CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205920Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205496

REFUSAL TO FILE

Armstrong Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs
25 John Rd.
Canton, MA 02021

Dear Dr. Campbell:

Please refer to your New Drug Application (NDA) dated 2 April 2013, received 8 April 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Primatene® HFA (epinephrine inhalation aerosol USP, 125 mcg/actuation).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. The application is not *organized* in a manner to allow substantive review to begin. For example, it is not indexed and paginated appropriately. A separate section title "Orphaned Files" is included; it is not apparent what clinical data are or are not included in these files.
   - Significant filing deficiencies related to the electronic submission were communicated to you at a teleconference on April 25, 2013.
   - Documents do not conform to format specifications for eCTDs or to requirements stipulated in 21 CFR 314.50(c)(1) or 21 CFR 314.50(d)(5).

2. The application cannot be *navigated* in a manner to allow substantive review to begin. For example, hyperlinks between the tabular listing of studies and complete study reports are not provided. A separate, single file should be submitted for each clinical study.

3. The application does not include the required discipline summaries (i.e., Module 2 summaries). Instead of a separate Integrated Summary of Efficacy (ISE) and Safety (ISS) in Module 5, the NDA includes these documents in place of the usual summaries found in Module 2.

4. The application does not include a formal benefit-risk analysis. A summary and rationale (21 CFR 314.50(d)(5)(viii)) can be included in Module 2.

5. Narrative summaries are not provided for adverse event dropouts.

6. Case Report Forms for adverse event dropouts should be clearly identified and easily accessible (i.e., hyperlinked).

7. Study reports for the label comprehension and human factors studies did not include accompanying datasets.

8. No analysis datasets were submitted in the eCTD submission.

9. Only part of the submitted SAS codes to create the analysis datasets ran successfully. Four analysis datasets (tempfevdata, tempfevdataA, tempfevdataB, and tempfevdataC) were created. However, only a handful of variables in the analysis datasets had labeled descriptions. We were able to match some of the descriptive outputs (e.g., mean, std) for Table 7.4-2 of the study report, but not the results from the t-test. The primary endpoint variable (AUC0-6hr of Δ%FEV1) in Study D was not in any of analysis datasets. We were unable to reproduce the results summarized in Tables 7 and 8 of the Study D report. The AE datasets have no MedDRA coding.

10. No datasets for the two dose-finding studies (A and A2) were provided.

11. Subjects' disposition data that include the reasons for dropout and time of dropout for Study C and Study D were not provided.

12. We received the following sample errors in the log file when the program code E004_C_Pre_Run.sas was run:
    - Macro %getMedDra did not work
    - Macro %impData2 did not work
    - Macro %getScreen did not work
    - Macro %getPVC did not work
    - eMacro %Get_BE_Data_E004_C did not work
    - ERROR: At least one file associated with fileref SHARED is still in use; ERROR: Error in the FILENAME statement
    - ERROR: At least one file associated with fileref PRERUN is still in use
    - ERROR: At least one file associated with fileref SUMMARY is still in use
    - ERROR: At least one file associated with fileref INDIVID is still in use
    - %GetXportData(F_F22, F_F22); ERROR 180-322: Statement is not valid or it is used out of proper order
    - %GetXportData(F_F23, F_F23); ERROR 180-322: Statement is not valid or it is used out of proper order
    - ERROR: File WORK.DEVIATION.DATA does not exist. ERROR: Not all variables in the list disqualified5_0-disqualified5_7

13. We received the following sample errors in the log file when running the program code E004_D_Pre_Run.sas:
    - ERROR: Connect: Class not registered; ERROR: Error in the LIBNAME statement

- ERROR: File WORK.FEV1CONSISTENCY.DATA does not exist
- ERROR: File WORK.SCRSUMMARY.DATA does not exist
- ERROR: A character operand was found in the %EVAL function or %IF condition where a numeric operand is required. The condition was: &&scr&s; The %TO value of the %DO I loop is invalid; The macro GETSCREEN will stop executing
- ERROR: File WORK.AELIST.DATA does not exist
- ERROR: Variable AE__ not found
- ERROR: BY variable SID is not on input data set WORK.TEMP2.
- ERROR: Variable MEDRA not found
- ERROR: File WORK.PVC_ORIGINAL.DATA does not exist

14. The ISS does not include an adequate, detailed analysis of worldwide postmarketing safety data. Limited analysis from the website www.ehealthme.com is not adequate because the quality of that data is unknown. There is a lack of details of serious AEs and deaths listed in Tables 4 and 5 of the "Five Years Summary Report for Distributed Primatene Mist (CFC)." In an addendum to the minutes of the meeting on 31 January 2013, we stated that an analysis of AERS and post-marketing databases should be submitted including narrative summaries and analyses of serious cardiovascular events and deaths.

Please also submit labeling that includes annotated font specifications (21 CFR 201.66).

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call CDR Daniel Reed, Regulatory Project Manager, at (301) 796-2220.

Sincerely yours,

{See appended electronic signature page}

Shaw Chen, M.D., Ph.D.
Acting Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Amphastar Pharmaceuticals, Inc.
1170 6th St.
Rancho Cucamonga, CA 91730

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

/s/

SHAW T CHEN
06/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074286 **MEETING MINUTES**

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

Please refer to your Investigational New Drug Application (IND) file for epinephrine inhalation aerosol.

We also refer to the meeting between representatives of your firm and the FDA on January 31, 2013, that discussed the content of your epinephrine inhalation aerosol NDA submission.

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

If you have any questions, call Janice Adams-King, Regulatory Project Manager, at 301-796-3713.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

Application Number:	074286
Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	January 31, 2013 10:00AM – 11:00AM EST
Application Number:	IND 074286
Product Name:	Epinephrine inhalation aerosol
Indication:	Temporary relief of symptoms of asthma
Sponsor/Applicant Name:	Amphastar Pharmaceuticals, Inc. Armstrong Pharmaceuticals, Inc.
Meeting Chair:	Joel Schiffenbauer, M.D.
Meeting Recorder:	Janice Adams-King, R.N., B.S.N., M.S.

FDA ATTENDEES

CDER participants:

Division of Nonprescription Clinical Evaluation

Shaw Chen, M.D., Acting Director
Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Linda Hu, M.D., Medical Officer
Steven Osborne, M.D., Medical Officer
Janice Adams-King, Regulatory Project Manager

Division of Pulmonary, Allergy, and Rheumatology Products

Sally Seymour, M.D., Deputy Director for Safety
Susan Limb, M.D., Medical Team Leader
Banu Karimi-Shah, M.D., Medical Team Leader
Jennifer R. Pippins, M.D., Medical Officer

Division of Biometrics II

Yan Wang, Ph.D., Mathematical Statistician Team Leader
Feng Zhou, M.S., Mathematical Statistician Reviewer
Yunfan Deng, Ph.D., Mathematical Statistician Reviewer

Office of Clinical Pharmacology

Suresh Doddapaneni, Ph.D., Clinical Pharmacology Team Leader
Liang Zhao, Ph.D., Clinical Pharmacology Reviewer

Office of Regulatory Policy, Division of Regulatory Policy I

Martha Nguyen, J.D., Regulatory Counsel

Office of Management

Michael D. Jones, Sr. Program Manager

SPONSOR ATTENDEES

Amphastar Pharmaceuticals, Inc.
Anthony Marrs, Assoc. Vice President, Clinical Affairs
Stephen Campbell, Esq., Sr. Vice President, Regulatory Affairs
Mary Luo, Ph.D., COO, Chief Scientist
Jacob Liawatidewi, Assoc. Vice President, Business Development
Jason Shardell, SVP, General Counsel
Diane Gerst, Vice President, Quality Assurance
Ralph Tyler, Venable, LLP

1.0 BACKGROUND

In accordance with the Montreal Protocol, Amphastar Pharmaceuticals (Amphastar) no longer markets epinephrine CFC-MDI, Primatene Mist®. As a result, the Sponsor requested a second Pre-NDA, Type B, meeting for the proposed product, epinephrine (b) (4) MDI using a hydrofluoroalkane (HFA) propellant.

2.0 DISCUSSION

On January 30, 2013, FDA sent preliminary responses to Amphastar to address the questions provided in their January 3 and 21, 2013 meeting package. The questions from Amphastar appear below followed by the preliminary FDA responses in italics. The Sponsor agreed with FDA responses and agreed to provide the requested data to support the NDA. Amphastar, however, requested to have a clarifying discussion with FDA. To aid in the discussion, the Sponsor provided a presentation from which they spoke, which is attached. A record of the discussion that occurred during the meeting is presented following select questions and Administrative Comments.

3.0 QUESTIONS

1. Based on the results of the phase III clinical studies, API-E004-CL-C and API-E004-CL-C2, which demonstrate the efficacy and safety profile for E004, does the Agency agree that the efficacy primary endpoints of the studies were achieved, the safety data is established, the statistical analysis is acceptable, and all data is sufficient and appropriate to support the NDA filing and no additional data is needed to support the indication of "the temporary relief of mild symptoms of intermittent asthma."

   FDA Preliminary Response:
   The clinical development program summarized in the meeting package appears to contain the elements necessary to support NDA filing; however, formal decisions regarding filing are made by the Agency after NDA submission.

   As described during the preNDA meeting held on September 23, 2011, an evaluation of device performance during real-life use, evidence of device ruggedness, and a discussion of the potential for device clogging need to be included in your NDA submission.

We also remind you that we requested frequent blood pressure (BP) and heart rate measurements around Cmax from 2 to 5 minutes. Also requested were individual subject data, confidence intervals for E004 effects and for differences in effects between E004 and a comparator, and an assessment of variability particularly in those with elevated response to epinephrine exposures.

Whether the safety database is sufficient depends upon whether additional analyses (i.e., maximal increases in heart rate, patient characteristics of patients with heart rate increases, PVCs or other arrhythmias on the ECGs, etc.) of the existing data are reassuring regarding the heart rate increases.

As part of your safety database and analysis you should submit:

- *detailed descriptions of chest pain adverse events(AEs) and an analysis of these AEs in the context of the corresponding BP and heart rate*
- *analyses of AEs leading to discontinuation*
- *all serious AEs*
- *BP and heart rate measurements early after inhalation around the time of Tmax for high dose E004*
- *analysis of the literature and evaluation of FDA Adverse Event Reporting System (AERS) and your post-marketing database for epinephrine inhalers used for asthma over the last 5 years*

The adequacy of the efficacy and safety data to support the proposed indication will be a review issue.

Discussion: (see Amphastar's meeting handout)
In response to FDA comments, Amphastar stated that a literature analysis regarding the safety of epinephrine inhalers is underway and that they would provide an analysis of postmarketing safety findings related to Primatene CFC. Additionally, Amphastar stated that ECG and other safety data, such as blood pressure and heart rate were available and would be reported as requested by the Agency. FDA also reminded Amphastar to provide justification for device cleaning instructions as well as information to support the robustness of the overall device and dose counter with real use. Amphastar agreed to include this information in the NDA.

Amhastar plans to submit the NDA in mid-March for an asthma indication in adults. (b) (4) The Sponsor plans to include available pediatric study data with the initial NDA (b) (4) FDA asked whether the NDA would be filed as a 505(b)(2) submission. The Sponsor replied it will be filed as a 505(b)(1) because Amphastar owns the product. However, at the time of the meeting, it was not clear who owned the data required for approval and FDA requested that Amphastar formally submit an inquiry with supporting documentation to

determine whether the NDA should be submitted as a 505(b)(2) or a 505(b)(1). Amphastar agreed to this request.

2. Phase I/II and Phase III studies for adult patients demonstrate the safety and efficacy of E004. (b) (4)

FDA Preliminary Response: (b) (4)

Discussion: (b) (4) FDA requested that Amphastar submit an updated protocol.

3. Three Label Comprehension Studies (Study F) have been completed with progressively improved package inserts. Based upon the results of Study #1 and the improvements observed in Study #2, Study #3, and the behavioral study (Study G), does the Agency agree that the collected data is sufficient to support the proposed Insert/labeling and that no additional data is needed?

FDA Preliminary Response:
During the September 23, 2011 meeting with your company we outlined that the consumer testing program should include label comprehension and behavioral use studies to ensure that consumers can 1) understand instructions for cleaning, priming and re-priming and 2) administer and use the drug product properly. Whether the collected data is sufficient to support the proposed labeling will be a review issue.

Additional Comments

1. *We request that you include efficacy analyses based on the mean change in FEV1, in addition to the AUC ΔFEV%.*

Discussion:

Amphastar requested clarification regarding this comment. The Agency requests that Amphastar provide mean serial FEV1 over time in order to facilitate the evaluation of effect size.

2. *In Studies C and D, you propose to evaluate the primary endpoint based on the evaluator per-protocol population. We remind you of our discussion at the September 23, 2011 meeting, during which we recommended that the primary analysis for Trial D be performed using the Intent-to-Treat (ITT) population. While your approach will likely produce no missing data since you are only including patients who completed the trial and who potentially adhered to the protocol, we are concerned that these post-baseline evaluator-based criteria will introduce bias. In many cases, the use of per-protocol population may not preserve the baseline comparability between treatment groups achieved by randomization. In addition, excluding patients who dropped out related to outcome may introduce bias and influence the results. Furthermore, it is unclear whether this subset of patients can adequately address the primary objective of the study since you are only evaluating those patients who complete the study and adhered to the protocol. You also propose to test the difference between treatment arms using one-side t-test with $\alpha=0.05$. The primary analysis should be performed using two-sided t-test with $\alpha=0.05$ based on the intent-to-treat population (defined as all randomized patients regardless of whether they discontinue from treatment or study).*

3. *In your statistical analysis plan, provide a detailed description on how you plan to handle missing data. Discuss potential mechanisms which may cause FEV1 data to be missing, and how those mechanisms affected your selection of the primary analysis method. In addition, describe the underlying estimand, and explain why the estimand is appropriate for this study we also recommend that you outline additional analyses to gauge the sensitivity of your primary analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in a different direction from the result of the primary analysis. We also recommend that the reasons for discontinuation be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdraw consent', etc. If a patient is 'lost to follow-up,' you should provide a plan for attempting to contact the patient so that a more informative category can be assigned. "Refer to the National Research Council of the National Academy's report, titled "The Prevention and Treatment of Missing Data in Clinical Trials" for further information.*

4. *Should you intend to make labeling claims based on the results from analyses of the other secondary endpoints, your statistical analysis plan must include sufficient details regarding missing data, and the method you will use to control the probability of Type 1 error.*

5. *In the NDA submission, provide all raw datasets (in SDTM format or in other format), as well as analysis datasets (including all efficacy and safety variables) for the clinical trials, and consumer studies used to generate the results presented in your study report.*

In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.

- *Include the programs used for creating main efficacy analysis datasets from submitted raw datasets (in SDTM format or in other format) and the programs used for the efficacy and main safety analyses. In addition, provide a document that explains what each program is used for.*
- *Provide the analysis datasets and programs used to generate the specific analyses results contained in the ISE reports.*
- *Provide the analysis datasets and programs used to generate the inferential analyses results in the ISS.*
- *You can check the FDA website to find the information about current document and guidance: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf*

6. *Where data is presented and graphed as percent change (e.g., p. 49 and 50 of the clinical safety section), also present the same data using the actual values. For example, a 2% change in BP may correspond to a 3mm Hg change.*

7. *Your application may be discussed at an advisory committee meeting.*

   Discussion:
   Amphastar noted that their preference would be to not have an advisory committee meeting. Amphastar also inquired whether there is any particular issue that would require such a meeting. The Agency responded that the decision regarding an advisory committee meeting will be made after NDA submission, and will depend both on the nature of the data submitted as well as on an assessment of the public health issues pertinent to the application.

8. *We remind you to submit annotated specifications of your Drug Facts label for each stock keeping unit that you propose to market under your NDA.*

Additional Administrative Comments:

Comments shared with you today are based upon the contents of the January 3 and 21, 2013 meeting package, which is considered to be an informational aid to facilitate the meeting discussion. The comments are not meant to be viewed as commitments from the Agency.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

The July 9, 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) changes the timeline for submission of a Pediatric Study Plan and includes a timeline for the

implementation of these changes. You should review this law and assess if your application will be affected by these changes.

Discussion:

(b) (4)

Since this is a new product due to the change in dose, a pediatric plan, including a timeline for completing the trials is required to be submitted with the NDA. Amphastar asked whether there would be an issue due to their intent to restrict the NDA to adults 18 years of age and older; FDA stated that the decision to limit the initial submission to an adult population was at Amphastar's discretion. However, FDA noted that the proposed restriction to adults for the initial submission will be a review issue, given that the original Primatene CFC product was labeled down to the age of 4 years and the concern is that it will be used in this age range even if only approved for adults. FDA advised Amphastar to submit all available pediatric data with the NDA application, even if the proposed age range is limited to adults.

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

- Amphastar will submit a formal inquiry to FDA with supporting documentation to determine whether the NDA should be submitted as a 505(b)(2) or a 505(b)(1).

4.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION

-
- Amphastar agreed to provide all the requested data to support the NDA for the adult population. (b) (4) Amphastar will submit available pediatric data in the NDA submission for adults/adolescents.
- Findings and data from all protocols, including the Label Comprehension Studies and Consumer Use Studies will be included in the NDA.
- Amphastar will also provide an analysis of mean serial FEV1 over time, in addition to the AUC analysis.
- Amphastar understands that the application may be presented to an Advisory Committee.
- Amphastar agreed to submit the proprietary name for review.

5.0 ATTACHMENTS AND HANDOUTS

- Amphastar Preliminary Responses to the FDA Comments Dated 1/30/2013 for E004 1/31/2013 Pre-NDA Meeting.

6.0 POST MEETING ADDENDUM

- In your analysis of AERS and post-marketing databases, include narrative summaries and analyses of serious CV events and deaths.

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/s/

JOEL SCHIFFENBAUER
02/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074286

MEETING MINUTES

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

Please refer to your Investigational New Drug Application (IND) file for epinephrine inhalation aerosol.

We also refer to the meeting between representatives of your firm and the FDA on September 23, 2011. The purpose of the meeting was to discuss your clinical plan for the remaining Phase III investigations, the December 31, 2011 phase-out of epinephrine CFC, and the possibility of Fast Track Designation for the planned NDA submission.

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

If you have any questions, call Janice Adams-King, Regulatory Project Manager, at 301-796-3713.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 23, 2011 9:00AM – 10:00AM EST
Application Number:	IND 074286
Product Name:	Epinephrine inhalation aerosol
Indication:	Temporary relief of symptoms of asthma
Sponsor/Applicant Name:	Amphastar Pharmaceuticals, Inc. Armstrong Pharmaceuticals, Inc.
Meeting Chair:	Joel Schiffenbauer, M.D.
Meeting Recorder:	Janice Adams-King, R.N., B.S.N., M.S.

FDA ATTENDEES

Office of Drug Evaluation IV
Charles Ganley, M.D., Director

Division of Nonprescription Clinical Evaluation
Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Linda Hu, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacologist/Toxicologist
Melissa Furness, Chief Project Management Staff
Janice Adams-King, Regulatory Project Manager

Office of New Drug Quality Assessment
Alan C. Schroeder, Ph.D., CMC Team Leader
Xavier Ysern, Ph.D., Chemistry Reviewer

Division of Nonprescription Regulation Development
Elaine Abraham, R.Ph., Acting Team Leader, Interdisciplinary Scientist

Division of Pulmonary, Allergy, and Rheumatology Products
Badrul Chowdhury, M.D., Ph.D, Director
Lydia Gilbert-McClain, M.D., Deputy Director
Sally Seymour, M.D., Deputy Director for Safety
Jennifer R. Pippins, M.D., Medical Officer

Division of Clinical Pharmacology II
Suresh Doddapaneni, Ph.D., Deputy Director
Liang Zhao, Ph.D., Clinical Pharmacology Reviewer

Office of Regulatory Policy
Martha Nguyen, J.D., Regulatory Counsel

Office of Chief Counsel
Sherene Sepehri, J.D., Associate Chief Counsel

SPONSOR ATTENDEES

Amphastar Pharmaceuticals, Inc.
Anthony Marrs, Assoc. Vice President, Clinical Affairs
Stephen Campbell, Esq., Sr. Vice President, Regulatory Affairs
Mary Luo, Ph.D., COO, Chief Scientist
John Gao, M.D., Medical Director
Jacob Liawatidewi, Assoc. Vice President, Marketing
Robert Dormer, Esq., Hyman Phelps & McNamara
Jack Zhang, Ph.D., President, CEO, Chief Science Officer
Diane Gerst, Vice President, Quality Assurance
Rong Zhou, Vice President, Scientific Affairs
Marilyn Purchase, Executive Vice President, Operations
James Luo, Vice President, Operations
William Blight, Logistics Manager

1.0 BACKGROUND

In accordance with the Montreal Protocol, epinephrine metered dose inhalers (MDIs) that contain chlorofluorocarbons (CFC) are being phased out and cannot be sold in the United States after December 31, 2011. As a result, Amphastar Pharmaceuticals (Amphastar) will not be able to market its current epinephrine CFC-MDI, Primatene Mist®, after that date. The Sponsor requested a Type B meeting to discuss the remaining Phase III investigations of the drug development program for their proposed product, epinephrine (b) (4) MDI using a hydrofluoroalkane (HFA) propellant, the December 31, 2011 phase-out of epinephrine CFC, and the possibility of Fast Track Designation for the planned NDA submission.

2.0 DISCUSSION

On September 22, 2011, FDA sent preliminary responses to Amphastar Pharmaceuticals and Armstrong Pharmaceuticals to address the questions provided in their August 23, 2011 meeting package. The questions from Amphastar appear below followed by the preliminary FDA responses in italics. Questions 1, 2, and 3 were discussed during the meeting. A record of the discussion that occurred during the meeting is presented following questions 1, 2, and 3.

3.0 QUESTIONS

1. Are these completed and on-going studies acceptable to the FDA to support approval of the E004 NDA?

- Study C, safety and efficacy study, adult patents, 12 weeks, 3 arms, parallel, n=300 (200 for E004, 50 for placebo, and 50 for active control, Primatene®);

- Study D, safety and efficacy study, pediatric patients, 4 weeks, 2 arms, parallel, n=30 (30 for E004 and 30 for Primatene®);
- (b) (4)

FDA Preliminary Response:
The proposed clinical program is inadequate to support a New Drug Application. We refer you to our comments on the scope of the phase 3 program, as summarized in the December 23, 2009, written communication and the November 23, 2010, EOP2 Meeting Minutes. As discussed in the November 23, 2010, EOP2 Meeting, a long-term safety trial of at least 6 months duration is required. This is of particular importance given that the results of Trials API-E004-CL-B and API-E004-CL-B2 demonstrate a higher systemic exposure for epinephrine HFA MDI as compared to epinephrine CFC MDI.

The clinical program must also provide a reasonable demonstration of device performance throughout the life of the device. This should include asking subjects to report devices they perceive to be broken or malfunctioning and to return all such devices for laboratory evaluation and identification of the problem. In addition, a number (e.g., 100) of devices that are apparently functioning normally in subjects' hands should be collected near the end of the life of the device and evaluated by in vitro performance testing to ensure ruggedness throughout the product's intended span of use. We recommend that you incorporate this device assessment into the long-term safety study.

In addition, the program must address the issue of potential device clogging. Experience has shown that HFA MDI devices are prone to clogging. Conduct in vitro testing to determine the following: 1) the appropriate method and frequency of cleaning and 2) the number of actuations required for priming (i.e., priming prior to first use) and repriming after different resting intervals. At each time point in the study, actuations should be repeated and analyzed individually until delivered medication per actuation reaches a plateau. Develop proper patient instructions from the results of this study for cleaning, priming, and repriming. Evaluate these instructions in a large label comprehension study to determine if they are appropriate for an OTC setting.

In terms of the proposed trials, the study design of the adult safety and efficacy trial (Trial API-E004-CL-C) is generally acceptable.

Regarding the pediatric safety and efficacy trial (Trial API-E004-CL-D), we recommend the following:

1) *Conduct your primary analysis using the Intention to Treat (ITT) population. You may choose to conduct secondary and sensitivity analyses using the Per Protocol Population (PPP).*
2) *Enroll children who are capable of performing spirometry and revise the primary endpoint to be based on FEV1 alone,* (b) (4)

(b) (4)

In addition, if the directions with regard to administering the drug are not the same as Primatene Mist (e.g., priming, re-priming, cleaning the device and proper dosing which includes the timing of inhalation with respect to timing of actuation), a behavioral use study will be needed to assure that consumers can administer and use the drug properly.

We recommend you request a second pre-NDA meeting when data from the completed phase 3 program become available.

Discussion:

Amphastar requested clarification regarding the Agency's statement that a long-term safety trial of at least 6 months duration is required. Amphastar stated that their 3-month efficacy and safety trial (Protocol API-E004-CL-C) is underway and requested Agency guidance on an acceptable method for extending this trial 3 months in order to gather additional safety information. Amphastar stated that 120 subjects (out of 350 randomized) remain in Protocol C, with 15-20 participants completing the trial each week. Amphastar asked if it would be acceptable to re-enroll those who have already completed their participation in order to meet the Agency's requirement of obtaining 6 months of safety data. This would result in a 1-3 month gap in trial participants' use of product. The Agency noted that the proposal to re-enroll subjects who have already exited the trial is nontraditional and less desirable than enrolling subjects at the outset for the required duration of 6 months. The Agency and Amphastar agreed it would be appropriate to drop the active comparator arm, particularly after the December 31, 2011, sunset date for epinephrine CFC.

Amphastar initially estimated that with their new proposal, 6 months of safety data would be available for 50 to 100 subjects treated with epinephrine HFA. The Agency replied that this would be inadequate. Amphastar then revised their estimate, stating that 6-month data may be available for 100 to 150 subjects; the Agency replied that 150 may be sufficient, but ultimately, the adequacy of the size of the safety database will depend on the nature on the safety findings observed. However, the Agency stated that Amphastar should submit a protocol for review and comment, and Amphastar indicated that they intend to do so. In the interim, the Agency suggested Amphastar move forward with their proposed extension.

In regard to the pediatric trial (Trial API-E004-CL-D), Amphastar inquired about the Agency's comment that the primary analysis be performed using the Intent-to-Treat (ITT) population, as opposed to the per protocol (PP) population. The Agency reiterated that the primary analysis should be done for the ITT population, but Amphastar may choose to conduct a secondary analysis for the PP population. Amphastar also inquired about the Agency's comment that FEV1 be used as the sole primary endpoint, questioning the ability of young children (4-5 years of age)

to perform FEV1. The Agency stated that other programs have successfully enrolled 4 to 5 year olds capable of performing FEV1, and that Amphastar should attempt to do so as well.

The Agency noted that an Advisory Committee Meeting would likely be arranged during the NDA review. The Agency recommended that Amphastar request another pre-NDA meeting for further guidance once their safety/efficacy trials are complete.

2. Any Further Requests for E004 OTC NDA

- Any other CMC requests to Support E004 OTC NDA?

  FDA Preliminary Response:
  As you have indicated, your product has been developed in accordance with "Guidance for Industry: MDI and DPI Drug Products Chemistry, Manufacturing, and Controls Documentation" 1998 CMC, CDER, FDA (Draft) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070573.pdf). At this point we do not have additional CMC requests; however, evaluation of your response to the recommendations in the guidance will be a review issue.

- Any other Clinical requests to Support E004 OTC NDA?

  FDA Preliminary Response:
  See our response under the section "Clinical Plan for Phase III of E004." You will also need to provide an integrated safety data analysis, including post-marketing safety data and a literature review of epinephrine inhaler products.

- Assumption: since the Labeling for Primatene® (CFC MDI) has been on the U.S. Market as OTC for more than 30 years, a Label suitability assessment (n=24) for E004 (HFA MDI) may be waived, as the labeling will be updated per latest FDA OTC Monograph for bronchodilators, and provided to the FDA for review, and approval.

  FDA Preliminary Response:
  You will only need to test labeling where it differs from the Primatene Mist label. Since the E004 (HFA MDI) will have directions which differ from Primatene Mist with regard to how to administer the product and how to clean the device, a consumer study will be required to demonstrate that consumers can understand the directions and use the device as specified in the labeling. See the response to Question #1.

Discussion:
With respect to the issue of device performance, Amphastar stated that Trial API-E004-CL-C has included evaluation of the device, e.g. the assessment of malfunctioning units. Amphastar also commented initially that the device requires daily cleaning and that clogging was demonstrated by in vitro testing. The Agency informed Amphastar that the need for daily cleaning and the

potential for clogging are of concern. The Agency recommended that Amphastar refer to the prior precedent set by the early Albuterol HFA programs for guidance on the assessment of device performance. The Agency further noted that the issue of clogging with Albuterol HFA was noted only after the product was brought to market; to that extent, a larger sized premarketing database may be needed in order to adequately assess this new product. Amphastar noted that the intended use of their product (i.e., for mild asthma) differs from that of Albuterol, and questioned the relevance of the Albuterol HFA experience. FDA replied that they will ultimately take into account both the intended use and the real-life experience of study participants using the product. The Agency also noted that a need for once-daily cleaning further underscores the importance of having sufficient long-term safety data.

Amphastar clarified that the proposed labeling will recommend daily cleaning of the device although they believe that the device (b) (4) Amphastar stated that they will include labeling instructions regarding cleaning (i.e., daily). The Agency asked for representative performance data under in use conditions, to demonstrate the effect of not cleaning the mouthpiece for several days to one week. These performance data should include the following attributes: delivered dose uniformity, aerodynamic particle size distribution and spray pattern. Amphastar stated that they are collecting and will submit in use data on compliance with cleaning recommendations from the ongoing clinical trial where they estimate to collect approximately 1600 units. The Agency inquired about the specific cleaning instructions and Amphastar confirmed that cleaning will involve removal of the actuator and running water through it. The Agency said that Amphastar should address the situation in which a consumer may need to use the unit before the actuator is dry. Amphastar stated that they will evaluate the efficacy of the product under those conditions.

The Agency informed Amphastar that a behavior study should also be conducted to test whether consumers use the product correctly according to the label, including all the steps from priming and cleaning of the device as recommended to proper dosing which includes timing of inhalation relative to actuation. The Agency noted that often Sponsors first conduct the evaluation of label comprehension, in order to optimize the label prior to conducting the behavior study. Amphastar inquired what would constitute a "large" label comprehension study; the Agency replied that while there is no specific size required, it may include 300-400 subjects depending on the issues that need to be addressed. The Agency stated that the label comprehension study does not need to evaluate all the elements of the label; it should test only items that differ between the labels for the epinephrine HFA and epinephrine CFC products, noting that the Agency has yet to be provided a label for the proposed product. However, the Agency recommended that Amphastar submit the proposed label and a label comprehension study protocol to the Agency for their review and comment.

3. (b) (4)

FDA Preliminary Response:
After December 31, 2011, the sale or distribution of Primatene CFC MDIs is banned by the Clean Air Act. According to the Environmental Protection Agency, the federal agency that enforces the Clean Air Act, the ban applies to a product's entire distribution chain up to and including the ultimate consumer (b) (4)

If you have additional questions about the nonessential products ban under the Clean Air Act, please contact the following individual:

Jeremy Arling
Attorney Advisor
U.S. EPA Stratospheric Protection Division
arling.jeremy@epa.gov

Discussion:

Amphastar stated that sales for the epinephrine CFC product (approximately (b) (4) units monthly) have not changed indicating that there is no ongoing stockpiling and expressed concern about the extent to which underserved users are being reached with news about the phase-out. Amphastar noted that labeling describing the phase-out of the product is on the currently marketed product.

(b) (4)

4. We would like to request the Agency:

(b) (4)

Additional Administrative Comments:
Comments shared with you today are based upon the contents of the meeting package, which is considered to be an informational aid to facilitate the meeting discussion. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the NDA, and any subsequent NDA, might identify additional comments or information requests.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We remind you that under the Pediatric Research Equity Act (PREA), all NDA applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients of all ages. The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It includes data that are adequate to assess safety and effectiveness and support dosing and administration in the pediatric population. If pediatric studies have not yet been conducted, you must submit a pediatric plan detailing how you plan to address PREA along with a request for deferral and/or waiver in each pediatric age group. Waivers and deferrals for conducting pediatric studies may be requested by providing written justification for the deferral and/or waiver and evidence to support the request. See Guidance for Industry: How to Comply with the Pediatric Research Equity Act.
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues were identified.

4.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION

- Amphastar was informed that this NDA may need to go to an Advisory Committee.
- Amphastar should provide long term safety (6 months) data. Amphastar plans to submit a protocol for their proposed extension of the ongoing Trial API-E004-CL-C. Amphastar's proposal to have 6 months of data for 150 patients may be acceptable; however, the adequacy of the long-term safety database will depend on the nature of the safety findings observed.
- Amphastar will need to perform the primary analysis of Trial API-E004-CL-D using the Intent-to-Treat population; a secondary analysis may be conducted using the per protocol population. The trial should enroll 4- to 5- year-olds capable of performing FEV1, and use FEV1 as the sole primary endpoint.
- The Agency raised concerns regarding clogging and cleaning of the device that Amphastar will need to address.
- Amphastar will provide *in vitro* data including dose content uniformity, aerodynamic particle size distribution, and spray pattern of product when used after cleaning and not completely dry. Additionally, Amphastar will provide clear instructions for the subjects to follow regarding dose administration and cleaning.
- Amphastar will consider optimizing labeling for the proposed product before conducting the behavior study.
- A study should be conducted to test whether consumers can follow the product directions for use correctly according to the label, including all the steps from priming and cleaning of the device to proper dosing which includes timing of inhalation relative to actuation.

5.0 ATTACHMENTS AND HANDOUTS

No handouts were provided for this meeting.

6.0 POST MEETING ADDENDUM

We continue to have internal discussions regarding your proposed safety database and the potential clogging issue. Additional comments will be forthcoming regarding further recommendations.

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

/s/

JOEL SCHIFFENBAUER
10/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074286

MEETING MINUTES

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

Please refer to your Investigational New Drug Application (IND) file for epinephrine inhalation aerosol.

We also refer to the meeting between representatives of your firm and the FDA on October 29, 2010. The purpose of the meeting was to discuss the results of the Phase I and Phase II trials and finalize the clinical plan for Phase III investigations of this epinephrine inhalation aerosol.

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

If you have any questions, call Janice Adams-King, Regulatory Project Manager, at 301-796-3713.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

Application Number: IND 074286
Product Name: Epinephrine inhalation aerosol
Indication: Temporary relief of symptoms of asthma
Sponsor/Applicant Name: Amphastar Pharmaceuticals, Inc.
Armstrong Pharmaceuticals, Inc.

Meeting Chair: Andrea Leonard-Segal, M.D.
Meeting Recorder: Janice Adams-King, R.N., B.S.N., M.S.

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation
Andrea Leonard-Segal, M.D., Director
Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Victor Alexander, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacologist/Toxicologist
Murewa Oguntimein, MHS, CHES, Social Science Analyst
Melissa Furness, Chief Project Management Staff
Janice Adams-King, Regulatory Project Manager

Office of New Drug Quality Assessment
Ali Al-Hakim, Ph.D.,Branch Chief
Xavier Ysern, Ph.D., Chemistry Reviewer

Division of Nonprescription Regulation Development
Elaine Abraham, R.Ph., Interdisciplinary Scientist

Division of Pulmonary, Allergy, and Rheumatology Products
Badrul Chowdhury, Director
Sally Seymour, M.D., Deputy Director for Safety
Susan Limb, M.D., Medical Team Leader
Jennifer R. Pippins, M.D., Medical Officer

Pediatric and Maternal Health Staff
Elizabeth Durmowicz, M.D., Medical Officer
Millie Wright, Regulatory Project Manager

Office of Clinical Pharmacology
Yun Xu, Ph.D., Clinical Pharmacology Team Leader

SPONSOR ATTENDEES

Amphastar Pharmaceuticals, Inc.
Anthony Marrs, Assoc. Vice President, Clinical Affairs

Stephen Campbell, Esq., Sr. Vice President, Regulatory Affairs
Jim Shi, M.D., Ph.D., Medical Director

1.0 BACKGROUND

In accordance with the Clean Air Act, epinephrine metered dose inhalers that contain chlorofluorocarbon (CFC) are being phased out and cannot be sold in the United States after December 31, 2011. As a result of the sunset, Amphastar Pharmaceuticals (Amphastar) will not be able to market its current epinephrine with CFC metered dose inhaler (MDI), Primatene® and requested an End-of-Phase II meeting to discuss the next phase of their drug development program with the Agency for their proposed product, epinephrine (b) (4) in a pressurized metered dose inhaler using a hydrofluoroalkane (HFA) propellant.

2.0 DISCUSSION

On October 28, 2010, FDA sent preliminary responses to Amphastar Pharmaceuticals and Armstrong Pharmaceuticals to address the questions in their October 1, 2010 meeting package. The questions from Amphastar and Armstrong appear below followed by the preliminary FDA responses in italics. Amphastar expressed primary interest in discussing the *Introductory Comments* with questions to be discussed as time permitted. For this reason, discussion follows each bullet of the *Introductory Comments* as well as questions 2 and 8. For all other questions, Amphastar acknowledged the FDA response and there was no further discussion on that issue during the meeting.

Introductory Comments:
The Agency has the following concerns regarding the clinical development program:

- *Dose selection does not appear to be adequately supported. We note that the dose-ranging trial did not incorporate the Agency's previous recommendations to compare doubling doses of the proposed product (e.g., 1 vs. 2 puffs of E004, at each dosing level) to doubling doses of the reference product and placebo (Agency's communication dated December 23, 2009). Results from Trial A do not allow for discrimination between the E004 doses evaluated and suggest that lower doses may be efficacious. We also note that systemic exposure (Cmax and AUC) associated with the proposed dose of 2 x 125 mcg/inh of the test product is higher than that of the reference product. Given the above comments, we recommend assessment of lower doses prior to progressing to Phase 3.*

  Additional Discussion:
  Based on the Agency recommendations, Amphastar stated that they would explore a lower dosing range (e.g. 90 mcg to 125 mcg) and compare these doses to Primatene® and placebo. Amphastar requested clarification with respect to the Agency's recommendation to conduct a dose-ranging trial using doubling doses (e.g., 1 vs. 2 puffs of E004). The Agency replied that there were different ways to design a dose-ranging trial. While acknowledging that dose content uniformity may be altered with 1 puff vs. 2 puffs, the Agency noted that administration of doubling doses (e.g., 1 vs. 2 puffs) may allow for a demonstration of dose separation based on pharmacodynamic parameters (i.e., spirometry). The Agency added that it would be willing to provide feedback on additional dose-finding protocols submitted by Amphastar.

- *Dose-ranging should be conducted in an appropriate population to optimize characterization of the relationship between dose and efficacy response. We suggest that you consider the use of a challenge model, such as methacholine challenge, which may facilitate demonstration of a dose response. In the event that a dose response cannot be demonstrated in an adequately designed trial, dose selection may be based on a dose with an appropriate pharmacokinetic profile. However, we remind you that pharmacokinetics are informative primarily in terms of systemic safety; an adequate demonstration of efficacy and local safety will still be required in the Phase 3 program, regardless of the relative systemic exposure.*

  Additional Discussion:
  The Agency stated that there are different approaches that may be taken with regards to dose finding. One approach would be to conduct a single-dose study using methacholine challenge; another would be to assess dose response in a sensitive population such as individuals with nocturnal asthma symptoms. The Agency referred to the use of the methacholine challenge model used in the clinical development programs for albuterol generic products, which has been described in the literature.[1] Amphastar inquired as to whether such a study could be done with their proposed patient population; the Agency replied that it could. The Agency also clarified that it does not prefer one approach over another, but is presenting one option that may be useful for characterizing the proposed product. Amphastar expressed understanding of the Agency's position.

  The Agency noted that, ideally, a dose response should be demonstrated for the proposed product that matches that of the reference product. If a dose response cannot be demonstrated for the reference product, then Amphastar may need to rely on pharmacokinetic (PK) data to guide dose selection.

  Amphastar asked if PK data alone could be used to establish efficacy. The Agency replied that this would not be acceptable. PK data may be used to address issues of systemic safety, but additional clinical trial data will be required to support efficacy and local safety. The extent of the Phase 3 data required will depend on how closely the PK and pharmacodynamics match between the proposed and reference products. For example, if a dose response is demonstrated with the proposed product and the reference product, the Phase 3 program may be less extensive.

  Amphastar noted that the AUC for the proposed product is not statistically significantly different from that of the reference drug; however, the Cmax is higher. They attributed this to a formulation change resulting in more rapid delivery of drug to the lung. The Agency responded that Amphastar will need to show, in clinical trials, that a higher Cmax of the new product does not affect safety. Amphastar stated that an increased

[1] Creticos PS, Adams WP, Petty BG, et al. A methacholine challenge dose-response study for development of a pharmacodynamic bioequivalence methodology for albuterol metered-dose inhalers. *J Allergy Clin Immunol.* 2002; 110:713-20.

Cmax may reflect increased efficacy, and, thus, be favorable. The Agency replied that pharmacokinetic parameters do not necessarily reflect efficacy for inhalation products. The Agency acknowledged that differences are likely to exist between the proposed and reference products. The Phase 3 trials would have to address and support the differences. The Agency further stated that this comment is not directed specifically to this Sponsor or product, but is guidance provided to all Sponsors regarding drug development when relying on a reference product.

Amphastar inquired whether there was a need to conduct 6-hour serial spirometry. The Agency responded while study design depends on the model being employed, it is likely that early studies would not require serial spirometry, while Phase 3 trials would.

- *The scope of the Phase 3 program required (e.g. the need for replicate trials; the duration of study treatment) will depend on the results of the Phase 2 dose ranging trials. For example, as described in the Agency's December 23, 2009, communication, if the proposed product is more bioavailable than the reference product, a greater amount of safety information will be required. Alternatively, the requirements for Phase 3 efficacy and safety data may be less if Phase 2 data indicate that the proposed product and the reference product are similar in terms of both pharmacodynamics and pharmacokinetics. A single efficacy trial of a duration that reflects the expected life of the device, in addition to the long-term safety trial, such as for at least 6 months, may be acceptable. In general, you will need to identify any differences between the proposed and reference products and support the differences in your clinical program.*

  Additional Discussion:
  Amphastar inquired about the Agency's recommendation for a 6-month long-term safety study. They asked whether a controlled study of 20 days duration (a full cycle of product use) followed by an open-label safety study would be adequate. The Agency noted that the duration of the Phase 3 trials will depend on the results of Phase 2 trials. Assuming similar pharmacokinetics, a 1-month efficacy trial may be reasonable with additional safety data collected after this one month period.

  Moreover, the Phase 3 program should include an active comparator. Inclusion of a placebo control will depend on what is seen in the Phase 2 program; if the proposed and active products are very different, it will be important to include a placebo control along with an active control in the Phase 3 trials. Amphastar noted that blinding in the setting of an active control is difficult. The Agency also noted that if the long-term safety trial is open-label in design, all adverse events would be attributed to the proposed product. Amphastar stated that they will include an active comparator in the trial.

  Amphastar also inquired whether scheduled QID dosing (b) (4) for the long-term safety trial. The Agency stated that scheduled dosing is appropriate in the controlled clinical trial setting to assess safety. The Agency referred to the long-term safety trials conducted for the albuterol CFC to HFA switch programs. In principle, the Agency wants to see scheduled dosing to provide for maximum use, but the Agency added that a proposal may be put forward in a protocol for Agency review.

- *As stated in the Agency's December 23, 2009, and November 25, 2008, communications, the proposed 2-week pediatric trial (Study D; n=48) is too small and too short in duration to provide adequate safety data for pediatric asthma patients 4-11 years of age. Also see our response to question 7.*

  Additional Discussion:
  Amphastar stated that they plan on conducting a 4-week pediatric trial.

- *We remind you that the clinical program will need to include a robust evaluation of human factors, demonstration of device ruggedness, and assessment of dose counter performance, as were recommended in the Agency's communication dated December 23, 2009, and during the pre-IND meeting on March 27, 2007.*

  A robust evaluation of the device in the clinical program should include the following at a minimum: assessment of device ruggedness, assessment of device reliability over the life of the device, and in vitro assessment of the MDI performance characteristics from a reasonable sampling of devices from the clinical trials. The clinical program demonstrating device robustness will need to be supported by appropriate related in vitro testing for device robustness and reliability. We refer you to the Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products (March 2003) for further information on assessment of the dose counter.

  Additional Discussion:

  The Agency reminded Amphastar that human factor studies, distinct from the planned Phase 3 trials, as well as CMC in vitro evaluation of device reliability and ruggedness will be required. Amphastar stated that their clinical program would include a robust evaluation of human factors.

QUESTIONS

1. Based on the efficacy and safety data collected in the dose ranging study, is a final dose of 125 mcg/inhalation acceptable?

FDA Preliminary Response:
No, we recommend exploration of lower doses. See our Introductory Comments.

2. Since this is an NDA drug, and since our Phase I and II studies have demonstrated efficacy of E004, which has 43% lower dose (125 mcg/inh) than that for the currently marketed OTC drug epinephrine CFC MDI (220 mcg/inh), is it acceptable that in Phase III we test and compare just E004 versus placebo, without the need of including an active reference control drug, for Study C and Study D? This will allow a double-blinded study

design, instead of an evaluator-blind design, for more objective efficacy and safety evaluations.

FDA Preliminary Response:
The Phase 3 placebo-controlled trials should include the reference product.

In addition, we have the following comments regarding the drug products used:

The drug product needs to be well characterized and a close to a 'to be marketed formulation' should be used in Phase III clinical trial. The following information should be provided under the CMC section of the IND for our review.

- *The size of the spray pattern should be added to the spray pattern specification per the MDI draft guidance.*
- *Individual unknown impurity needs to be tightened to (b)(4)% per the MDI draft guidance.*
- *Particle size distribution information and the amount of drug per metered spray deposited at each of the individual stages in tabular format should be provided.*
- *The number of doses per aluminum canister unit that will be used for the clinical trial.*
- *A drug product label for this trial has not been provided. The required cautionary statement must be printed on the drug label as required by 21CFR 312.6(a).*

Additional Discussion:
Further comments on the FDA response to question 2 are included within the discussion sections for the Introductory Comments above.

3. Is the study design, with a total of 250 subjects (200 for E004 to establish a safety database and 50 for placebo), with a total of 5 clinical visits for safety and compliance evaluations, while making for serial postdose FEV1 evaluations in 3 of the 5 visits (Visit-1, 3 and 5), and twelve (12) week treatment duration, adequate for this pivotal Study C Phase III trial?

FDA Preliminary Response:
In the absence of adequate dose-ranging, it is premature to comment on the specific Phase 3 trial design. In general, we note that the scope of the Phase 3 program may be reduced depending on the results of the complete Phase 2 dose ranging data. See our Introductory Comments.

4. Since epinephrine MDI products have been used for asthma symptom relief for many years, with satisfactory safety records, is it acceptable to use the 12-week Phase III study safety data through Study C to support E004 clinical safety?

FDA Preliminary Response:
The proposed Phase 3 clinical trial (Study C) will not be adequate to establish safety. A long-term safety trial of 6 months or longer will be required. A trial of 12-week duration will not be sufficient to establish the safety of chronic use, which may be impacted by factors related to

long-term device performance. The duration of the safety trial will depend on the pharmacokinetic data and safety information obtained in the Phase 2 program. See our Introductory Comments.

5. Is it acceptable to use the dosing regimen of two inhalations of E004 QID, (b) (4) in study C?

FDA Preliminary Response:
(b) (4) *we recommend the use of albuterol MDI for rescue.* (b) (4)

6. (b) (4)

FDA Preliminary Response:
No, see response to Question 5.

7. Regarding the clinical study for pediatric asthma patients, the efficacy and safety studies will be performed through a 2-week trial (Study D), is this acceptable? Longer durations may pose safety concerns in pediatric patients who are assigned to a placebo arm.

FDA Preliminary Response:
No, the duration of the trial is not acceptable; we recommend a minimum of 4 weeks. See our Introductory Comments.

(b) (4)

Additional Discussion:

(b) (4) The Agency further stated that with the NDA submission, Amphastar will need to address PREA requirements. Amphastar inquired as to whether it would be possible to

conduct trials in children as part of their post-marketing program. The Agency replied that this may be possible. A pediatric plan, required under PREA, must be part of the NDA submission.

9. Does FDA approve that E004 Phase III studies can start?

FDA Preliminary Response:
While the decision to initiate Phase 3 trials is at your discretion, we do not recommend that you proceed to Phase 3 until you have conducted adequate dose-ranging. See our Introductory Comments.

(b) (4)

FDA Preliminary Response:

(b) (4)

Additional Discussion:

(b) (4)

(b) (4)

Additional Administrative Comments:
Comments shared with you today are based upon the contents of the meeting package, which is considered to be an informational aid to facilitate the meeting discussion. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the NDA, and any subsequent NDA, might identify additional comments or information requests.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We remind you that under the Pediatric Research Equity Act (PREA), all NDA applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients of all ages. The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It includes data that are adequate to assess safety and effectiveness and support dosing and administration in the pediatric population. If pediatric studies have not yet been conducted, you must submit a pediatric plan detailing how you plan to address PREA along with a request for deferral and/or waiver in each pediatric age group. Waivers and deferrals for conducting pediatric studies may be requested by providing written justification for the deferral and/or waiver and evidence to support the request. See Guidance for Industry: How to Comply with the Pediatric Research Equity Act.
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf). Please note that such a request can be made as early as at the end of Phase 2 of the IND review process.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

- Validate the age of pediatric population for inclusion in the study and for labeling purposes. Specifically, it needs to be decided whether children $\geq$ 12 years of age can be included in the adult population for purposes of administering the proposed product.

4.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION

- Dose finding studies may use a single dose methacholine challenge model or a trial comparing doubling doses of the proposed product versus the reference product and placebo.

- Dose response data need to be generated before the Phase 3 trial.
  PK studies alone will not be acceptable to support efficacy but, if the bioavailability is less than the reference product the PK studies may lend safety support. For example, Amphastar needs to provide data to support safety of a formulation with a higher Cmax and/or AUC.
- Phase 3 trials should include a placebo and/or active control arm.
- (b) (4)
- Amphastar stated that their clinical program would include a robust evaluation of the ability of consumers to properly use the new inhaler.

5.0 ATTACHMENTS AND HANDOUTS

- No handouts were provided for this meeting.

POST MEETING ADDENDUM

- NDA filing can include adults only, as long as a pediatric plan required under PREA is part of the NDA submission. The study population should be children with asthma, (b) (4)
- All amendments and correspondence with the Agency should be sent to the attention of the Division of Nonprescription Clinical Evaluation.

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

/s/

ANDREA LEONARD SEGAL
11/23/2010