CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209360Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

NDA: 209360
Drug: Giapreza (LJPC-501 – angiotensin II)
Class: Vasoconstrictor
Applicant: La Jolla Pharmaceutical Company
Proposed Indications: Treatment of hypotension in adults with distributive shock
Date of submission: June 29, 2017
PDUFA date: February 28, 2018
Target Action date: December 21, 2017

II. REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Product

Cross Discipline Team Leader (CDTL): Martin Rose
Medical Reviewers: Fortunato Senatore, Tzu-Yun McDowell
Pharmacology & Toxicology: Gowra Jagadeesh
Regulatory Health Project Manager: Sabry Soukehal

Office of Pharmaceutical Quality

Drug Product and environmental assessment (EA): Rao Kambhampati
Drug Substance: Raymond Frankewich
Microbiology: Jianli Xue
Process: Yahong Wang
Facility: Jonathan Swoboda
Biopharmaceutics: Gerlie Gieser
Application Technical Lead: Mohan Sapru

Office of Clinical Pharmacology

Venkateswaran ChithambaramPillai

Office of Surveillance and Epidemiology

DPV: Amy Chen
DMEPA: Sarah Thomas
DEPI: Margie Goulding
DRISK: Theresa Ng

Office of Prescription Drug Promotion
Puja Shah

Office of Biostatistics
Ququan (Cherry) Liu

III. BACKGROUND

LJPC-501 is a first-in-class, octapeptide, vasopressor, that activates the renin-angiotensin system. It is a synthetic human angiotensin II, with the following sequence: aspartic acid – arginine – valine – tyrosine – isoleucine – histidine – proline – phenylalanine. This sequence is identical to the (b) (4) product as shown in the illustration below. LJPC-501 differs from Hypertensin® by 2 amino acids in the 1st and 5th positions as illustrated. LJPC-501 also differs from a bovine analogue by 1 amino acid in the 5th position as illustrated. LJPC-501 has not previously been marketed as a drug. Consequently, the Office of Pharmaceutical Quality classified LJPC-501 as a New Molecular Entity.

LJPC-501[a]	Asp[1]-Arg-Val-Tyr-**Ile**[5]-His-Pro-Phe[8]	(Ile[5]-angiotensin II)
Ile[5]-angiotensin II (b) (4)	Asp[1]-Arg-Val-Tyr-**Ile**[5]-His-Pro-Phe[8]	(Ile[5]-angiotensin II)
Hypertensin®	Asn[1]-Arg-Val-Tyr-**Val**[5]-His-Pro-Phe[8]	(Val[5]-angiotensin II amide)
Bovine	Asp[1]-Arg-Val-Tyr-**Val**[5]-His-Pro-Phe[8]	(Val[5]-angiotensin II)

[a] Ile[5]-angiotensin II used to manufacture LJPC-501 is identical to the endogenous human form of angiotensin II.

The bovine angiotensin II, known as Hypertensin®, was approved on 23 Feb 1961 under NDA 012791 for treatment of shock and circulatory collapse and was withdrawn effective 18 June 2009. The NDA withdrawal was not due to safety or efficacy reasons.

LJPC-501 was originally submitted under the 505(b)(2) pathway and relied on a Phase 3 study conducted under a Special Protocol Assessment agreement (Protocol LJ501-CRH01 entitled "A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501in Patients with Catecholamine-Resistant Hypotension (CRH)) approved by the Division on February 2, 2015, and published literature on angiotensin II. However, as documented in Dr. Rose's and Dr. Stockbridge's memos, reliance on published literature was not necessary for approval. Thus, the regulatory pathway was adjusted to 505(b)(1).

IV. APPLICATION REVIEW

1. Regulatory Timeline

- Special Protocol Assessments: February 2, 2015
- End-of Phase 2 meeting: August 16, 2016
- Pre-NDA meeting: May 9, 2017
- NDA Receipt Date: June 29, 2017
- Filing Day 60: August 28, 2017
- Filing 74-Day: September 11, 2017

- Mid-cycle Communication Meeting:
- Late-cycle Meeting: N/A. The Applicant elected to cancel the meeting (see DARRTS memo, Reference # 4195439)
- Advisory Committee: N/A
- PDUFA Date: February 28, 2018

2. User Fee

The user fee for this application was paid in full on June 21, 2017 (User Fee ID 3017015).

3. Advisory Committee

There was no Advisory Committee meeting for this NDA because there were no controversial issues that would benefit from an Advisory Committee discussion.

4. Pediatric Review Committee (PeRC)

The NDA submission included an agreed amended initial Pediatric Study Plan approved by the Division on March 24, 2017, where the Applicant requested deferral of pediatric studies.

The Applicant planned two clinical studies in pediatric patients (b) (4) who remain hypotensive despite (b) (4).

- Study LJ501-CRH02 to evaluate the safety and efficacy of LJPC-501 in patients (b) (4) o 17 years old.
- Study LJ501-CRH03 to evaluate the safety and efficacy of LJPC-501 in patients ≤ 2 years old (including neonates).

The Applicant clarified that study LJ501-CRH03 would take place after the safety and efficacy of LJPC-501 is established in the (b) (4)– 17 years old patient population, and the review of the nonclinical toxicology study in newborn (b) (4) (age < 1 week) is completed.

The Applicant proposed to initiate the studies as follows:

- Pediatric patients (b) (4)– 17 years old: No later than August 2017
- Nonclinical toxicology study: No later than November 2018
- Pediatric patients ≤ 2 years old: No later than May 2019

A PeRC meeting was held on December 13, 2017 to discuss the Applicant's deferral requests. The committee agreed to the deferral plan but recommended to initiate the toxicology study and the pediatric study in patients ≤ 2 years old sooner. This suggestion was accepted by the Division and communicated to the Applicant on December 14, 2017. The Applicant agreed to the below new timeline (see DARRTS memo Reference # 4195831)

Nonclinical toxicology study:

- Final Protocol Submission: March 2018
- Study/Trial Completion: September 2018
- Final Report Submission: January 2019

Pediatric patients ≤ 2 years old:

- Draft Protocol Submission: February 2019
- Final Protocol Submission: March 2019
- Study Completion: September 2023
- Final Report Submission: March 2024

All deferred studies (clinical and nonclinical) are post marketing requirements communicated in the action letter.

5. Trade name

On February 8, 2017, the Applicant submitted the proposed proprietary name (b) (4) to IND 122708. This name was denied by the Division of Medication Error Prevention and Analysis (DMEPA) on August 4, 2017, because it could be confused with the currently marketed product, (b) (4).

On August 17, 2017, the Applicant submitted the proposed proprietary name (b) (4) to the NDA. This name was denied by DMEPA on November 14, 2017 because it could result in medication errors due to confusion with another product that was also under review by DMEPA.

On November 21, 2017, the Applicant submitted the proposed proprietary name (b) (4). DMEPA found it unacceptable based on 21CFR201.10(c)(5) because orthographic similarity to the currently marketed proprietary name, (b) (4)

On December 6, 2017, the Applicant submitted the proposed proprietary name (b) (4). DMEPA found it unacceptable based on 21CFR201.10(c)(5) because of similarity in pronunciation to the currently marketed proprietary name, (b) (4)

On December 11, 2017, the Applicant submitted the proposed proprietary name Giapreza for review. This name was considered conditionally acceptable. A grant letter was issued on December 19, 2017

6. Facilities Inspections

The Division of Clinical Compliance Evaluation within the Office of Scientific Investigations did not conduct a facility inspection at the request of the Division of Cardiovascular and Renal Products because the preliminary review of the site-specific database led to the conclusion that there were no outlier sites that would have warranted a site audit. Based on a funnel-plot provided by the statistician, the only site that may have qualified for an audit was the Cleveland Clinic. However, given the highly robust overall results of the study in favor of angiotensin II, exclusion of the data from this site from the primary efficacy analysis could not have materially affected the results.

7. Reviews

Below are the conclusions reached by the LJPC-501 team members.

a) Office of Drug Evaluation I decisional memorandum – December 21, 2017

Dr. Unger performed a benefit-risk assessment and concluded that the demonstrated benefit of LJPC-501 outweighed its potential harms. Dr. Unger concurred with the Division Director and Cross-Disciplinary Team Leader conclusions to approve the NDA and provided additional points not highlighted in the reviews.

b) Division Memorandum – December 21, 2017

Dr. Stockbridge documented his concurrence with Dr. Rose's memos and supported approval of LJPC-501 as a pressor for use in distributive shock.

c) Cross-Discipline Team Leader Memorandums – December 16, 2017 and December 21, 2017

In his memo dated December 16, 2017, Dr. Rose summarized the reviews provided by each discipline. He performed a benefit-risk assessment and concluded that despite the lack of a confirmed benefit for any outcome other than Mean Arterial Pressure (MAP), the benefits of LJPC-501 outweighs its potential risks. His review addendum dated December 21, 2017, clarified that this NDA can be approved as a 505 (b)(1) application as the team's decision was based solely on safety and effectiveness data generated by the Applicant.

d) Clinical review – December 7, 2017

Recommendation: Approval.

There were two primary reviewers: Dr. Fred Senatore (efficacy) and Dr. Tzu-Yun McDowell (safety). The basis of the efficacy evaluation was the Phase-3 clinical trial LJ501-CRH01. The basis of the safety evaluation included the Phase-3 clinical trial LJ501-CRH01 as well as 9 studies listed in Table 7 of the clinical review. However, the emphasis for the safety evaluation resided with the Phase-3 clinical trial.

Dr. Senatore reviewed the relevant individual trials used to support efficacy and concluded that LJPC-501 was shown to be efficacious in raising the MAP to target levels: > 75 mmHg or a 10 mmHg increase in baseline MAP. Efficacy appeared to be consistent across all subgroups, including critically high-risk subjects whose baseline MAP was < 65 mmHg. He performed a benefit-risk assessment and concluded that the safety profile of LJPC-501 was mostly like that of placebo. The major safety concern was an excess of venous and arterial thromboembolic events with active treatment (12.9% vs. 5.1% of subjects in the LJPC 501 and placebo arms, respectively). Achieving target blood pressure goals in patients with distributive shock outweighed the risk of thrombotic events that could be routinely managed in the intensive care setting by standard prophylactic anticoagulation therapy. The decision was to recommend approval.

e) Clinical Pharmacology review – December 2, 2017:

Recommendation: Approval.

Dr. ChithambaramPillai's review had the objective to address whether (a) the submitted pharmacokinetic and pharmacodynamic information for angiotensin II were adequate to inform product labeling, and (b) the proposed dosing regimen was adequate for the treatment of hypotension in adults with Catecholamine-Resistant Hypotension (CRH).

Dr. ChithambaramPillai reviewed the pharmacokinetics, pharmacodynamics, and dosing information as well as published literature reports which used bovine ^{5}Val-angiotensin II amide. He noted that no distribution, metabolism, and excretion studies were conducted using human angiotensin II because both human and bovine angiotensin II exert comparable binding affinities. He also reported that because LJPC-501 is administered in a controlled clinical setting and the dose is titrated to effect, drug-drug and drug-disease interactions do not limit the use of LJPC-501 in patients with CRH.

f) Pharmacology/Toxicology review – November 20, 2017

Recommendation: Approval.

Dr. Jagadeesh focused his review on published literature as nonclinical studies were not conducted by the Applicant.

His review noted that the actions of angiotensin II extend beyond blood pressure increase. At physiological doses, it impairs insulin signaling, increases oxidative stress, and promotes production of superoxide radicals. At two- to three-fold the physiological levels, it is associated with hypertension, atherosclerosis, aortic aneurysms, acute coronary syndrome and myocardial infarction. Additionally, chronic exposure to angiotensin II causes vascular inflammation and thrombosis.

Dr. Jagadeesh stated that the toxicities of exogenously administered Ang II are manifested as a result of excessive pressor effects on the vasculature, heart and kidney, considered to be the target organs of action. Furthermore, published In vitro and in vivo studies have demonstrated that angiotensin II has a genotoxic potential as it causes DNA single and double strand breaks in abasic sites.

Dr. Jagadeesh reported that angiotensin II has no adverse effect on male or female reproductive organs, fertility, organogenesis, or fetus development, survival and birth but that there is no information on the effect of Ang II on lactation in women.

g) Tertiary Pharmacology Review – December 14, 2017

Dr. Brown acknowledged the thorough evaluation conducted by Dr. Jagadeesh and did not express concerns regarding the lack of toxicology, carcinogenicity, or animal reproduction data because LJPC-501 is intended to be used acutely and because the active ingredient is an endogenous peptide. He indicated that angiotensin II can be classified as a vasoconstrictor as its Established Pharmaceutical Class.

Dr. Brown agreed with the pharmacology/toxicology reviewer's conclusion to approve the NDA.

h) Statistical review – November 22, 2017

Recommendation: Approval.

Dr. Liu's review acknowledged the efficacy of LJPC-501 in increasing MAP. She described the statistical analysis methodology, which consisted of using a logistic regression for the primary endpoint analysis, adjusted by fixed covariates. She noted that the percent of responders achieving the target MAP at Hour 3 was statistically significantly higher in the LJPC-501 group compared to the placebo group. She also indicated that the efficacy trended in favor of LJPC-501 across the subgroups of age, gender, geographic regions and selected special populations.

Dr. Liu concluded that the study supports that LJPC-501 is superior in the treatment of CRH compared to the placebo.

i) Office of Pharmaceutical Quality integrated review – December 11, 2017

Recommendation: Approval.

- *Drug Substance*: The drug substance is the acetate salt of synthetic angiotensin II. The active pharmaceutical product, a synthetic Ile5-angiotensin II acetate, has been classified as a New Molecular Entity (NME) because it does not have the same amino acid sequence, chemical

form and origin as the previously-marketed bovine angiotensin II (Hypertensin® NDA 12791).

- *Drug Product*: Angiotensin II injection for intravenous infusion drug product is a sterile, aqueous solution containing 2.5 mg/mL angiotensin II and 25 mg/mL mannitol in water, adjusted to pH 5.5, supplied in single-dose vials. It is supplied in two strengths: 2.5 mg angiotensin II/vial (2.5 mg/mL) and 5 mg angiotensin II/vial (2.5 mg/mL). There are no differences in the formulation or container closure system used for packaging for the two strengths. LJPC-501 drug product is diluted in 0.9% (v/v) sodium chloride solution prior to administration. All excipients utilized in the LJPC-501 drug product formulation are compendial. The level of each excipient is at or below levels typically found in other parenteral products. All critical quality attributes are controlled by product specification.
- *Manufacturing*: The manufacturing proces (b) (4) The process steps include (b) (4)
- *Microbiology*: (b) (4) The results of the microbiological in-use study support a 24-hour hold period at 25°C/60% Relative Humidity.
- *Biopharmaceutics*: The drug product had the same formulation, concentration, presentation, API supplier, and manufacturing process steps as the lots that have been evaluated for efficacy, safety, and PK/PD in the pivotal Phase 3 clinical trial. Therefore, bridging data was not required, nor was a biowaiver request.
- *Container Closure System*: It consisted of a clear 3 mL USP/Ph. Eur. Type (b) (4) glass vial with a 13 mm elastomeric stopper, sealed with an aluminum closure and a plastic flip-off cap. The applicant has demonstrated compatibility with the active ingredient, excipients, container and closure components, and dosing components.
- Product Stability and In-Use Studies: The stability results demonstrated that the product was stable for 18 months under long-term conditions and (b) (4) months under accelerated conditions. The applicant also performed an in-use study to evaluate the compatibility of the drug product with saline (0.9% sodium chloride) solution. Results from this in-use study demonstrated that LJPC-501 drug product was stable and compatible when diluted in normal saline IV bags of both the PVC and non-PVC bag types for (b) (4) hours at 25°C.
- Expiration Date and Storage Conditions: The stability data support a shelf-life of 18 months for the product when stored at 2°C – 8°C in the proposed commercial container closure system.
- *Assessment of Manufacturing Facilities*: Overall approval of all listed manufacturing facilities was recommended.

The OPQ team concluded that the NDA can be approved and that Post-Marketing Commitments are not necessary.

8. Consults

a) Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (DMEPA) – November 16, 2017, and December 6, 2017

DMEPA performed a risk assessment of the proposed angiotensin II container labels, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and areas for improvement. Several deficiencies that may lead to medication errors were noted. DMEPA provided recommendations to promote the safe use of the product prior to the final labeling discussions with the Applicant.

b) Office of Surveillance and Epidemiology, Division of Risk Management (DRISK) – December 19, 2017

The focus of DRISK was to evaluate whether a risk evaluation and mitigation strategy (REMS) for this New Molecular Entity was necessary to ensure its benefits outweigh its risks. The risks associated with LJPC-501 include transient hypertension and hypotension (b) (4) The safety data from the clinical development program found the adverse events of LJPC-501 are similar to that of placebo. The Applicant did not submit a proposed REMS or risk management plan with this application, however DRISK agrees that a REMS is not needed.

c) Office of Prescription Drug Promotion (OPDP) – December 1, 2017

OPDP reviewed the draft prescribing information and carton and container labeling. Comments were provided to the Division prior to the final labeling discussions with the Applicant.

d) Division of Pediatric and Maternal Health (DPMH) – November 30, 2017

DPMH reviewed the draft prescribing information for compliance with the PLLR. Revisions to subsections 8.1 and 8.2 were made and communicated to the Division prior to the final labeling discussions with the Applicant.

9. Labeling

Labeling (prescribing information, carton and container labels) was thoroughly reviewed throughout the review cycle. Several labeling discussions occurred with the Applicant. The final agreed-upon labeling was attached to the approval letter.

V. CONCLUSION

The review team recommended approval. An approval letter was signed by Dr. Unger on December 21, 2017.

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/s/

SABRY SOUKEHAL
12/22/2017

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**209360**
PMR/PMC Set (####-#)	3320-1
Product Name:	**LJPC-501**
Applicant Name:	**La Jolla Pharmaceutical Company**
ODE/Division:	**ODE1/Division of Cardiovascular and Renal Products**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a toxicology study in newborn lambs aged less than 1 week to evaluate overall safety, including development of kidneys, heart, blood vessels, and brain, of LJPC-501 to support clinical study in children ages 0-2 years.

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	n/a
Final Protocol Submission:	03/2018
Study/Trial Completion:	09/2018
Interim /Other:	n/a
Final Report Submission:	01/2019

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The renin-angiotensin system plays a vital role in the tissue-specific development (i.e., function and maturation) of essential organs and is critical in cardio-renal adaptation to life after birth. Given that the expression of AT1 and AT2 receptors on various tissues, including heart, vasculature, brain, and kidney, vary depending on developmental stage, studies with angiotensin II should be conducted in newborn (b) (4) (Ref: Sadoutounnissa S. and Sandberg K.; Ontogeny of angiotensin II receptors; Cell Biol. Int. 1996; 20:169-176) prior to studying in humans (b) (4) years of age.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]

☐ *For non-PREA pediatric studies/trials only*: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☐ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

   ☒ The study/clinical trial meets criteria for a PMR or a PMC.

   ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

   ☒ The applicant has adequately justified the choice of milestone dates.

   ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

   - There is a significant question about the public health risks of the drug.
   - There is not enough existing information to assess the public health risks of the drug.
   - Information about the public health risks cannot be gained through a different kind of investigation.
   - The trial will be appropriately designed to answer question about a drug's efficacy or safety.
   - The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☐ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality**.

Insert electronic signature (usually the D puty Director for Safety)

Mary R. Southworth -S

Digitally signed by Mary R. Southworth -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300234574, cn=Mary R. Southworth -S
Date: 2017.12.20 10:26:50 -05'00'

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

Appendix A
PMR/PMC Development Template (FRM-ADMIN-60)
Instructions for Use

[click here to return to the template]

Purpose:
The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:
The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:
The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.[10] The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:
The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.[11] This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

---

[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

[11] A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click here to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click here to return to Section B of the template]

1. **PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

   PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.[12]

   Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

   Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed ***[see Appendix B for examples]***.

2. **PMR/PMC Milestones**: List the PMR/PMC milestones in the specified format.

   Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

   The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

   The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.[13]

[12] The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

[13] "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See FDA guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

"Other" milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.[14]

SECTION C: PMR/PMC Rationale [Click here to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

[14] Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section applies only to FDAAA PMRs and 506B "reportable" PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS[15] and Sentinel's ARIA[16] system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

***Question 4.a*: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

***Questions 4.b-d*: Explanation of whether FAERS and Sentinel's postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

***Question Q4.e*: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, in include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control

[15] FDA Adverse Event Reporting System (FAERS)
[16] Active Risk Identification and Analysis (ARIA)

- Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f*: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either "type of study" or "type of clinical trial." Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click here to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select "yes" if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select "not applicable."

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 "core" milestones).

Note: Additional milestones also must be tracked by the division (see MAPP 6010.2, *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click here to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. **This PMR/PMC has been reviewed for clarity and consistency… reliability of drug quality**.

   This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy**.**

- Drug-Drug Interactions (gastric acid reducing agents)

  Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

  Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Anti-Drug Antibody Responses

  Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient's test sample at each sampling point.

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

/s/

Lori A WACHTER
12/20/2017

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**209360**
PMR/PMC Set (####-#)	3320-2
Product Name:	**LJPC-501**
Applicant Name:	**La Jolla Pharmaceutical Company**
ODE/Division:	**ODE1/Division of Cardiovascular and Renal Products**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Pediatric Assessment

Conduct an open-label multicenter study of LJPC-501 to assess effects on mean arterial pressure and collect safety data in pediatric patients aged >2-17 years in distributive shock who remain hypotensive despite receiving fluid therapy and vasopressor therapy.

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	n/a
Final Protocol Submission:	04/2017
Study/Trial Completion:	08/2021
Interim /Other:	n/a
Final Report Submission:	02/2022

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

LJPC-501 is intended for use in critically ill adult patients who present with distributive shock (b) (4) [redacted] As a new molecular entity, a pediatric trial will evaluate the effect of LJPC-501in patients aged (b) (4) 17 years who present with (b) (4) distributive shock (b) (4) [redacted] The objective of this study is to fulfill requirements under the Pediatric Research Equity Act.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

   ☐ Yes
   ☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**
   [Select all that apply]

   ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
   ☐ Geriatric population
   ☐ Lactating/nursing mothers
   ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
   ☐ Orphan or rare disease population
   ☐ Pregnant women
   ☐ Racial/ethnic population
   ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

No additional comments.

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality**.

Insert electronic signature (usually the Deputy Director for Safety)

Mary R. Southworth -S

Digitally signed by Mary R. Southworth -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300234574, cn=Mary R. Southworth -S
Date: 2017.12.15 11:34:47 -05'00'

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

Appendix A
PMR/PMC Development Template (FRM-ADMIN-60)
Instructions for Use

[click here to return to the template]

Purpose:
The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:
The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:
The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.[10] The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:
The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.[11] This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

[11] A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click here to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click here to return to Section B of the template]

1. **PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

   PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.[12]

   Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

   Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed ***[see Appendix B for examples]***.

2. **PMR/PMC Milestones**: List the PMR/PMC milestones in the specified format.

   Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

   The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

   The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.[13]

[12] The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

[13] "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See FDA guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

"Other" milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.[14]

SECTION C: PMR/PMC Rationale [Click here to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

[14] Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section applies only to FDAAA PMRs and 506B "reportable" PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS[15] and Sentinel's ARIA[16] system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

***Question 4.a*: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

***Questions 4.b-d*: Explanation of whether FAERS and Sentinel's postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

***Question Q4.e*: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, in include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control

[15] FDA Adverse Event Reporting System (FAERS)
[16] Active Risk Identification and Analysis (ARIA)

- Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f*: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either "type of study" or "type of clinical trial." Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click here to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select "yes" if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select "not applicable."

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 "core" milestones).

Note: Additional milestones also must be tracked by the division (see MAPP 6010.2, *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click here to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. **This PMR/PMC has been reviewed for clarity and consistency… reliability of drug quality**.

   This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy**.**

- Drug-Drug Interactions (gastric acid reducing agents)

  Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

  Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Anti-Drug Antibody Responses

  Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient's test sample at each sampling point.

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/s/

Lori A WACHTER
12/20/2017

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**209360**
PMR/PMC Set (####-#)	3320-3
Product Name:	**LJPC-501**
Applicant Name:	**La Jolla Pharmaceutical Company**
ODE/Division:	**ODE1/Division of Cardiovascular and Renal Products**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct an open-label multicenter study of LJPC-501 to assess effects on mean arterial pressure and collect safety data in pediatric patients aged 0-- ≤2 years in distributive shock who remain hypotensive despite receiving fluid therapy and vasopressor therapy.

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	02/2019
Final Protocol Submission:	03/2019
Study/Trial Completion:	09/2023
Interim /Other:	n/a
Final Report Submission:	03/2024

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

LJPC-501 is intended for use in critically ill adult patients who present with distributive shock (b) (4) As a new molecular entity, a pediatric trial will evaluate the effect of LJPC-501in patients aged 0—≤ 2 years who present with (b) (4) distributive shock (b) (4) The objective of this study is to fulfill requirements under the Pediatric Research Equity Act.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]

☐ *For non-PREA pediatric studies/trials only*: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☐ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

Prior to performing the pediatric study in the 0 -- ≤ 2 year age population, a newborn (b) (4) toxicology study will be conducted to ensure safety in this age group.

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality**.

Insert electronic signature (usually the Deputy Director for Safety):

Mary R. Southworth -S

Digitally signed by Mary R. Southworth -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300234574, cn=Mary R. Southworth -S
Date: 2017.12.15 11:37:21 -05'00'

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

Appendix A
PMR/PMC Development Template (FRM-ADMIN-60)
Instructions for Use

[click here to return to the template]

Purpose:
The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:
The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:
The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.[10] The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:
The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.[11] This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

[11] A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click here to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click here to return to Section B of the template]

1. **PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

   PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.[12]

   Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

   Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed ***[see Appendix B for examples]***.

2. **PMR/PMC Milestones**: List the PMR/PMC milestones in the specified format.

   Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

   The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

   The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.[13]

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[12] The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

[13] "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See FDA guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

"Other" milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.[14]

SECTION C: PMR/PMC Rationale [Click here to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

[14] Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section applies only to FDAAA PMRs and 506B "reportable" PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS[15] and Sentinel's ARIA[16] system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

***Question 4.a*: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

***Questions 4.b-d*: Explanation of whether FAERS and Sentinel's postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

***Question Q4.e*: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, in include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control

[15] FDA Adverse Event Reporting System (FAERS)
[16] Active Risk Identification and Analysis (ARIA)

- Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususual course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f*: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either "type of study" or "type of clinical trial." Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click here to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select "yes" if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select "not applicable."

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 "core" milestones).

Note: Additional milestones also must be tracked by the division (see MAPP 6010.2, *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click here to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. **This PMR/PMC has been reviewed for clarity and consistency… reliability of drug quality**.

   This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy**.**

- Drug-Drug Interactions (gastric acid reducing agents)

  Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

  Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Anti-Drug Antibody Responses

  Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient's test sample at each sampling point.

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/s/

Lori A WACHTER
12/20/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 6, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209360
Product Name and Strength:	Angiotensin II Injection, 2.5 mg/mL and 5 mg/2 mL
Applicant/Sponsor Name:	La Jolla Pharmaceutical Company Inc. (La Jolla)
Submission Date:	November 30, 2017
OSE RCM #:	2017-1332-1
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels, carton labeling, and prescribing information (PI) for Angiotensin II (Appendices A and B) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

From our previous label and labeling review,[1] the recommendation to add the statement "(b) (4) to Section 2 of PI was discussed with the Review Team. The Review Team discussed the fact that:

1. The use of this proposed product is in the ICU setting with close blood pressure monitoring by highly trained healthcare professionals.
2. The risk of overlooking the differences in the units of measurement is minimized because of the small package size of the proposed product. For example, if an end user overlooks the "ng" for a 20 mg/kg/min dose, then it would require an unreasonably large number of 5 mg/(b) (4) mL vials to obtain just a 1-minute dose for a 72 kg patient, which should prevent the error.

Based on the Review Team's discussion, this recommendation was not supported by the team and was not communicated to the Applicant.

[1] Thomas, S. Label and Labeling Review for Angiotensin II (NDA 209360). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 16. RCM No.: 2017-1332.

The revised container labels, carton labeling, and PI incorporated some of our recommendations from our previous review, but they can still be improved to promote safe use and to mitigate the risk of medication errors. We provide our recommendations in Section 3 below.

Also, we note the package type term is still absent from the Dosage Forms and Strengths section in the Highlights of PI and Full PI. We also note the use of the (b) (4) in Section 16.1 of the Full PI and on the container labels and carton labeling. Per La Jolla's November 30, 2017 submission cover letter, "(b) (4) ." We again contacted CMC on November 30, 2017 to inform them of this deficiency in the labeling and La Jolla's comments. We defer to CMC for the determination of the correct packaging type term, and we recommend consistently applying the appropriate packaging type term across the container labels, carton labeling, and prescribing information.

3 RECOMMENDATIONS FOR LA JOLLA PHARMACEUTICAL COMPANY INC.

We recommend the following be implemented prior to approval of this NDA:

A. See our recommendations for the Prescribing Information in tracked changes in Appendix B.
B. Container Labels and Carton Labeling
    1. As currently presented, the 2.5 mg/mL and the 5 mg/2 mL vials have the same commercial package size numbers (last 2 digits) in the NDC number despite their different quantities (i.e. both vials use (b) (4)). We recommend differentiating the package size numbers between the vials to reflect the different quantities in the package size. Ensure revisions to NDC numbers are carried over to Section 16 of the Full PI as well.

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/s/

SARAH E THOMAS
12/06/2017

CHI-MING TU
12/06/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 1, 2017

To: Sabry Soukehal, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

Michael Monteleone, MS, Associate Director for Labeling, DCaRP

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Pharm.D., RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for LJPC-501 (angiotensin II)

NDA: 209360

In response to DCaRP's consult request dated July 10, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for LJPC-501 (angiotensin II).

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCaRP (Sabry Soukehal) on November 28, 2017, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 29, 2017, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 or Puja.Shah@fda.hhs.gov.

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/s/

PUJA J SHAH
12/01/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health PLLR Labeling Review

Date: November 30, 2017 **Date consulted:** August 25, 2017

From: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Angiotensin II

NDA: 209360

Applicant: La Jolla Pharmaceutical

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

Materials Reviewed:

- Applicant's NDA submission, dated June 29, 2017
  - Proposed labeling
  - Module 2.7.4 Clinical Summary of Safety
  - Response to Request for Information sent on October 23, 2017, submitted October 31, 2017

Consult Question: DCRP requests input regarding proposed PLLR labeling

INTRODUCTION

On June 29, 2017, the applicant (La Jolla Pharmaceutical) submitted a 505(b)(2) NDA for angiotensin II for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy. The application relies upon the

findings of safety and efficacy from a single Phase 3 clinical trial and a review of published literature. DCRP consulted the Division of Pediatric and Maternal Health (DPMH) to provide input regarding compliance of the proposed labeling with the Pregnancy and Lactation Labeling Rule (PLLR) [1].

BACKGROUND

Regulatory History

- Angiotensin II acetate (human sequence, 5-isoleucine [Ile5]-angiotensin II) has not previously been approved for marketing in the United States.
- This 505(b)(2) NDA relies primarily on a Phase 3 clinical trial for safety and efficacy, and additionally supported by published literature on angiotensin II. In agreement with the Agency, an adequately powered Phase 3 randomized, placebo controlled trial in patients with catecholamine-resistant hypotension could be used to establish the safety and efficacy of angiotensin II. The protocol (LJ501-CRH01) was approved in the US as part of a Special Protocol Assessment. The Phase 3 study was conducted between May 2015 and February 2017 and enrolled patients in the US, Australia, Canada, Belgium, Finland, France, Germany, New Zealand, and the United Kingdom.

Drug Characteristics[2]

- A synthetic human angiotensin II in aqueous solution for intravenous (IV) administration
- Mechanism of action: raises blood pressure by vasoconstriction, increased aldosterone release and renal control of fluid and electrolyte balance; by binding to the G-protein-coupled angiotensin II receptor type 1 on vascular smooth muscle cells which stimulates Ca^{2+}/calmodulin-dependent phosphorylation of myosin and causes smooth muscle contraction.
- $t_{1/2}$: less than one minute

DISCUSSION

Nonclinical

No GLP genotoxicity, carcinogenicity, or reproductive and developmental toxicology studies were conducted.

Clinical

For the Phase 3 clinical trial (LJ501-CRH01), pregnancy was an exclusion criterion and no incidental pregnancies were reported.

The applicant reviewed the published literature for use of angiotensin II in human subjects from PubMed, Medline, Scopus, and Cochrane. The initial broad search (using angiotensin II, administration or infusion or injection and filtered to exclude animal and in vitro studies, regardless of whether safety was discussed) yielded 18,468 studies; after abstract review, 1,124 studies were selected for a review of physiological effects and adverse events associated with angiotensin II intravenous (IV) administration. The systematic search is summarized and

[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[2] From proposed labeling for angiotensin II.

published by Busse LW *et al*. 2017[1]. Only six studies reflected the experience with angiotensin II in pregnant and postpartum women.

In further targeted searches on all published studies of IV administration of angiotensin II to pregnant, postpartum, or lactating women and related to effects of angiotensin II on human male or female fertility, the applicant reports that three additional studies were found valuable that had not been included in the Busse 2017 systematic review of safety or the NDA (Strickland 1994[2], Ramsay 1992[3], and Yunohara 1994[4]) but no additional safety findings were found. The applicant found no clinical literature on angiotensin II use during lactation or effects on females and males of reproductive potential.

The applicant summarizes the literature to describe physiologic effects of angiotensin II and that a progressive resistance to the pressor effects of angiotensin II during normal pregnancy has been documented. Angiotensin II has been studied in pregnant women for its role in pre-eclampsia, as a potential diagnostic test, and as treatment for hypotension during spinal anesthesia associated with Caesarean section. Pressor sensitivity to exogenous angiotensin II is reported to decrease in normal pregnancy, but women who eventually develop preeclampsia become hyper-responsive in late pregnancy. Doses up to 64 ng/kg/min were reported.

- There was no difference in metabolic clearance of angiotensin II between 11 non-pregnant and 37 pregnant women (mean 30 weeks, SEM 0.3 weeks) administered pressor doses of angiotensin II.
- Adverse events during infusions of angiotensin II to pregnant women included headache, dizziness, dyspnea, chest oppression, palpitation, abdominal pain, dyspepsia (fish oil capsules also administered), bradycardia, and low backache.
- A study compared sensitivity to angiotensin II amide at biweekly intervals throughout pregnancy in three groups: 120 primigravid patients who remained normotensive throughout pregnancy, 72 primigravid patients who developed pregnancy-induced hypertension, and 10 nonpregnant, normotensive women. The pregnant subjects were 13 to 17 years old. Two complications at delivery were reported among 2 patients who developed preeclampsia: one stillbirth with placental abruption and one grand mal seizure following delivery of a healthy infant. These events occurred 6 and 12 days after the last angiotensin II infusion, respectively. No AEs or pregnancy complications were reported for the 120 girls who remained normotensive during pregnancy.
- In a study of 26 pregnant subjects aged 14 to 20 years, who received a weekly angiotensin II infusion (titration to dose sufficient to cause 20 mmHg increase in diastolic blood pressure then stopped) from week 29 to week 32 of gestation, there were 2 premature deliveries in women who did not develop pregnancy-induced hypertension.

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[1] Busse LW, Wang XS, Chalikonda DM, Finkel KW, Khanna AK, Szerlip HM, Yoo D, Dana SL, Chawla LS. Clinical experience with IV angiotensin II administration: A systematic review of safety. Crit Care Med. 2017 Aug;45(8):1285-1294. Also, Supplemental digital content 4 - Effects of angiotensin II by organ system (http://links.lww.com/CCM/C620).

[2] Strickland DM, Cox K, McCubbin JH, Whalley PJ, MacDonald PC, Mitchell MD. Plasma prostaglandins during the intravenous infusion of angiotensin II in pregnant women. Am J Obstet Gynecol 1984;150(8):952-5.

[3] Ramsay M, Broughton Pipkin F, Rubin P. Comparative study of pressor and heart rate responses to angiotensin II and noradrenaline in pregnant and non-pregnant women. Clin Sci (London) 1992;82(2):157-62.

[4] Yunohara T, Ito M, Sakoda Y, Okamura H. The effect of angiotensin II on utero-placental and umbilical circulation in normotensive pregnant women. Int J Gynaecol Obstet 1994;45(2):117-23.

Babies were delivered 3 and 4 weeks premature (as per authors, presumably 37 and 36 weeks of gestation, or at least 4 weeks after the last infusion of angiotensin II).

- In 2 studies involving a total of 37 normotensive pregnant subjects, some of whom had a history of or risk factors for preeclampsia, Doppler velocimetry was performed to assess uteroplacental blood flow before and during angiotensin II infusion that was titrated to increase diastolic BP by 20 mmHg. Results indicated no significant alterations in systolic-diastolic ratios in the uterine and umbilical arteries that were associated with angiotensin II infusion; similarly, fetal biophysical profile scores did not change significantly. One of the two studies assessed and reported no congenital anomalies in the infants of the 23 pregnant women enrolled. There is no mention of such assessment in the study of 14 pregnant women.
- Angiotensin II was administered to counteract hypotension associated with spinal anesthesia in 39 pregnant women at term undergoing elective C-section without fetal or newborn adverse effects.

The applicant concludes that these studies did not monitor the pregnant women or their infants for long-term outcomes and it is not known whether angiotensin II can cause fetal harm. Further, the applicant states that "given the critically ill population that angiotensin II will be serving, the time of exposure to the drug, and the short half-life of the molecule, the issues of pregnancy, lactation, and the effect on reproductive organs, albeit critical, are not as immediately important as other chronic disease states."

Reviewer Comment
The applicant's review of literature found studies on exogenous use of angiotensin II in pregnant women published mostly from the 1960's through the 1990's. No safety signals were identified; however, studies were not designed to evaluate for major birth defects or miscarriage. The few reported adverse outcomes are not sufficient to support an association of angiotensin II use during pregnancy. This reviewer agrees with the applicant's conclusions. There are risks to the mother and fetus associated with hypotension associated with distributive or vasodilatory shock. Treatment should not be delayed for a life-threatening condition.

No additional information on angiotensin II is described in the following reproduction and lactation databases or texts: MicroMedex (includes ReproTox and TERIS), LactMed, *Medication's and Mother's Milk* by Thomas Hale, *Drugs in Pregnancy* by GG Briggs and RK Freeman.

CONCLUSIONS
The published data on angiotensin II use in pregnancy are not sufficient to inform of any drug-associated risk of adverse developmental outcomes. There is no relevant clinical information to inform use of angiotensin II in lactating women, or females and males of reproductive potential.

The Pregnancy and Lactation, subsections of the angiotensin II labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Subsection 8.1**
    - The "Pregnancy" subsection of labeling was formatted in the PLLR format to include: "Risk Summary" and "Clinical Considerations" headings.

- **Lactation, Subsection 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include: the "Risk Summary" heading.

LABELING RECOMMENDATIONS

DPMH made revisions to subsections 8.1 and 8.2 of the labeling for compliance with the PLLR. DPMH labeling recommendations are below. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

TABLE OF CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The (b) (4) published data on angiotensin II use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. (b) (4)

(b) (4)

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

(b) (4)

Delaying treatment in pregnant women with hypotension associated with distributive (b) (4) shock (b) (4) increase the risk of maternal and fetal morbidity and mortality. (b) (4)

8.2. Lactation

Risk Summary

It is not known whether angiotensin II is present in human milk. No data are available on the effects of angiotensin II on the breastfed child or the effects on milk production. (b) (4)

[redacted]

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/s/

TAMARA N JOHNSON
11/30/2017

LYNNE P YAO
11/30/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 16, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209360
Product Name and Strength:	Angiotensin II Injection, 2.5 mg/mL and 5 mg/2 mL
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	La Jolla Pharmaceutical Company Inc.
Submission Date:	June 29, 2017 and September 8, 2017
OSE RCM #:	2017-1332
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA review process for Angiotensin II, the Division of Cardiovascular and Renal Products consulted us to review the proposed Angiotensin II container labels and carton labeling, as well as the proposed Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Angiotensin II container labels, carton labeling, and PI to identify deficiencies that may lead to medication errors and areas for improvement.

We note that the strength units (mg/mL) and dosing units (ng/kg/min) do not match and differ by a factor of 10^6, which we generally discourage since expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and has led to dosing errors.[a] However, we also note that the proposed product is only intended to be administered following dilution to final concentrations of 5,000 ng/mL or 10,000 ng/mL. Thus, at point of care, the final concentration of the proposed product would have matching units between strength and dose (**ng**/mL and **ng**/kg/min, respectively).

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Additionally, we note the Applicant proposed language in PI (b) (4) we recommend this information also be included in Section 2.

We note the package type term is absent from the Dosage Forms and Strengths section in the Highlights of PI and Full PI. We also note the use of the (b) (4) in Section 16.1 of the Full PI and on the container labels and carton labeling. We defer to CMC for the determination of the correct packaging type term, and we recommend consistently applying the appropriate packaging type term across the container labels, carton labeling, and prescribing information.

We also request clarification in regards to some aspects of the preparation, dosing, administration, and storage for Angiotensin II in Sections 2 and 16 of the full PI. We provide our recommendations in section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Angiotensin II container labels, carton labeling, and PI can be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on our review, we recommend the following changes to the PI be implemented prior to the approval of this NDA:

A. Prescribing Information (PI)
   1. Dosage and Administration, Highlights and Section 2 of Full PI
      a. Specify the amount in mg of Angiotensin II to be withdrawn from the vial, the volume in mL of 0.9% sodium chloride that Angiotensin II should be diluted in, and the final concentration in ng/mL of Angiotensin II in 0.9% sodium chloride.
      b. We recommend deleting the term "(b) (4)" used in the Dosage and Administration section of the Highlights and in Section 2 of the Full PI and only using "0.9% sodium chloride".
      c. We note the use of the abbreviation, "IV", throughout the Dosage and Administration, Highlights and Section 2 of the full PI. The route of administration should be described without abbreviation, and so we recommend spelling out "intravenous".[b]
      d. Clarify by specifying the (b) (4) (font underlined) in the statement (b) (4)

         Also, specify in what dosing decrements should be used for the down-titration.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

e. Add an "s" on to the end of the word "dose" in the following sentence: "Maintenance dose**s** should not exceed 40 ng/kg/min."
f. Add the following information to Section 2 of the full PI: (b) (4)

2. In Sections 3 and 16 of Full PI, add appropriate information to facilitate identification of the injection dosage form (e.g., color of injection solution and other identifying characteristics).
3. Dosage Forms and Strengths in Highlights and Sections 3 of Full PI
    a. Revise the strength presentation to provide the total quantity per total volume followed by the concentration per mL, as follows: [c]

        Injection: 2.5 mg/mL and 5 mg/2 mL (2.5 mg/mL) in a vial
4. In Section 16.1 of Full PI,
    a. Add a space and remove trailing zeros so the statements read:[d]

        2.5 mg/mL vial: NDC 68547-501-02: A carton of one 1 mL single use vial containing 2.5 mg angiotensin II (as a sterile liquid).

        5~~.0~~ mg/2 mL vial: NDC 68547-(b) (4): A carton of one 2 mL single use vial containing 5~~.0~~ mg (2.5 mg/mL) angiotensin II (as a sterile liquid).

    b. The 2.5 mg per mL vial container label and carton labeling have differing commercial package size numbers (last 2 digits) of the NDC numbers (e.g., container label NDC number ending in "(b) (4) and carton labeling NDC number ending in "-02"). We recommend revising the package size number of the 2.5 mg per mL vial carton labeling NDC number to match that of the container label ((b) (4) for consistency purposes.
5. In Section 16.2 of Full PI,
    a. Remove the second bulleted sentence in Section 16.2 (b) (4) as this is commonly known among healthcare providers.
    b. In the "Discard prepared diluted solution after 24 hours." statement, specify under what conditions (e.g. in the refrigerator, at room temperature) the diluted Angiotensin II preparation can be stored for up to 24 hours.

[c] USP General Chapter <1> Injections

[d] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2017 NOV 15]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

4.2 RECOMMENDATIONS FOR LA JOLLA PHARMACEUTICAL COMPANY INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling

1. The proposed container labels and carton labeling use the proprietary name "(b) (4)" which was found unacceptable on August 2, 2017. We recommend removing "(b) (4)" from the labels and labeling and replacing with the conditionally approved proprietary name once that decision is made.
2. The established name lacks prominence commensurate with the proprietary name. Increase the size of the established name taking into account all pertinent factors, including topography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3. Add the statement "Discard unused portion" immediately after the package type term statement. For example, commonly seen in drug products is the presentation: "Single-dose vial. Discard unused portion."[e]
4. Decrease the prominence of the "Rx Only" statement on the Principal Display Panel (PDP) of the container labels and carton labeling, as the proposed presentation competes in prominence with other important information (e.g., the strength, established name, and route of administration).[f]
5. We note the use of sequential numbers for the product code (middle digits) of the NDC numbers for the 2.5 mg per mL and 5 mg per 2 mL (2.5 mg per mL) vial strengths, which is not an effective differentiating feature. The middle digits are traditionally used by healthcare providers to check the correct product and strength, and so similarity of product code numbers has led to selection and dispensing errors of the wrong strength. Therefore, revise the middle digits of the NDC numbers for the two strengths on the container labels and carton labeling, or alternatively, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type.[g] Ensure revisions to NDC numbers are carried over to Section 16 of the Full PI as well.
6. We note that the 2.5 mg per mL vial container label and carton labeling have differing commercial package size numbers (last 2 digits) of the NDC numbers

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[e] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[g] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

(e.g., container label NDC number ending in "(b) (4)and carton labeling NDC number ending in "-02"). We recommend revising the package size number of the 2.5 mg per mL vial carton labeling NDC number to match that of the container label ((b) (4)) for consistency purposes.

7. Revise the strength expression on the container labels and carton labeling by removing the (b) (4) presentation and providing the total quantity per total volume followed by the concentration per mL, as follows:[h]
    a. 2.5 mg/mL
    b. 5 mg/2 mL (2.5 mg/mL)
8. Consider revising the preparation and administration instructions on the container labels and carton labeling as follows: "Must dilute prior to intravenous infusion."
9. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).

B. Carton Labeling

1. We note the usual dose statement on the side panel of the carton labeling reads, (b) (4) We recommend revising the usual dose statement to read, "Usual dosage: See Prescribing Information."
2. (b) (4) graphic designs on the PDP to a shade similar to the graphics on the side panels to increase contrast and improve legibility.

[h] USP General Chapter <1> Injections

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Angiotensin II that La Jolla Pharmaceutical Company Inc. submitted on September 8, 2017.

Table 2. Relevant Product Information for Angiotensin II	
Initial Approval Date	N/A
Active Ingredient	Angiotensin II
Indication	Indicated for the treatment (b) (4) in adults with distributive (b) (4) shock (b) (4) y.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	2.5 mg/vial and 5 mg/vial (2.5 mg/mL)
Dose and Frequency	-Start BRAND NAME intravenously at 20 nanograms (ng)/kg/min. Titrate as frequently as every five minutes by increments (b) (4) ng/kg/min as needed to maintain target blood pressure. (b) (4) When (b) (4) is sufficiently improved drug can be down-titrated as frequently as every 5 minutes based on (b) (4) During the first 3 hours the maximum dose should not exceed 80 ng/kg/min. Maintenance dose should not exceed 40 ng/kg/min. Doses as low as 1.25 ng/kg/min may be used. (b) (4)
How Supplied	BRAND NAME (angiotensin II) Injection is a solution for administration by intravenous infusion supplied as a (b) (4) vial in two strengths: -2.5 mg/vial: NDC 68547-501-02: A carton of one 1 mL single use vial containing 2.5 mg (2.5 mg/mL) angiotensin II (as a sterile liquid).

	-5 mg/vial: NDC 68547 (b) (4): A carton of one 2 mL single use vial containing 5 mg (2.5 mg/mL) angiotensin II (as a sterile liquid).
Storage	- BRAND NAME should be stored in the refrigerator (36-46°F, 2-8°C). - (b) (4) . -Discard prepared diluted solution after 24 hours.
Container Closure	The container closure system for LJPC-501 drug product consists of a clear 3 mL USP/Ph. Eur. Type (b) (4) glass vial with a 13 mm elastomeric stopper, sealed with an aluminum closure and plastic flip-off cap. The same container closure system is used for LJPC-501 drug product in both the 2.5 mg/vial (2.5 mg/mL) strength and 5 mg/vial (2.5 mg/mL) strength with the exception of the cap color. The 2.5 mg/vial strength is provided with a blue plastic flip-off cap and the 5 mg/vial strength is provided with a green plastic flip-off cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 31, 2017, we searched DMEPA's previous reviews using the terms, "Angiotensin" and NDA number "209360" to identify reviews previously performed by DMEPA and related to this labels and labeling review. Our search identified no previous reviews relevant to this labels and labeling review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Angiotensin II labels and labeling submitted by La Jolla Pharmaceutical Company Inc.

- Container labels submitted on June 29, 2017
- Carton labeling submitted on June 29, 2017
- Prescribing Information (Image not shown) submitted on September 8, 2017

G.2 Label and Labeling Images

Container Labels

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CHI-MING TU on behalf of SARAH E THOMAS
11/16/2017

CHI-MING TU
11/16/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209360	NDA Supplement #: S- --	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name (proposed): (b) (4) Established/Proper Name: Angiotensin II Dosage Form: Injection Strengths: 2.5mg/vial, 5.0mg/vial Route(s) of Administration: Intravenous		
Applicant: La Jolla Pharmaceutical Company Agent for Applicant (if applicable): --		
Date of Application: June 29, 2017 Date of Receipt: June 29, 2017 Date clock started after Unacceptable for Filing (UN): --		
PDUFA Goal Date: February 28, 2018	Action Goal Date (if different): --	
Filing Date (Day 60): August 28, 2017	Date of Filing Meeting: July 27, 2017	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s): Treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) ☐ 351(k)

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 122708	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		User fee ID: PD3017015

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☒		FDA did not approve a pharmaceutically equivalent product.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	5 years of exclusivity, under 21 CFR 314.108(b)(2) based upon the following: - LJPC-501 (angiotensin II acetate) is a New Chemical Entity
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☐	☒		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		The form was received on August 24, 2017 after a request was made.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	This is an electronic submission

Controlled Substance/Product with Abuse	**YES**	**NO**	**NA**	**Comment**

Potential				
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	Agreed amended initial pediatric study plan dated 3/24/17
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	A risk management plan was submitted, but no REMS. However DRISK is part of the review team.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		Some deficiencies were noted and included in the filing letter.
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** August 16, 2016	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** May 9, 2017	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** February 2, 2015	☒			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8/25/17

BACKGROUND:

LJPC-501 is a synthetic human angiotensin II developed by La Jolla Pharmaceutical Company (La Jolla) for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy (also referred to as catecholamine-resistant hypotension, or CRH).

LJPC-501 is being submitted under the 505(b)(2) pathway and relies on a Phase 3 study conducted under a Special Protocol Assessment agreement Protocol (LJ501-CRH01) entitled "A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501in Patients with Catecholamine-Resistant Hypotension (CRH)." and published literature on angiotensin II.

Regulatory timeline:
Special Protocol Assessments**:** February 2, 2015
End-of Phase 2 meeting**:** August 16, 2016
Pre-NDA meeting: May 9, 2017
NDA submission: June 29, 2017

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sabry Soukehal	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Martin Rose		Y
Division Director/Deputy	Norman Stockbridge / Stephen Grant		Y / Y
Office Director/Deputy	Ellis Unger		Y
Clinical	Reviewer:	Fred Senatore	Y
	TL:	Martin Rose	Y
Social Scientist Review (*for OTC products*)	Reviewer:	--	
	TL:	--	
OTC Labeling Review (*for OTC products*)	Reviewer:	--	
	TL:	--	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	--	

	TL:	--	
Clinical Pharmacology	Reviewer:	Venki ChithambaramPillai	Y
	TL:	Sudharshan Hariharan	Y
• Genomics	Reviewer:	--	
• Pharmacometrics	Reviewer:	--	
Biostatistics	Reviewer:	Cherry Liu	Y
	TL:	Jim Hung	N
Nonclinical Pharmacology/Toxicology)	Reviewer:	Gowra Jagadeesh	Y
	TL:	Tom Papoian	Y
Statistics (carcinogenicity)	Reviewer:	--	
	TL:	--	
Product Quality (CMC) Review Team:	ATL:	Mohan Sapru	Y
	RBPM:	Grafton Adams	N
• Drug Substance	Reviewer:	Raymond Frankewich	N
• Drug Product	Reviewer:	Rao Kambhampati	N
• Process	Reviewer:	Peter Guerrieri	N
• Microbiology	Reviewer:	Jianli Xue	Y
• Facility	Reviewer:	Jonathan Swoboda	N
• Biopharmaceutics	Reviewer:	Gerlie Gieser	Y
• Immunogenicity	Reviewer:	--	
• Labeling (BLAs only)	Reviewer:	--	
• Other (e.g., Branch Chiefs, EA Reviewer)	Jing Li (Biopharm – TL), Angelica Dorantes (Biopharm – acting branch chief), Nandini Bhattacharya (Microbiology)		N (to all)
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	--	
	TL:	--	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Zarna Patel	N
	TL:	--	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sarah Thomas	Y
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	Theresa Ng	N
	TL:	Leah Hart	Y

OC/OSI/DSC/PMSB (REMS)	Reviewer:	--	
	TL:	--	

Bioresearch Monitoring (OSI)	Reviewer:	Naveed Homayouni	Y
	TL:	Janice Pohlman	Y
Controlled Substance Staff (CSS)	Reviewer:	--	
	TL:	--	
Other reviewers/disciplines			
OSE/DEPI	Reviewer:	Margie Goulding	N
	TL:	Marie Bradley	N
OSE/DPV	Reviewer:	Amy Chen / Daniel Woronow	N / Y
	TL:	Thao Tran	Y
Other attendees	Ellis Unger (ODE1 Director)		Y
	Colleen Locicero (ADRA)		Y
	Mary Ross Southworth (Deputy Director for safety)		Y
	Tzu-Yun McDowell (Safety Reviewer)		Y
	Michael Monteleone (ADL)		Y
	Meg Pease-Fye (DCaRP RPM)		Y
	Darrell Lyons (OSE PM)		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☒ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	The Applicant relied on a Phase 3 Study conducted under a special protocol assessment and published literature
• Per reviewers, are all parts in English or English	☒ YES

translation? **If no**, explain:	☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: There were no outlier sites that would have warranted a site audit	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: **The application did not raise significant safety or efficacy issues.**
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**: Refer to the meeting minutes dated 6/6/17 – FDA's response to question 3	 ☒ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	Site audit reports and site monitoring reports.
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ellis Unger, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 10/03/17

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: Review Milestones were communicated to the review team at the filing/planning meeting.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review

ACTION ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

SABRY SOUKEHAL
08/25/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 209360

Application Type: New NDA

Drug Name(s)/Dosage Form(s): LJPC-501 (Angiotensin II) for Injection, 2.5 mg/ml

Applicant: La Jolla Pharmaceutical Company

Receipt Date: June 29, 2017

Goal Date: February 28, 2018

1. Regulatory History and Applicant's Main Proposals

LJPC-501 is a synthetic human angiotensin II developed by La Jolla Pharmaceutical Company (La Jolla) for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy (also referred to as catecholamine-resistant hypotension, or CRH).

LJPC-501 is being submitted under the 505(b)(2) pathway and relies on a Phase 3 study conducted under a Special Protocol Assessment agreement Protocol (LJ501-CRH01) entitled "A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501in Patients with Catecholamine-Resistant Hypotension (CRH)." and published literature on angiotensin II.

Regulatory timeline:
Special Protocol Assessments**:** February 2, 2015
End-of Phase 2 meeting**:** August 16, 2016
Pre-NDA meeting: May 9, 2017
NDA submission: June 29, 2017

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.
All SRPI format deficiencies of the PI will be conveyed to the applicant in the filing communication letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 8, 2017. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 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:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *The length of HL is over half-page.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) 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 HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. 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:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. 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:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

N/A 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (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.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

Selected Requirements of Prescribing Information

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: (b) (4)

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

SABRY SOUKEHAL
08/25/2017