CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211363Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 105989

**MEETING REQUEST-
WRITTEN RESPONSES**

Amphastar Pharmaceuticals, Inc.
Attention: Ms. Gisela Sharp
Sr. Manager, Regulatory Affairs
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Ms. Sharp:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Epinephrine Injection, USP, 0.1 mg/mL, 10 mL Prefilled Syringe.

We also refer to your submission dated July 26, 2017, containing a pre-IND meeting request via teleconference. The purpose of the requested meeting was to discuss a proposed 505(b)(2) NDA for Epinephrine Injection, USP.

Further reference is made to our Meeting Request Granted letter dated July 31, 2017, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your August 24, 2017 background package.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-IND
Application Number:	Pre-IND 105989
Product Name:	Epinephrine Injection, USP, 0.1 mg/mL, 10 mL Prefilled Syringe
Indication:	To increase mean arterial blood pressure (MAP) in adult patients with hypotension associated with septic shock.
Sponsor/Applicant Name:	Amphastar Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(2)

1.0 BACKGROUND

Amphastar Pharmaceuticals, Inc. requested this Pre-IND meeting to discuss the feasibility of using the available literature to support a 505(b)(2) New Drug Application (NDA) for Epinephrine Injection, USP. A Pre-IND meeting was previously held on September 29, 2009. At the time, Amphastar had intended to pursue several indications.

Subsequently, on December 13, 2010, the Division issued an Advice Letter stating that (b) (4) (b) (4) (b) (4) it may be possible to approve the product without further outcome studies for increasing systemic arterial blood pressure in certain acute hypotensive states.

Currently, Amphastar is pursuing the following proposed indication: to increase mean arterial blood pressure (MAP) in adult patients with hypotension associated with septic shock. This proposed indication is the same as that currently approved for Belcher Pharmaceuticals, LLC's NDA 205029 for Epinephrine Injection, USP (approved on July 29, 2014). Although the current labeling approved for Belcher's product has additional indications, Amphastar intends to only pursue the indication stated above.

In the Meeting Request Granted letter dated July 31, 2017, the Division had stated that written responses to the sponsor's questions would be provided in lieu of a meeting. Per the sponsor's email dated August 25, 2017, there are no further questions from those originally proposed in the meeting request. The sponsor's questions are listed below followed by the Division's responses.

2.0 QUESTIONS AND RESPONSES

2.1. Regulatory

Question 1:
Does the Agency agree that the 505(b)(2) NDA route is an acceptable approval pathway for the proposed product with Belcher NDA 205029 as the reference drug?

FDA Response to Question 1:

A 505(b)(2) application appears acceptable, at this time, based on the available information. For additional information for sponsors considering the submission of an application through the 505(b)(2) pathway, please refer to the information in the 505(b)(2) REGULATORY PATHWAY subsection of section 3.0 of this document.

Question 2:

Does the Agency agree that the literature review provided will adequately support the indication being pursued for this product?

FDA Response to Question 2:

If you plan to rely on FDA's findings of safety and effectiveness for Belcher Pharmaceuticals, LLC's NDA 205029 for Epinephrine Injection, USP, as you have indicated, a literature review will not be necessary. However, if you do not plan to rely on FDA's findings for Belcher's NDA 205029, then the literature review provided will probably be adequate.

3.0 505(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 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. by 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR

314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness 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 A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
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.

4.0 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.

5.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP should be submitted in

PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP 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 Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

6.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

7.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

8.0 SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

9.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

/s/

NORMAN L STOCKBRIDGE
09/18/2017

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via email to:	StephenC@amphastar.com
Attention:	Stephen A. Campbell, Esq.
Sponsor:	Amphastar Pharmaceuticals, Inc.
Phone:	(909) 942-4176
Subject:	**Pre-IND Meeting Minutes**
Date:	November 30, 2009
Pages, including this sheet:	5

From:	**Quynh Nguyen, Pharm.D., RAC**
Phone:	**301-796-0510**
Fax:	**301-796-9838**
E-mail:	**quynh.nguyen@fda.hhs.gov**

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Pre-IND Meeting with Sponsor

Application Number:	Pre-IND 105,989
Sponsor:	Amphastar Pharmaceuticals, Inc.
Drug:	Epinephrine HCL Injection, USP
Type of Meeting:	Pre-IND
Classification:	B
Meeting Date:	September 29, 2009
Briefing Package Received:	September 2, 2009
Confirmation Date:	July 23, 2009
Meeting Request Received:	July 14, 2009
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Recorder:	Quynh Nguyen, Pharm.D., RAC

List of Attendees:

Food and Drug Administration

Office of New Drugs, Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Medical Team Leader
Shen Xiao, M.D.	Clinical Reviewer
Albert DeFelice, Ph.D.	Pharmacology Team Leader
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Quynh Nguyen, Pharm.D., RAC	Regulatory Health Project Manager

Office of New Drugs, Guidance and Policy Team

Sally Loewke, M.D.	Medical Team Leader

Office of Compliance, Division of New Drugs and Labeling Compliance, Prescription Drugs Team

Astrid Lopez-Goldberg, J.D.	Regulatory Counsel

Amphastar Pharmaceuticals, Inc.

Stephen A. Campbell, Esq.	Senior Vice President, Regulatory Affairs
Tony Marrs	Associate Vice President, Clinical Affairs
Jim Shi, M.D., Ph.D.	Medical Director
Jin Yao Ma	Associate Director of New Technology, IMS

BACKGROUND

Amphastar Pharmaceuticals, Inc. requested this meeting to discuss the requirements for submission of a 505(b)(2) NDA for Epinephrine HCl Injection. (b) (4) (b) (4) (b) (4) According to the sponsor, the product has been widely used for more than half a century (b) (4) (b) (4) (b) (4), although low-dose combination products

containing epinephrine and local anesthetic agents in a syringe for emergency self-administration for allergic reactions have been approved. The Division's Preliminary Responses were sent to the sponsor on September 24, 2009. Only Questions 2 and 3 were discussed as noted below.

DISCUSSION

1. Given the extensive history of the use of Epinephrine HCl Injection, USP, will the Agency grant a waiver of preclinical toxicology and pharmacology evaluation?

Preliminary Response

Nonclinical toxicology or pharmacology studies will not be required in support of clinical investigation of iv epinephrine, and it is anticipated that our evaluation of the safety of iv epinephrine (b) (4) will be based on clinical investigation or published studies.

(b) (4)

Discussion during Meeting

Reliance on published literature

The sponsor asked for further clarification on the Division's concerns regarding their proposal to rely on the published literature. Dr. Stockbridge explained that the decision to approve a product could not be based on the product's previous use, no matter how extensive, or on guidelines that have been

promulgated by various organizations. For approval to market a drug, the sponsor must provide objective data that demonstrate substantial evidence of efficacy, generally from adequate and well-controlled trials. It is unclear if such data exist for epinephrine. Dr. Stockbridge added that "adequate" trials include measures intended to assure the trials have been conducted well enough to have confidence in the data generated, e.g., through verification of the source data and site inspections. The presence or absence of such measures often cannot be determined from literature reports of trials, especially trials conducted prior to the widespread use of such measures.

(b) (4)

CONCLUSION

The sponsor's plans for submission of a marketing application for epinephrine HCl injection were discussed. The Division encouraged the sponsor to submit their clinical development plans for review.

Minutes preparation: Quynh Nguyen, Pharm.D., RAC

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Rd:

N Stockbridge	11/25/09
E Fromm	11/25/09
S Grant	11/24/09
T Marciniak	11/24/09
S Xiao	11/24/09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105989	GI-1	AMPHASTAR PHARMACEUTICALS INC	Epinephrine Hydrochloride Injection USP

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

/s/

NORMAN L STOCKBRIDGE
11/30/2009