CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212593Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Pre-NDA 212593

MEETING MINUTES

Luitpold Pharmaceuticals, Inc.
Attention: Marsha E. Simon
Director, Clinical Regulatory Affairs
800 Adams Avenue
Suite 100
Norristown, PA 19403

Dear Ms. Simon:

Please refer to your Pre-New Drug Application (Pre-NDA) file for Vasopressin Injection, USP, 20 units/mL.

We also refer to the meeting via teleconference between representatives of your firm and the FDA on November 8, 2018. The purpose of the meeting was to discuss your planned submission of a 505(b)(2) NDA.

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

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:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 8, 2018 at 9:00 – 10:00 AM ET
Meeting Location:	via Teleconference
Application Number:	Pre-NDA 212593
Product Name:	Vasopressin Injection, USP, 20 units/mL
Indication:	To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
Sponsor/Applicant Name:	Luitpold Pharmaceuticals, Inc.
Meeting Chair:	Quynh Nguyen, Pharm.D., RAC
Meeting Recorder:	Norman Stockbridge, M.D., Ph.D.

FDA ATTENDEES

Office of Drug Evaluation I, Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Michael Monteleone, M.S., RAC	Associate Director for Labeling
Fortunato (Fred) Senatore, M.D., Ph.D., FACC	Clinical Reviewer
Martin Rose, M.D., J.D.	Clinical Team Leader
Xuan Chi, Ph.D.	Nonclinical Team Leader (Acting)
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Quynh Nguyen, Pharm.D., RAC	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Venkateswaran ChithambaramPillai, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products

Division of New Drug API

Suong Tran, Ph.D.	Branch Chief

Division of New Drug Products I

Thomas Oliver, Ph.D.	ONDP/OPQ, Division Director
Mohan Sapru, M.S., Ph.D.	CMC Lead for Cardiovascular and Renal Products
Stephanie Emory, Ph.D.	CMC Reviewer

SPONSOR ATTENDEES

Representing Luitpold Pharmaceuticals, Inc.

Linda M. Mundy, M.D., Ph.D.	Vice President & Chief Medical Officer
Gopal Anyarambhatla, Ph.D.	Vice President R&D and Regulatory Affairs
Geoffrey Mukwaya, M.D.	Senior Medical Director, Head of Clinical R&D
Anthony DiGuglielmo, D.P.M.	Medical Director, Head of PV
Matthew R. Yudt, Ph.D.	Scientific Director, Multisource Generics
Kenneth Thompson, D.V.M., PhD.	Head of Non-Clinical Development
Nicole Blackman, Ph.D.	Executive Director, Head of Quantitative Sciences
Saral Patel	Sr. Manager, R&D
Richard Lawrence	Director, R&D
Don Wang	Director, R&D
Raenel Gibson	Regulatory Affairs Director
Marsha E. Simon, Director	Clinical Regulatory Affairs

1.0 BACKGROUND

Vasopressin Injection, USP is a sterile, aqueous solution of synthetic vasopressin (8-Larginine vasopressin) from the posterior pituitary gland for intramuscular or subcutaneous use. It is substantially free from the oxytocic principle and is standardized to contain 20 pressor units/mL.

Vasopressin Injection, USP is an unapproved product marketed in the United States (US) by Luitpold Pharmaceuticals, Inc. (American Regent). Since September 1993, Vasopressin Injection, USP has been marketed for prevention and treatment of postoperative abdominal distention, use in abdominal roentgenography to dispel interfering gas shadows, and use in diabetes insipidus.

A Pre-NDA Teleconference was previously held on June 26, 2013 to discuss the possible filing of a 505(b)(2) New Drug Application (NDA) for Vasopressin Injection, USP under Pre-IND 118380. Subsequently, Luitpold submitted NDA 206643 for (b) (4) (Vasopressin Injection, USP), 20 units/mL on March 4, 2014. On May 2, 2014, FDA issued a Refusal to File Letter for the NDA primarily for product quality issues, namely that the application lacked sufficient stability data to grant the expiry for drug product (b) (4) .

Luitpold has requested this second Pre-NDA meeting via teleconference to obtain concurrence from the Division that the extant literature supports the safety and efficacy of Luitpold's request for approval of Vasopressin Injection, USP via the 505(b)(2) NDA process. Additionally, the applicant would like to discuss chemistry, manufacturing, and controls (CMC), nonclinical, and clinical issues.

FDA sent Preliminary Comments to Luitpold on November 6, 2018. The sponsor emailed Talking Points in response to the FDA Preliminary Comments on November 7, 2018 (see attached). Only the responses to Questions 1, 3, and 4 were discussed.

2.0 DISCUSSION

2.1 Chemistry, Manufacturing, and Controls (CMC)

Question 1:

PharmaForce, Inc., a wholly owned subsidiary of Luitpold Pharmaceuticals, Inc., has manufactured three exhibit batches of Vasopressin Injection, USP using Vasopressin, USP raw material manufactured by

(b) (4)

Question 10:
Based on the proposed use of this product, and the summary information provided in the technical package, are there any other concerns or recommendations that the Agency would like to discuss?

FDA Response to Question 10:
We have identified no other issues.

Discussion
The sponsor accepted FDA's response; no discussion occurred.

2.2 Nonclinical

Question 11:
Luitpold believes the published non-clinical literature supports the safety and toxicology of vasopressin relevant to the short-term therapeutic indication to increase blood pressure (b) (4) in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. Therefore, no further non-clinical work will be undertaken by Luitpold. Does the Division agree?

FDA Response to Question 11:
Yes, we agree in general. Although you have not conducted any nonclinical studies with the investigative drug (vasopressin), extensive nonclinical studies reported in the literature on vasopressin provide a full understanding of its pharmacology, ADME, and toxicology, and directly support the safety of vasopressin. At the time of NDA submission, you should provide written and tabulated summaries of all the published studies specific for each section.

You note in your briefing package that no published studies are available on the carcinogenic, mutagenic or teratology effects of vasopressin. The lack of these studies would be reflected in the label.

Discussion
The sponsor accepted FDA's response; no discussion occurred.

2.3 Clinical

Question 12:
Luitpold believes the efficacy and safety data in the literature supports an approval for Increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines as a 505(b)(2) application? Does the Division agree?

FDA Response to Question 12:
In principle, we agree that a 505(b)(2) application can be supported by safety and efficacy data from the published literature. The submitted efficacy data should address the treatment effect on the change from baseline in mean arterial pressure over background catecholamine administration. To fulfill the requirement to provide substantive evidence of effectiveness, we recommend that you focus on publications describing the results of randomized controlled clinical trials.

Discussion
The sponsor accepted FDA's response; no discussion occurred.

Question 13:
As previously agreed by the Division during our **preNDA meeting held on 26JUN2013**, Luitpold believes the efficacy and safety data in the literature continue to support increasing arterial pressure in vasodilatory shock as a 505(b)(2) application? Does the Division agree?

FDA Response to Question 13:
See response to question # 12.

Discussion
The sponsor accepted FDA's response; no discussion occurred.

(Additional Questions not included in the Meeting Package)

Question 14:
Would [Luitpold] be exempt from PREA since we are aligning with Par's labeling?

FDA Response to Question 14:
Exemption from PREA statutory requirements can be granted if the following conditions are met:
1) not a new active ingredient; 2) not a new indication; 3) not a new dosage form; 4) not a new dosage regimen; and 5) not a new route of administration. If you believe that PREA does not apply to your product, please include a side-by-side comparison of the PREA criteria for your proposed product and Par's product. This would facilitate our assessment of whether you would be exempt.

Discussion
The sponsor accepted FDA's response; no discussion occurred.

Question 15:
Would the agency agree that Luitpold only needs to conduct [a literature] search to cover any new literature since the PAR approval date (from 04/17/2014) through the date of our submission?

FDA Response to Question 15:
If your application relies on the Agency's determination of safety and effectiveness for Vasostrict, then the proposed approach would be considered acceptable. However, your label will need to conform to PLLR. For additional information on this issue, see the section below titled "Prescribing Information."

If your application will not be relying on the Agency's determination of safety and effectiveness for Vasostrict, and will instead be relying exclusively on the literature, then you will need to submit literature and/or data to support all aspects of your application.

Discussion
The sponsor accepted FDA's response; no discussion occurred.

3.0 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.

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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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 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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started 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 started on or 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.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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

6.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an

analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

7.0 SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. 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.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

8.0 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).

9.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

10.0 505(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.

11.0 ATTACHMENTS AND HANDOUTS

Luitpold Talking Points emailed on November 7, 2018.

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

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

/s/

NORMAN L STOCKBRIDGE
12/03/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206643

REFUSAL TO FILE

Luitpold Pharmaceuticals, Inc.
Attention: Ms. Marsha Simon
800 Adams Avenue
Suite 100
Norristown, PA 19403

Dear Ms. Simon:

Please refer to your March 4, 2014 New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (Vasopressin Injection, USP), 20 units/mL.

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:

PRODUCT QUALITY

Your application does not have sufficient stability data to grant the expiry for drug product supplied (b) (4)

Resubmit your NDA with sufficient stability data to grant the expiry (b) (4) of your drug product. Note that your proposed storage conditions (b) (4), the minimum stability data should follow ICH Q1A(R2) stability protocols, i.e., three batches of each configuration stored in the inverted and upright positions at 40 ºC /75% RH (6 months), 25 ºC/60% RH (12 months minimum), 30 ºC/65% RH (if the product exceeds shelf life specifications at accelerated conditions; 12 months), and 5 ºC (12 months). The stability testing should include levels of the individual impurities for all storage conditions.

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.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

During our filing review of your application, we identified the potential review issues listed below. We are providing the below comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review when you resubmit the application.

PRODUCT QUALITY

1. Since the drug product [redacted] (b) (4)

2. Provide the results of the compatibility studies for vasopressin diluted to 0.1 to 1 unit/ml with sodium chloride 0.9% and dextrose 5% in water.

3. Provide legible and typed (not a handwritten) Appendixes to the sections 3.2.P.5.2 and 3.2.P.5.3. Provide the description of the analytical methods in tabulated form, and provide the summary report of the validation of analytical methods in tabulated form.

4. Provide a legible copy of the deviation report for Lot #0294, Appendix 3.2.P.8.3a, in Section 3.2.P.8.

5. Provide the batch analysis for drug product [redacted] (b) (4) .

BIOPHARMACEUTICS

Provide a side-by-side comparison of your proposed drug product and the drug product(s) used in the published literature upon which you rely. Include the following: a qualitative and quantitative drug product formulation, drug product stability information, container closure system, storage conditions, indication, dosage, route of administration, osmolality, pH, and instructions for dilution.

PRODUCT QUALITY MICROBIOLOGY

Your Antimicrobial Effectiveness Testing (AET) is not the recommended approach. [redacted] (b) (4) study was not found in the submission and we request that you submit this information.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

Highlights

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
   Comment: *Please correct the margins to be 1/2 inch on all sides and between columns.*

2. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column). The headings should be in UPPER CASE letters.
   Comment: *Please correct so that the* **INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND ADVERSE REACTIONS** *headings are presented in the center of the horizontal line.*

3. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
   Comment: *Please correct the numerical identifier in parenthesis for* **WARNINGS AND PRECAUTIONS** *to be 5.1 instead of 5.*

HIGHLIGHTS DETAILS

Highlights Limitation Statement

4. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.
   Comment: *Please correct the name of the drug product to* (b) (4)*. In addition, the name should appear in UPPER CASE letters in both sentences as follows: "***These highlights do not include all the information needed to use** (b) (4) **safely and effectively. See full prescribing information for** (b) (4)**."**

Initial U.S. Approval in Highlights

5. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Please insert periods after the letters* "U" and "S" *in the verbatim statement* "**Initial U.S. Approval:**".

Contents: Table of Contents (TOC)

6. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
   Comment: *Please correct the subsection headings to be in title case for subsections 5.1, 16. 1, and 16.2.*

7. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
   Comment: *Please correct the following section and subsection headings to match in the TOC and FPI: 8.4, 8.5, 16, and 17. In addition, please insert as subsection headings the text "* (b) (4) *" for subsections 5.1 and 5.2, respectively, in the FPI.*

8. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."
   Comment: *Please correct the section number for* **CLINICAL STUDIES** *to 14 instead of 15. Please delete section 17 as there is no patient labeling being proposed.*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

9. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.
   Comment: *Please make the following corrections:*
   - *Add an "***S***" to section header 4 to read as "***CONTRAINDICATIONS***"*
   - *Correct the section number for* **CLINICAL STUDIES** *to 14 instead of 15*
   - *Correct the section header for section 16 to read as "***HOW SUPPLIED/STORAGE AND HANDLING**"
   - *Correct the section header for section 17 to read as "***PATIENT COUNSELING INFORMATION**"

FULL PRESCRIBING INFORMATION DETAILS

PATIENT COUNSELING INFORMATION Section in the FPI

10. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Please delete this section as there is no patient labeling being proposed.*

In addition, please ensure that the font and font size of the text are consistent in section **6 ADVERSE REACTIONS** through section **8 USE IN SPECIFIC POPULATIONS**, including in the subsections.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues at the time of NDA resubmission. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. However, your request does not follow the format of a Pediatric Study Plan. Please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm for guidance on submission of the PSP, including a PSP Template, and resubmit your request. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

In addition, we request that you submit the following information:

ADMINISTRATIVE

You have indicated in Section 20 of the Form FDA 356h that the Patent Certification is a "Statement of no relevant patents." Please specify where in the NDA submission this statement of no relevant patents is actually located.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health 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

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
05/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118380

MEETING MINUTES

Luitpold Pharmaceuticals, Inc.
Attention: Ms. Marsha Simon
800 Adams Avenue
Suite 100
Norristown, PA 19403

Dear Ms. Simon:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Vasopressin Injection, USP.

We also refer to the Pre-NDA Meeting via teleconference between representatives of your firm and the FDA on June 26, 2013. The purpose of the meeting was to discuss the possible filing of a New Drug Application (NDA) for Vasopressin Injection, USP.

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

If you have any questions, please contact me at (301) 796-0510 or via e-mail at Quynh.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 26, 2013 at 2:00 – 3:30 PM ET
Meeting Location: via Teleconference

Application Number: Pre-IND 118,380
Product Name: Vasopressin Injection, USP
Indication: (b) (4)

Sponsor/Applicant Name: Luitpold Pharmaceuticals, Inc.

Meeting Chair: Ellis Unger, M.D.
Meeting Recorder: Quynh Nguyen, Pharm.D., RAC

FDA ATTENDEES

Office of New Drugs, Office of Drug Evaluation I

Ellis Unger, M.D.	Director

Office of New Drugs, Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Shari Targum, M.D.	Clinical Team Leader
Monica Fiszman, M.D.	Clinical Reviewer
Thomas Papoian, Ph.D.	Pharmacology Team Leader
Rama Dwivedi, Ph.D.	Pharmacology Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Quynh Nguyen, Pharm.D., RAC	Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics I

Ququan (Cherry) Liu, M.D., M.S.	Biometrics Reviewer

Office of New Drug Quality Assessment

Kasturi Srinivasachar, Ph.D.	CMC Lead
Lyudmila Soldatova, Ph.D.	Chemistry Reviewer
Tien Mien Chen, Ph.D.	Biopharmaceutics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Peter Hinderling, M.D.	Clinical Pharmacology Reviewer

Office of Regulatory Policy, User Fee Staff

Michael Jones, R.Ph.	Senior Program Management Officer

Office of New Drugs, Pediatric and Maternal Health Staff

Hari Sachs, M.D.	Lead Medical Officer
Denise Pica-Branco, Ph.D.	Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Representing Luitpold Pharmaceuticals, Inc.

Mary Jane Helenek	President & CEO
Joseph Perno, M.D., Ph. D.	Medical Director, Clinical Operations
Marc Tokars	Sr. Director, Clinical Operations
Ken Thompson, Ph.D., D.V.M.	Head of Preclinical
Richard Lawrence	Director of Research and Development
Andy He, Ph.D.	Manager, Medical Affairs
Marsha E. Simon	Manager, Regulatory Affairs

1.0 BACKGROUND

Vasopressin Injection, USP is a sterile, aqueous solution of synthetic vasopressin (8-L-arginine vasopressin) of the posterior pituitary gland for intramuscular or subcutaneous use. It is substantially free from the oxytocic principle and is standardized to contain 20 pressor units/mL.

Vasopressin Injection, USP is an unapproved product marketed in the United States by Luitpold Pharmaceuticals, Inc. (American Regent) since September 1993, for prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus.

In accordance with the Food and Drug Administration's (FDA) September 2011 guidance entitled "Marketed Unapproved Drugs-Compliance Policy Guide (CPG)," Luitpold Pharmaceuticals is preparing a 505(b)(2) New Drug Application (NDA) of their Vasopressin formulation for the following proposed indication: (b) (4) Luitpold has requested this Pre-NDA Meeting to discuss the possible filing of their NDA.

The Division's Preliminary Responses were sent to Luitpold on June 20, 2013. On June 25, 2013, Luitpold provided a response via email to the Division's Preliminary Comments regarding Question 3 (**Administrative)** and Comment 2 of the ***FDA Additional Preliminary Comments*** for **Chemistry, Manufacturing, and Controls (CMC)** (see attachment). Only these responses were discussed during the meeting as noted below.

DISCUSSION

Question 1. *Luitpold believes the efficacy and safety data in the literature supports an approval for increasing arterial pressure in vasodilatory shock as a 505(b)(2) application? Does the Division agree?*

FDA Response:
We agree.

Question 2. *Luitpold believes the efficacy and safety data in the literature also supports an approval for* [redacted] (b) (4) *as a 505(b)(2) application? Does the Division agree?*

FDA Response:
We do not agree. We believe that an additional well-controlled clinical trial is necessary for approval of a NDA to market Vasopressin Injection, USP for [redacted] (b) (4).

Question 3. *Although Vasopressin Tannate in Oil (NDA 3-402) is listed in the Orange Book as Discontinued Drug Product List, it was removed from the market by the Manufacture for business reasons, and not for safety concerns. Vasopressin Injection, USP, contains the same active moiety and is formulated as* [redacted] (b) (4). *Luitpold intends to submit a 505(b)(2) application using literature to support the proposed indication along with a justification for changing* [redacted] (b) (4) *for the active moiety Vasopressin. Does the Agency agree with this proposed filing strategy?*

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

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

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

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug

product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. As noted above, if you are proposing to rely on published literature, include copies of the article(s) in your submission.

Finally, 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 ANDA that cites the duplicate product as the reference listed drug.

Luitpold 6-25-13 Response to FDA's Preliminary Comments for Question 3
Clarification is needed regarding the comment cited on page 3, "Finally, 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 ANDA that cites the duplicate product as the reference listed drug."

Questions:

1. Should circumstances change that would render another 505(b)(2) application receives approval shortly after our NDA has been accepted, 1) Will our NDA be allowed to move forward toward approval? 2) Will our NDA have to be converted to an ANDA? 3) If converted to am ANDA will the excess user be refunded to Luitpold?

   Discussion during Meeting
   The Division responded that approval of a pharmaceutically equivalent product after the submission of Luitpold's application would not render the submission of Luitpold's application via the 505(b)(2) pathway inappropriate. The user fee question is, therefore, irrelevant.

2. Can our 505(b)(2) application for Vasopressin be converted to a 505(j)? If so, will the Division, transfer the application to the Office of Generic Drug on behalf of Luitpold? If that could be done would our already paid user fee be applied to cover the ANDA fee? Would the rest be refunded?

   Discussion during Meeting
   The Division responded that as noted in the response to Question 1, the approval of a pharmaceutically equivalent product after submission of Luitpold's 505(b)(2) application would not render their 505(b)(2) application inappropriate. FDA would not convert the application to a 505(j) application and would continue to review the application as a 505(b)(2) application.

The sponsor asked if they would receive a refund of the user fee if they were to submit their 505(b)(2) application, but later withdraw it. Mr. Jones responded that 75 percent of the application fee would be refunded for the application if it is withdrawn before filing. Any further questions on refunds can be directed to Michael Jones at 301-796-3602.

Question 4. *The 505(b)(2) application will be filed with a reference to study literature for the non-clinical and clinical data sections. Does the Agency agree with this proposed plan?*

FDA Response:
We agree.

Question 5. *Luitpold will submit a comprehensive data package containing a summary of the global literature regarding the product. Does the Agency agree that the literature that will be provided in Module 5 is sufficient to fulfill the requirement for NDA approval?*

FDA Response:
The literature that will be provided in Module 5 appears sufficient to support NDA submission, but whether it is sufficient to fulfill the requirement for NDA approval is a review issue.

We urge you to be as thorough as possible in identifying all adequate and well-controlled studies published or indexed on websites to support any proposed indications and to describe in any submission how you searched for relevant studies. We also urge you to obtain, in addition to copies of manuscripts, the protocols and raw data or the rights to reference the data for major supportive studies.

Question 6. *The Sponsor will mitigate any risk to the patients with detailed dosing instructions and safety information to be provided in the labeling. Therefore the Sponsor does not believe any further REMS strategy is necessary for this product. Does the Agency agree?*

FDA Response:
We agree.

Question 7. *The pediatric data package consists of a summary of the literature. Luitpold has summarized the available data to support the pediatric dosing regimen proposed in the label. Per the FD&C Act, as amended by PREA, Section 505B(a)(4)(A)(i): (A) Full waiver.:[. ..] (i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed). The Sponsor believes that additional pediatric studies would be difficult to enroll due to the small population size for the proposed indication and are therefore not warranted. Does the Agency agree that a pediatric data package from the literature is sufficient and that no additional pediatric studies are warranted?*

FDA Response:
Under the Pediatric Research Equity Act (PREA), you are required to submit a pediatric assessment of the safety and efficacy of vasopressin and information to support dosing in pediatric patients. Whether the pediatric data package with a summary of the literature presented in your background meeting package is sufficient to support a pediatric assessment for all pediatric age groups for the proposed indications will be a review issue.

Additionally, under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2). If an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain a specific discussion of the adequacy of data to support a pediatric assessment for any proposed indications that trigger PREA. Additionally, the PSP must include an outline of the pediatric study or studies, if applicable, 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. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

Because it is not clear whether your summary of the literature will be sufficient to support a complete pediatric assessment, you recommend that you consider including in a plan to request waivers or deferrals for any relevant pediatric age groups in your initial Pediatric Study Plan.

Additional FDA Preliminary Comments

Biopharmaceutics:

Under CFR Sec.320.21 Requirements for submission of bioavailability and bioequivalence data, it is stated that

(a) Any person submitting a full new drug application (NDA) to the Food and Drug Administration (FDA) shall include in the application either:
(1) Evidence measuring the *in vivo* bioavailability of the drug product that is the subject of the application; or
(2) Information to permit FDA to waive the submission of evidence measuring *in vivo* bioavailability.

Therefore, you need to provide information and your justifications to allow FDA to waive the evidence for measuring *in vivo* bioavailability. Please also see CFR 320.22 for the criteria for waiver of evidence of *in vivo* bioavailability or bioequivalence.

FDA will review the submitted information and will determine if the waiver could be granted after NDA submission.

Chemistry, Manufacturing, and Controls:

1. The proposed specification for drug substance is not sufficient for release of drug substance Vasopressin. We recommend including the following tests and acceptance criteria in the specification: identification by amino acid analysis, specific optical rotation, each specified identified impurity with the proposed acceptance criteria and any unidentified impurity with the proposed limit, peptide content, heavy metals, and total microbial aerobic count.

2. To prove the proper structure of the vasopressin with disulfide bridge, we recommend you conduct a bioassay as a one-time characterization study of vasopressin synthesized by the proposed manufacturer, (b) (4).

   Luitpold 6-25-13 Response to *Additional FDA Preliminary Comments* for CMC Comment 2:
   Question:
   Please clarify the bioassay method referenced in comment 2 above. A copy of the USPXX monograph for Vasopressin Injection is attached for your review.

   Discussion during Meeting
   Dr. Soldatova stated that the bioassay specified in the USP XXII monograph for Vasopressin Injection is not considered reliable and asked whether the sponsor could provide an alternative method that is more reliable. If not, Dr. Soldatova suggested that the sponsor test for the presence of a disulfide bridge in the drug product release specification.

   The sponsor agreed to consider a strategy for determining the presence of a disulfide bridge and stated that they would request a follow-up teleconference with the CMC reviewers to discuss this issue further.

3. The proposed drug product specification is not sufficient for release of Vasopressin Injection, USP. The Agency recommends including the following in the drug product specification:
   - Include test and acceptance criteria for individual specified identified, for specified unidentified impurities, and for total impurities/degradation products.
   - Identification by HPLC retention time is not specific. Include either a specific test, e.g., molecular mass by mass-spectrometry or additional non-specific test.
   - Specify range of the acceptance criteria for chlorobutanol content.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

3.0 ATTACHMENTS AND HANDOUTS

Luitpold's 6-25-13 Response to FDA's Preliminary Comments

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

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

/s/

ELLIS F UNGER
07/16/2013