety data base would likely include at least 100 patients treated for at least one year, it is grossly inadequate to assess the safety of an inhaled antimuscarinic agent in an older population with many known cardiovascular, respiratory, and metabolic risk factors. We strongly recommend you look at the label of more recently approved antimuscarinic agents for COPD patients to get a feel for what would be the minimal size of the safety data base for your SUN-101 program.

Discussion:
Refer to Sunovion's slide #5, "Patient Exposure at Time of Registration." Sunovion asked about the comparison of the safety database needed between a 505(b)(1) and a 505(b)(2) product.

FDA responded with the following:

- **SUN-101 would be a first glycopyrrolate product for COPD, so it is advisable to have an adequate safety database, both in numbers and one that adequately reflects the severity of COPD and other co-morbidities of the patients likely to use the drug. For example, at a recent PADAC meeting, committee members noted that patients enrolled in the Breo Ellipta COPD studies "were not very sick." Because the Phase 3 trials did not evaluate a "real world" population, reflective of the patients who would be prescribed the drug, a recommendation was made that an additional post-marketing study be required. In addition, at another PADAC meeting for aclidinium, there were concerns that the size of the safety database for aclidinium was not sufficient, even though it was significantly larger than that proposed for SUN-101.**
- **Because FDA's view of LAMA safety in the COPD population is evolving, a specific number defining an adequate safety database cannot be provided. However, FDA suggested that Sunovion consider safety databases of other LAMA products at the time of approval to get a sense for what they would need. FDA noted that if a reasonably large safety database does not exist, a large post-marketing safety study may be likely.**
- **In response to Sunovion's inquiry, FDA strongly encouraged the sponsor to have an independent adjudication committee for a COPD study, especially for MACE and stroke-related events.**

3. We do not agree with your plan (and consider it unethical) to exclude the use of medications considered as "standard of care" for patients with COPD, such as LABAs, in your proposed phase 3 trials. As such, patients receiving LABAs prior to being enrolled in any phase 3 trial should be allowed to continue. You could consider stratifying for LABA use at randomization.

Discussion:
Sunovion expressed concern that inclusion of LABA use in the study would result in a small effect size and asked whether shorter term exclusion may be acceptable.

FDA stated that they understood that the effect size will be smaller for one drug when used with multiple standard of care medications; a smaller effect size has been taken into account for other programs. FDA noted that 12-weeks off of standard of care therapy is too long for a COPD population that is older and sicker, and would otherwise be prescribed LABAs. FDA encouraged the sponsor to look at exacerbation data carefully since even a nominal decrease in exacerbations would provide more evidence to support safety and efficacy. The Sponsor should also consider that triple therapy regimens (LABA/LAMA/ICS) are now being used for COPD patients.

4. We consider assessment of COPD exacerbations as an important component of COPD programs regardless of whether exacerbations are the primary endpoint and would expect at least a trend toward a decrease in exacerbations in favor of SUN-101 treatment. As such, while it is not the primary or a key secondary endpoint, you should carefully assess the frequency of and time to exacerbation in any phase 3 trial.
5. If approved, SUN-101 will likely be available to be prescribed to any COPD patient regardless of the presence or severity of concomitant risk factors. Therefore you should include all types of COPD patients, regardless of the presence or severity of concomitant risk factors, in any proposed long-term safety trial.

Discussion:
FDA added that PADAC is looking for "real world" use data, so including COPD patients with concomitant risk factors in the phase 3 program may mitigate the need for post-marketing commitments.

Clinical Development

Question 1: *Does the Division agree that the data and provided population PK analysis obtained from the completed clinical pharmacology studies are adequate to proceed with the proposed COPD clinical development program and that no additional clinical pharmacology studies are required for the proposed market application?*

FDA response:
We agree that no additional clinical pharmacology studies are required for the proposed product. However, adequacy of the collected data will be a review issue. Further, we advise you to use appropriate population PK approach when handling the drug concentrations that are below the lower limit of quantification, if any.

Question 2: *Sunovion requests the Division's opinion on the submitted Phase 3 clinical protocols and in particular the adequacy of the following to support the proposed indication:*
a. The selected dose and regimen
b. The endpoints proposed and key elements of the statistical analysis

c. The number of patients
d. The patient population

FDA response:
See FDA Introductory Comments above.

Question 3: *Several additional endpoints (FEV1 AUC[0-12] and AUC [12-24], peak FEV1, and time to onset of FEV1) will be determined in a subset of the population studied over a 24-hour period in one of the placebo-controlled efficacy studies and replicated in the 12-month safety study with active control. Does the Division agree with this approach?*

FDA response:
We agree that serial spirometry in a subgroup, performed at baseline and the end of the study period, is appropriate. However, as we stated during teleconference on September 17, 2012, given the variability of bronchodilator response patterns in the COPD population, we believe that 25 patients per arm in one double blinded study may not be sufficient to determine 12-hour FEV1 curves. Your proposal to add a serial spirometry group to the open-label, active control study will not address this, because the serial spirometry data between it and the double-blind study cannot be combined. As such, we recommend increasing the number of serial spirometry patients per arm in one double blinded phase 3 study.

Question 4: *The change from baseline in the Saint George's Respiratory Questionnaire for COPD patients (SGRQ-C) total symptom score will be assessed as a key secondary efficacy variable in the 2 pivotal efficacy studies. Does the Division agree, subject to review, that if both placebo-controlled studies demonstrate statistically significant and clinically meaningful differences compared to placebo, this information can be included in the prescribing information?*

FDA response:
In order for this information to be included in labeling, you will need to demonstrate replicate evidence of a statistically significant and clinically-meaningful change (MID is typically -4) in SGRQ (change from baseline compared to placebo). Note that because of lack of experience with the SGRQ-C, you should use the original SGRQ as the PRO instrument. In addition, we remind you that all patient-reported outcome measures (EXACT-PRO, SGRQ, etc.) should be completed at each study visit prior to any interview, examination or clinical testing procedures.

(b) (4)

(b) (4)

Question 7: *The pivotal efficacy studies will be conducted in the US only. The long-term safety study will be conducted internationally, with approximately 30% to 40% of subjects recruited in North America. Is this anticipated regional distribution acceptable to the Division?*

FDA response:
This will be a review issue. As long as the patient population in the open-label safety study can be generalized to that of the US COPD population evaluated in the phase 3 DB clinical trials, this would be acceptable. In addition, see FDA Introductory Comments with regard to the patient population recommended for long-term, open-label safety studies. Also note that study drugs used (including albuterol and tiotropium) need to comply with US-approved doses and devices.

Question 8: *Does the Division agree with the analytical approach for the primary efficacy endpoint in each of the 2 pivotal Phase 3 studies?*

FDA response:
The assumption of missing-at-random mechanism is not scientifically convincing because bronchodilators are generally considered symptomatic and not disease-modifying therapies, and their effects on FEV1 likely do not persist more than a few days after patients stop using them. In your protocol, you need to specify the estimand. Discuss potential mechanisms which may cause FEV1 data to be missing, and how those mechanisms affected your selection of the primary analysis method and how this may affect the estimand.

Your protocol should also include provisions to collect outcome data for patients who prematurely withdraw from treatment, begin taking prohibited medications, or are initially classified as 'lost to follow-up.' Reasons for study withdrawal should be limited to loss to follow-up, withdrawal of consent, and death. This approach helps prevent missing data, so that intention-to-treat analyses do not rely on imputation based on untestable assumptions. Collection of information on the rescue medications received by patients after discontinuation of study treatment may be helpful for exploratory analyses.

Discussion:
Discussion ensued regarding FDA's responses to Questions 8 and 9.

The sponsor acknowledged our concern regarding the primary analysis, specifically on the assumption of missing at random, and provided further clarification on the sensitivity analyses proposed.

One of the sensitivity analyses discussed at the meeting was the pattern-mixture model with placebo subjects' values as the basis for imputing missing values for all treatment groups. FDA noted that while this approach seems reasonable, they also cautioned Sunovion that there may be some limitations to this approach given that the placebo subjects who completed the trial and on which imputation will be based on, are likely to be different from those placebo subjects who did not complete the trial. There was a short discussion on the different types of estimand and that Sunovion should clearly specify what they intend in their protocol. FDA also emphasized the need to continue collecting efficacy (and safety) data when a subject discontinues treatment since this helps prevent missing data. FDA also recommended that Sunovion use all available data (including post-withdrawal data) in the primary analysis. FDA encouraged Sunovion to submit their statistical analysis plan along with their protocol to the IND for review.

Question 9: *Does the Division agree with the approach for assessing the robustness of the analyses to the presence of missing data?*

FDA response:
We need more details on the proposed sensitivity analyses before we can provide any comments.

Question 10: *Does the Division agree with the approach for controlling the Type I error rates for the primary and key secondary efficacy endpoints for each of the 2 pivotal Phase 3 studies?*

FDA response:
The proposed approach for multiplicity adjustments appears reasonable.

Question 11: *Does the Division agree that the planned program provides sufficient clinical exposure in this patient population to support review of the NDA and approval of an indication for the maintenance treatment of bronchoconstriction in patients with COPD?*

FDA response:
We do not agree. See FDA Introductory Comments.

Question 12: *Sunovion proposes to include appropriate safety monitoring in the Phase 3 trials to ensure safe use of SUN-101 during these clinical studies. Taking into account the safety data from the Phase 2 clinical studies, which did not identify any major adverse health outcome that would require additional oversight, Sunovion does not intend to include a Data Safety Monitoring Board (DSMB) in the Phase 3 trials. Does the Division concur with this approach?*

FDA response:
We do not agree. See FDA Introductory Comments. The clinical safety profile of LAMA drugs, especially with regard to MACE and stroke events, has been discussed at recent Advisory Committee meetings, and remains a concern for this sick patient population. Your protocols should propose a plan to formally monitor for MACE and other prospectively identified adverse events of interest. The monitoring plan should include an Adjudication Committee review for all events of interest. To further that goal, you should continue collecting data on all patients who discontinue from the studies, to inform the outcomes database.

Question 13: *In light of the established pharmacokinetic (PK) link to the reference-listed drugs and the existing literature for inhaled glycopyrrolate formulations, a thorough QTc study is not planned with SUN-101. Does the Division agree with this approach?*

FDA response:
Your briefing package stated that the systemic levels of your proposed glycopyrrolate inhalation solution are lower than that of the approved reference listed drug, and assessment of QTc intervals in routinely collected ECG recordings did not show any increase in QTc intervals. Considering these findings, a formal QTc study will not be required. However, adequacy of these data will be a review issue

Question 14: *We propose that this application can be granted a waiver of the pediatric study requirement - does the Division agree?*

FDA response:
Waivers for pediatric study are determined at the time of NDA review. However, it is reasonable to propose that the application could be granted a waiver at that time, since COPD is an adult-specific disease.

Chemistry, Manufacturing, and Controls (CMC)

Question 1: *Does the Division agree with the proposed drug product One-Time Characterization studies?*

FDA response:
The characterization studies you proposed are mostly consistent with some of those applied to nasal and inhalation sprays as outlined in the guidance (*Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation. July, 2002*). We have the following comments regarding your proposal.

a. In most cases, you proposed to perform the study with one registration batch. While using one batch may be sufficient to demonstrate some effects when an adequate number of replicates are used, for a more complete study of possible impact of batch related factors, we recommend two or more batches to be tested, as documented in the guidance.

b. We recommend that when you design your temperature cycling and shipping studies, you consider temperature exposure extremes that may be likely encountered (e.g., high and low temperatures encountered in mail order shipping with uncontrolled environmental conditions).

c. The aforementioned CMC guidance recommending characterization studies for dosing orientation was more intended for spray pump and actuator based products. For nebulizers, such as the eFlow device, the optimal dosing orientation is the position that allows complete dosing based on the basic principle of physical contact of solution and nebulizer. Therefore, it may not be necessary to conduct this study.

Question 2: *Does the Division agree with the proposed test plan for aerosol characterization study for dose labeling?*

FDA response:
Your proposal appears acceptable.

Question 3: *Based on the drug assay and impurity profile test results of nebulized SUN-101 using the Phase 3/to-be-marketed devices, does the Division agree that nebulization does not have an adverse effect on the aerosol impurity profile and that further characterization studies are not necessary?*

FDA response:
Based on our preliminary review of the data provided, it appears that nebulization does not have an adverse impact on the impurity profile of the drug product. Provided that the impurity analysis method used is adequately validated and suitable for this study, we do not expect further characterization studies related to nebulization on aerosol impurity profile.

Question 4: *Based on the registration stability plan and the Extractables/Leachables Study, does the Division agree that the information that will be provided adequately supports drug registration?*

FDA response:
We are in general agreement with the registration stability plan and Extractable/Leachable studies, and it is likely that they will generate the necessary data needed for our evaluation of your drug product.

Question 5: *Does the Division agree with the proposed information embossed on commercial ampoules?*

FDA response:
We do not agree. In addition to the proposed information, you should also emboss product strength on the vial.

Question 6: *Does the Division agree with the proposed plan to demonstrate the robustness of the device?*

FDA response:
Your proposed test plan for the robustness of the device appears reasonable.

Additionally, we remind you that a clinical return study on the nebulizers used in phase 3 clinical study should be conducted. Specifically, any eFlow CS nebulizer used in the phase 3 trial that malfunctions, has medical device reportable events, or is associated with patient complaints or patient adverse events should be properly documented, examined, and tested for route cause analysis. In addition it should have a performance evaluation that includes but is not limited to nebulization performance in terms of delivered dose and aerodynamic particle size distribution (APSD). Also, an adequate number of eFlow CS nebulizers used in the phase 3 trials that appear to function normally by the completion of the trials, should be returned and tested for performance parameters (i.e., delivered dose and APSD). Both study reports should be included in your NDA submission.

Question 7: *Does the Division agree with the design of the proposed protocol for the Summative Usability testing?*

FDA response:
We do not agree. Address the following comments regarding your protocol and submit a revised protocol for review:

a. You state that the Summative usability test is being conducted for three purposes; the first is to ensure that the nebulizer is not vulnerable to potentially harmful use errors that could lead to patient injury or death or delay in therapy or sub-optimal therapy. The other two purposes have to do with usability goals and additional insights which are not priorities for Agency Review. Missing from the first goal is consideration of use error causing clinically relevant delay of therapy or sub-optimal therapy in addition to “injury and death”. Update your stated purpose for these potential

outcomes in your Summative Usability Testing accordingly. Note that we will expect these to be covered in the analysis and testing regardless of the stated purpose. If there are no possible use error scenarios that could lead to clinically relevant delay of therapy or sub-optimal treatment, then this should be stated based on the results of your analysis of use-related risks.

b. The Use error detection section under Methodology states that one of the methods you will use to detect use errors will be to interview test participants following completion of a given hands-on task. Asking users for feedback after individual tasks can interrupt naturalistic flow of user-interaction however this may not be the case for the subject device. Add to your protocol an explanation of how this technique will not impact the naturalistic flow of user interaction in your planned testing.

c. You have described your intent to collect "operational difficulties" in your protocol, however, indicate how you will analyze any operational difficulties you identify with respect to use error risk and device use safety. If you do not intend to discuss operational difficulties in the context of clinical significance and the adequacy of the design of the user interface, clarify this in your report.

d. The protocol does not include interview questions directed towards any failure errors that users experienced while using the device. We view this component of subjective assessment as being of critical importance when reviewing HF/Usability validation testing. Modify your protocol to include direct discussion of any and all failures of critical tasks by any test participant who fails to perform a task correctly. Note that failures should be defined as actions or failure to act that would potentially or inevitably cause a negative clinical impact. We also ask that you include questions about use errors/close calls/reported difficulties that may result in patient harm.

e. Your Summative Usability Test protocol describes how tasks will be selected for testing. You mention a list of use errors addressed in the sponsor's FMEA with numerical estimates of the event's frequency and severity of consequences yielding a risk priority number. You identified use errors as failure modes with RPNs of at least 50, and potential operational difficulties as failure modes with RPNs of less than 50. We expect that priority should be based on the possibility of an error. Review the FMEA and other sources of risk identification and revise your task selection process if and as appropriate for the purposes of your testing. Also, provide your use-related risk FMEA along with the revised protocol.

f. You have indicated your intent to collect various kinds of data and perform analyses such as task times, and user rating scales. In addition, you defined the objective usability goals in terms of average task time and the subjective usability goals as average rating of 5.5 and above. Unless you believe that these data can be used to support a safe and effective use conclusion, note that when your Summative Usability report is reviewed, task failures and their implication, responses to open ended questions by test participants regarding performance failures, close calls, critical tasks, and overall use will be reviewed specifically. We advise you to ensure that reporting and evaluation of this data is not obscured by reporting other kinds of data collection and analyses and that any information reported could lead to a need for clarification if its relevance to use safety and effectiveness is not clearly explained.

Your use-safety analysis should focus not only on use errors, close calls and operational difficulties but subjective as well.

g. The testing provider has stated that they will not render a decision on whether or not the inhaler has passed or failed the Summative usability (validation) test. (The proper follow-up of the usability test is a review of objective performance data for each task.) We do not request the pass/fail result of the usability test; however, we do request that you use the collected HF/Usability data to support a conclusion that the device is safe or not safe for the intended users, intended uses, and use environments. Include in your report, the nature of all performance failures (not only the number of such failures), the test participant subjective assessments of them, critical and essential tasks, and the use of the device overall.

h. The instruction for use was not submitted for our evaluation. Submit the IFU for our review; we may have further comments and/or recommendations on the IFU.

In addition, we request that you submit the human factors summative usability (validation) protocol for review and comment before beginning the study. We also recommend that the summative usability (validation) study be completed before beginning Phase 3.

Discussion:
FDA reiterated that, although previous guidance stated that usability studies would be acceptable during Phase 3, it would be in the best interest of the sponsor that the summative usability study(ies) be conducted before Phase 3; this would allow the completed user interface design to be studied within the Phase 3 program.

Question 8: *Based on the 1-year simulated use test results, does the Division agree that the 1-year simulated use data are adequate to support the in-life duration of the open label and the planned Phase 3 clinical studies?*

FDA response:
The simulated use data is adequate to support phase 3 studies.

Nonclinical Development

Question 1: *Does the Division agree that studies conducted to date along with data to be referenced from approved NDAs (as listed in Table 25) will be sufficient to support the Phase 3 program and review of the NDA for approval in patients with COPD?*

FDA response:
We agree.

Electronic Submission

Question 1: *Does the Division concur with Sunovion's plan for the organization of the data definition file and is it acceptable to provide a define.xml for the 4 studies in CDISC format, and to provide a define.pdf for the 3 legacy studies?*

FDA response:
We agree.

Question 2: *Is the proposed format regarding the datasets for raw clinical data and analysis acceptable?*

FDA response:
We agree.

Additional FDA Comments:

As a combination product we remind you that it must comply with 21 CFR Part 4 Current Good Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2)

application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR

314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ATTACHMENTS:

Slides emailed by Sunovion on September 17, 2013

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

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

/s/

CHRISTINE H CHUNG
10/17/2013