

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209360Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 09/30/2019 See OMB Statement on last page.	
		NDA Number 209360	
		Name of NDA Applicant La Jolla Pharmaceutical Company	
Refer to instruction sheet (Form FDA 3542a Supplement) for more information. The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
Trade Name (or proposed Trade Name) (b) (4)		Active Ingredient(s) Angiotensin II	
Dosage Form(s) Injection		Strength(s) 2.5 mg/vial and 5.0 mg/vial	
Route(s) of Administration Intravenous Infusion		Type of Use ☒ Prescription ☐ Over-the-Counter	
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after the date of approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted on Form FDA 3542 pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. FDA will not list or publish patent information in the Orange Book if it is not submitted in the declaration form submitted upon or after approval.			
FDA will not list patent information if the patent declaration does not contain the information required by 21 CFR § 314.53(c)(2) or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete the section above and sections 5 and 6.			
1. GENERAL: (Please note: If 1.a is NOT entered, then section 5 later in form must be marked as "Yes" in its check box.)			
a. United States Patent Number 9,220,745		b. Issue Date of Patent 12/29/2015	c. Expiration Date of Patent 12/18/2034
d. Name of Patent Owner George Washington University, a Congressionally Chartered Not-for-Profit Corporation			
Address (of Patent Owner) 2121 I Street, N.W., Rice Hall, Suite 601		City Washington D.C.	
State/Province/Region District of Columbia		Country USA	ZIP or Postal Code 20052
FAX Number (if available)	Telephone Number (202) 994-1000		E-Mail Address (if available)
Click for additional set of 1.d. entries (includes all address and related contact items above). May be repeated. Add Section 1.d.			
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant does not reside or have a place of business within the United States) Name: Amara Conteh		Address (of agent or representative named in 1.e.) The George Washington University, 2033 K St. NW, Suite 750	
		City/State Washington, DC	
		ZIP Code 20052	FAX Number (if available)
		Telephone Number (202) 994-5866	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant does not reside or have a place of business within the United States) Name: Sun Lee		Address (of agent or representative named in 1.e.) La Jolla Pharmaceutical Company, 10182 Telesis Court, 6th Floor City/State San Diego, California <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">ZIP Code 92121</td> <td style="width: 50%;">FAX Number (if available)</td> </tr> <tr> <td>Telephone Number (858) 207-4264</td> <td>E-Mail Address (if available)</td> </tr> </table>		ZIP Code 92121	FAX Number (if available)	Telephone Number (858) 207-4264	E-Mail Address (if available)					
ZIP Code 92121	FAX Number (if available)											
Telephone Number (858) 207-4264	E-Mail Address (if available)											
Click for additional set of 1.e. entries (includes all address and related contact items above). May be repeated.												
Add Section 1.e.												
f. Name of NDA Applicant La Jolla Pharmaceutical Company <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="2">Address (of NDA Applicant) 10182 Telesis Court, 6th Floor</td> <td>City San Diego</td> </tr> <tr> <td>State/Province/Region California</td> <td>Country USA</td> <td>ZIP or Postal Code 92121</td> </tr> <tr> <td>FAX Number (if available)</td> <td>Telephone Number (858) 207-4264</td> <td>E-Mail Address (if available)</td> </tr> </table>				Address (of NDA Applicant) 10182 Telesis Court, 6th Floor		City San Diego	State/Province/Region California	Country USA	ZIP or Postal Code 92121	FAX Number (if available)	Telephone Number (858) 207-4264	E-Mail Address (if available)
Address (of NDA Applicant) 10182 Telesis Court, 6th Floor		City San Diego										
State/Province/Region California	Country USA	ZIP or Postal Code 92121										
FAX Number (if available)	Telephone Number (858) 207-4264	E-Mail Address (if available)										
g. Has the patent referenced above been submitted previously for the NDA or supplement? ☐ Yes ☒ No												
h. If the answer to question 1.g. is "Yes," identify all change(s) from the previously submitted Form 3542a and specify whether each change is related to the patent or related to an FDA action or procedure.												
For the patent referenced above, provide the following information on whether the patent claims the drug substance, drug product, and/or method of use that is the subject of the pending NDA, amendment, or supplement. • If the patent is eligible for listing as claiming the drug substance and section 2 is completed, it is not necessary to complete section 3 even if the patent also is eligible for listing as claiming the drug product. • If the patent is eligible for listing as claiming the drug product and section 3 is completed, it is not necessary to complete section 2 even if the patent also is eligible for listing as claiming the drug substance.												
2. DRUG SUBSTANCE (ACTIVE INGREDIENT)												
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? If yes, skip to Question 2.5. ☐ Yes ☒ No												
2.2 Does the patent claim only a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No												
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No												
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.												
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No												

2.6 Does the patent claim only an intermediate?		☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel?		☒ Not Applicable	☐ Yes ☐ No
3. DRUG PRODUCT (COMPOSITION/FORMULATION)			
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?		☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel?		☒ Not Applicable	☐ Yes ☐ No
4. METHOD OF USE			
<i>NDA applicants must submit the information in section 4 for each method of using the proposed drug product for which approval is being sought and that is claimed by the patent. An NDA applicant may list together multiple patent claims for each pending method of use; however, each pending method of use claimed by the patent must be separately identified within this section. Continuation pages may be used to separately list method of use information within this section. For each pending method of use claimed by the patent, provide the following information:</i>			
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes (only one pending method of use) ☐ No ☐ Yes (more than one pending method of use)	
4.2 Patent Claim Number(s) (as listed in the patent) (Please separate numbers with commas.) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29		Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," for each pending method of use, separately identify the specific section(s) and subsection(s) of the proposed labeling for the drug product that describe the method of use claimed by the patent. If there is more than one pending method of use, please use the "Add Section 4.2" button for additional entries as needed.		Use (In your answer below, please list each section on a separate line. Within each line, separate each subsection with a comma.) section 1, subsection 0 section 2, subsection 2.2	
If more than one pending method of use, click to add a new set of Section 4.2 entries. May be repeated. Add Section 4.2			
5. NO RELEVANT PATENTS			
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.			
☐ Yes			

6. DECLARATION CERTIFICATION

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Sign

20 June 2017

6.3 Countersignature of Authorized U.S. Agent

Date Signed

Countersign

NOTE: Only an NDA applicant may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant

☐ NDA Applicant's Attorney, Agent (Representative) or Other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

George F. Tidmarsh, MD, PhD

Address

La Jolla Pharmaceutical Company, 10182 Telesis Court, 6th Floor

City

San Diego

State/Province/Region

California

Country

USA

ZIP or Postal Code

92121

FAX Number (if available)

n/a

Telephone Number

858.207.4264

E-Mail Address (if available)

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 15 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 09/30/2019 See OMB Statement on last page	
		NDA Number 209360	
		Name of NDA Applicant La Jolla Pharmaceutical Company	
Refer to instruction sheet (Form FDA 3542a Supplement) for more information.			
The following is provided in accordance with Section 305(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
Trade Name (or proposed Trade Name)		Active Ingredient(s)	
ALTAVIQ		Angiotensin II	
Dosage Form(s)		Strength(s)	
Injection		2.5 mg/vial and 5.0 mg/vial	
Route(s) of Administration		Type of Use	
Intravenous Injection		☒ Prescription ☐ Over-the-Counter	
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after the date of approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted on Form FDA 3542 pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. FDA will not list or publish patent information in the Orange Book if it is not submitted in the declaration form submitted upon or after approval.			
FDA will not list patent information if the patent declaration does not contain the information required by 21 CFR § 314.53(c)(2) or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete the section above and sections 5 and 6.			
1. GENERAL. (Please note: If 1.a is NOT entered, then section 5 later in form must be marked as "Yes" in its check box.)			
a. United States Patent Number		b. Issue Date of Patent	c. Expiration Date of Patent
9,572,856		02/21/2017	09/10/2030
d. Name of Patent Owner			
George Washington University, a Congressionally Chartered Not-for-Profit Corporation			
Address (of Patent Owner)		City	
2121 I Street, N.W., Rice Hall, Suite 601		Washington D.C.	
State/Province/Region	Country	ZIP or Postal Code	
District of Columbia	USA	20052	
FAX Number (if available)	Telephone Number	E-Mail Address (if available)	
	(202) 994-1000		
Click for additional set of 1.d. entries (includes all address and related contact items above). May be repeated.			
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant does not reside or have a place of business within the United States) Name: Amara Conteh		Address (of agent or representative named in 1.e.)	
		The George Washington University, 2033 K St. NW, Suite 750	
		City/State	
		Washington, DC	
		ZIP Code	FAX Number (if available)
		20052	
		Telephone Number	E-Mail Address (if available)
		(202) 994-5866	

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f. Name of NDA Applicant La Jolla Pharmaceutical Company							
Address (of NDA Applicant) 10182 Telesis Court, 6th Floor		City San Diego					
State/Province/Region California	Country USA	ZIP or Postal Code 92121					
FAX Number (if available)	Telephone Number (858) 207-4264	E-Mail Address (if available)					
g. Has the patent referenced above been submitted previously for the NDA or supplement? ☐ Yes ☒ No							
h. If the answer to question 1.g. is "Yes," identify all change(s) from the previously submitted Form 3542a and specify whether each change is related to the patent or related to an FDA action or procedure.							
<i>For the patent referenced above, provide the following information on whether the patent claims the drug substance, drug product, and/or method of use that is the subject of the pending NDA, amendment, or supplement.</i> • If the patent is eligible for listing as claiming the drug substance and section 2 is completed, it is not necessary to complete section 3 even if the patent also is eligible for listing as claiming the drug product. • If the patent is eligible for listing as claiming the drug product and section 3 is completed, it is not necessary to complete section 2 even if the patent also is eligible for listing as claiming the drug substance.							
2. DRUG SUBSTANCE (ACTIVE INGREDIENT)							
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? If yes, skip to Question 2.5.		☐ Yes ☒ No					
2.2 Does the patent claim only a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?		☐ Yes ☒ No					
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).		☐ Yes ☐ No					
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.							
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)		☐ Yes ☒ No					

2.6 Does the patent claim only an intermediate?		☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel?		☒ Not Applicable	☐ Yes ☐ No
3. DRUG PRODUCT (COMPOSITION/FORMULATION)			
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?		☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel?		☒ Not Applicable	☐ Yes ☐ No
4. METHOD OF USE			
<i>NDA applicants must submit the information in section 4 for each method of using the proposed drug product for which approval is being sought and that is claimed by the patent. An NDA applicant may list together multiple patent claims for each pending method of use; however, each pending method of use claimed by the patent must be separately identified within this section. Continuation pages may be used to separately list method of use information within this section. For each pending method of use claimed by the patent, provide the following information:</i>			
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes (only one pending method of use) ☐ No ☐ Yes (more than one pending method of use)	
4.2 Patent Claim Number(s) (as listed in the patent) (Please separate numbers with commas.) 1, 5, 6, 7, 8		Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," for each pending method of use, separately identify the specific section(s) and subsection(s) of the proposed labeling for the drug product that describe the method of use claimed by the patent. If there is more than one pending method of use, please use the "Add Section 4.2" button for additional entries as needed.		Use (In your answer below, please list each section on a separate line. Within each line, separate each subsection with a comma.) section 1, subsection 0 section 2, subsection 2.2	
If more than one pending method of use, click to add a new set of Section 4.2 entries. May be repeated. Add Section 4.2			
5. NO RELEVANT PATENTS			
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.			
☐ Yes			

6. DECLARATION CERTIFICATION

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Sign

20 June 2017

6.3 Countersignature of Authorized U.S. Agent

Date Signed

Countersign

NOTE: Only an NDA applicant may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant

☐ NDA Applicant's Attorney, Agent (Representative) or Other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

George F. Tidmarsh, MD, PhD

Address

La Jolla Pharmaceutical Company, 10182 Telesis Court, 6th Floor

City

San Diego

State/Province/Region

California

Country

USA

ZIP or Postal Code

92121

FAX Number (if available)

n/a

Telephone Number

858.207.4264

E-Mail Address (if available)

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 15 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."



PEDIATRIC PAGE REPORT

December 6, 2017 8:54:23 PM GMT-05:00

Selection Criteria:

Appl Type Number:	NDA 209360
Submission Type(s):	ORIG
Sort Order:	Appl Type No

<Reports start from Page 2>

Organization: DCRP Product Name: (b) (4) [ANGIOTENSIN II (LJPC-501)]
 Appl Type No: NDA 209360 Applicant: LA JOLLA PHARMACEUTICAL CO
 Submission Type #: ORIG - 1 Submission Status: PENDING

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
6/29/2017	INJECTION	N	6/29/2017	2/28/2018	TYPE 1	TREATMENT OF VASOPRESSOR-RESISTANT HYPOTENSION

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
3,406	DEFERRED	FULL	0	16	ADEQUATELY LABELED	THE APPLICANT WANTED TO WAIT FOR THE RESULTS OF STUDY LJ501-CRH01 TO CHOOSE A DOSE / DOSING REGIMEN FOR THEIR PLANNED PEDIATRIC STUDIES.	3/31/2024
3,406	PENDING	YEARS	0	2			
3,406	PENDING	YEARS	2	17			

Orga	Product	Appl Typ	Subm Ty	Applic	Subm	FDA Rec	Dosag	Orph	Subm	Goal Du	Submi	Su	Pe	PREA S	Pediat	Min Va	Max V	Waive	Waive	Study
DC	(b) (4)	NDA	ORIG -	LA	PEN	6/29/20	INJE	N	6/29/	2/28/2	TYP	T	3	DEFE	FUL	0	16	ADE	THE	3/31/
DC		NDA	ORIG -	LA	PEN	6/29/20	INJE	N	6/29/	2/28/2	TYP	T	3	PENDI	YEA	0	2			
DC		NDA	ORIG -	LA	PEN	6/29/20	INJE	N	6/29/	2/28/2	TYP	T	3	PENDI	YEA	2	17			

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

La Jolla Pharmaceutical Company 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 LJPC-501 New Drug Application.

{see appended electronic signature}

George F. Tidmarsh, MD, PhD
President & Chief Executive Officer

Date

Signature Page for VV-REG-000069 v1.0

Approval	George Tidmarsh Medical 07-Jun-2017 00:01:43 GMT+0000
----------	---

Signature Page for VV-REG-000069 v1.0

1.3. Administrative Information

2. FIELD COPY CERTIFICATION

La Jolla Pharmaceutical Company (La Jolla) hereby certifies that the FDA district office has been notified in writing that the electronic archival copy of the NDA 209360 for (b) (4) (LJPC-501 [angiotensin II] Injection) can be accessed through the FDA network for the field copy technical sections described in 21 CFR 314.50 (1)(3):

{see attached electronic signature}

Doranne Frano

Vice President, Quality Assurance and
Regulatory Affairs

Date

Signature Page for VV-REG-000081 v1.0

Approval	Doranne Frano Regulatory 23-Jun-2017 17:09:06 GMT+0000
----------	--

Signature Page for VV-REG-000081 v1.0



La Jolla Pharmaceutical Company
10182 Telesis Court, 6th Floor
San Diego, CA 92121

June 29, 2017

Food and Drug Administration
Mid-Atlantic Regional District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215

**RE: NDA 209360; SN0001
LJPC-501 (angiotensin II)
Field Copy Notification**

To Whom It May Concern,

La Jolla Pharmaceutical Company (La Jolla) hereby notifies the FDA District Office that the electronic archival copy of the NDA 209360 for (b) (4) (LJPC-501 [angiotensin II] Injection) can be accessed through the FDA network for the field copy technical sections described in 21 CFR 314.50 (1)(3). This application is being submitted to the Center for Drug Evaluation & Research, Division of Cardiovascular and Renal Products in electronic CTD format.

Sincerely,

A handwritten signature in dark ink, appearing to read "Doranne Frano", written over a horizontal line.

Doranne Frano
Vice President, Regulatory Affairs and Quality Assurance
La Jolla Pharmaceutical Company



La Jolla Pharmaceutical Company
10182 Telesis Court, 6th Floor
San Diego, CA 92121

June 29, 2017

Food and Drug Administration
Pacific Regional District Office
19701 Fairchild Road
Irvine, CA 92612

**RE: NDA 209360; SN0001
LJPC-501 (angiotensin II)
Field Copy Notification**

Dear Mr. Cruz,

La Jolla Pharmaceutical Company (La Jolla) hereby notifies the FDA District Office that the electronic archival copy of the NDA 209360 for (b) (4) (LJPC-501 [angiotensin II] Injection) can be accessed through the FDA network for the field copy technical sections described in 21 CFR 314.50 (1)(3). This application is being submitted to the Center for Drug Evaluation & Research, Division of Cardiovascular and Renal Products in electronic CTD format.

Sincerely,

A handwritten signature in cursive script that reads "Doranne Frano".

Doranne Frano
Vice President, Regulatory Affairs and Quality Assurance
La Jolla Pharmaceutical Company

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/s/

ASHLEY N WALLACE
12/28/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209360	NDA Supplement # --	If NDA, Efficacy Supplement Type: -- <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Giapreza Established/Proper Name: angiotensin II Dosage Form: Injection		Applicant: La Jolla Pharmaceutical Company Agent for Applicant (if applicable): n/a
RPM: Sabry Soukheal		Division: Cardiovascular and Renal Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>2/28/18</u>		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain: n/a		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): NME
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: None

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) AP 12/21/17
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	11/14/17, 12/19/17 11/10/17, 12/18/17
❖ Labeling reviews (indicate dates of reviews)	RPM: 8/25/17 DMEPA: 11/16/17, 12/06/17, DMPP/PLT (DRISK): ☒ None OPDP: 12/01/17 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: DPMH 11/30/17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	8/25/17 / 8/25/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC <u>12/13/17</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i>	☒ Yes
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	☒ Yes
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	5/9/17
EOP2 meeting <i>(indicate date of mtg)</i>	8/16/16
Mid-cycle Communication <i>(indicate date of mtg)</i>	10/10/17
Late-cycle Meeting <i>(indicate date of mtg)</i>	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	☒ N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	12/21/17
Division Director Summary Review <i>(indicate date for each review)</i>	12/21/17
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	12/16/17 / 12/21/17
PMR/PMC Development Templates <i>(indicate total number)</i>	3
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>		See CDTL review
• Clinical review(s) <i>(indicate date for each review)</i>		12/08/17
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>		☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not <i>(indicate date of review/memo)</i>		12/08/17 (Page 142 of the clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> ⁵		☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>		☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> - REMS Memo(s) and letter(s) <i>(indicate date(s))</i> - Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>		-- -- 12/19/17
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>		☒ None requested
Clinical Microbiology ☒ None		
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>		☐ No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>		☐ None
Biostatistics ☐ None		
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>		☒ No separate review 11/22/17
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>		☐ None
Statistical Review(s) <i>(indicate date for each review)</i>		11/21/17
Clinical Pharmacology ☐ None		
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>		☒ No separate review 12/02/17
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>		☒ No separate review 12/01/17
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>		12/01/17
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>		☒ None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☐ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	11/20/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	12/14/17 (Tertiary Review)
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☐ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	12/11/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	
☐ Review & FONSI (indicate date of review)	
☒ Review & Environmental Impact Statement (indicate date of each review)	12/11/17
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done (requested that the proprietary name be changed to (b) (4))
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

SABRY SOUKEHAL
12/22/2017



NDA 209360

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

La Jolla Pharmaceutical Company
4550 Towne Centre Ct.
San Diego, CA 92121

ATTENTION: Doranne Frano
Vice President, Regulatory Affairs

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) dated and received June 29, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Angiotensin II Injection, 2.5 mg/mL.

We also refer to your correspondence, dated and received December 11, 2017, requesting review of your proposed proprietary name, Giapreza.

We have completed our review of the proposed proprietary name, Giapreza and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 11, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022,
(<https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Sabry Soukehal, Regulatory Project Manager in the Office of New Drugs at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
12/19/2017



NDA 209360

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

La Jolla Pharmaceutical Company
4550 Towne Centre Ct.
San Diego, CA 92121

ATTENTION: Doranne Frano
Vice President, Regulatory Affairs

Dear Ms. Frano:

(b) (4)

Please refer to your New Drug Application (NDA) dated and received June 29, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Angiotensin II Injection for Infusion, 2.5 mg/mL.

We refer to our December 11, 2017, teleconference.

We also refer to your correspondence, dated and received on December 11, 2017, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). Therefore, (b) (4) is considered withdrawn as of December 11, 2017.

Finally, we refer to your correspondence, dated and received December 11, 2017, requesting review of your proposed proprietary name, Giapreza. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Therefore, the user fee goal date is March 11, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Sabry Soukehal, Regulatory Project Manager in the Office of New Drugs at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Darrell Lyons
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DARRELL LYONS
12/15/2017

From: [Doranne Frano](#)
To: [Soukehal, Sabry](#)
Cc: [Megan Eddleman](#)
Subject: Re: NDA 209360: Proposed timelines for post marketing studies
Date: Thursday, December 14, 2017 6:59:38 PM

Hello Sabry,

La Jolla agrees to the proposed updated timelines for the planned toxicology study and the planned clinical study in patients 0-2 year olds.

La Jolla has already initiated the (b) (4) lamb toxicology study. In order to meet timelines, this study was initiated early to accommodate the fall birthing of the lambs. This study was conducted per the agreed iPSP. Being that this study is underway, we would not be able to submit a draft protocol and would instead propose to submit the current protocol to the IND with the next IND update (January/February 2018). The remaining timelines are acceptable.

I will send the response to your request for a completion date for LJ501-CRH02 as soon as I receive it from Clinical Team.

Best Regards,
Doranne

From: "Soukehal, Sabry" <Sabry.Soukehal@fda.hhs.gov>
Date: Thursday, December 14, 2017 at 11:06 AM
To: Doranne Frano <dfrano@ljpc.com>
Subject: NDA 209360: Proposed timelines for post marketing studies

Hello Doranne,

Your application was reviewed by the Pediatric Review Committee, and in concurrence with the Division, we would like to propose new timelines for your planned toxicology study in (b) (4) as well as your planned clinical study in the pediatric population 0 – 2 years of age (Study LJ501-CRH03).

Tox study:

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

Peds study in 0 – 2 years old:

Draft Protocol Submission: February 2019

Final Protocol Submission: March 2019
Study/Trial Completion: September 2023
Final Report Submission: March 2024

Please review these timelines with your team and let me know as soon as possible if they are acceptable. Of note, your proposed timeline for study LJ501-CRH02 was deemed acceptable.

Thank you,

Sabry Soukehal

Regulatory Health Project Manager

Division of Cardiovascular and Renal Products

Center for Drug Evaluation and Research

Food and Drug Administration

sabry.soukehal@fda.hhs.gov

p: (240) 402 6187

f:(301) 796-9838

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/s/

SABRY SOUKEHAL
12/14/2017

MEMORANDUM of TELECONFERENCE

MEETING DATE: December 11, 2017

TIME: 2:00 P.M. EST

LOCATION: Teleconference

APPLICATION: NDA 209360

DRUG NAME: (b) (4) (Angiotensin II) Injection, 2.5 mg/mL and 5 mg/2 mL (2.5 mg/mL)

TYPE OF MEETING: Proprietary Name Review

MEETING CHAIR: Danielle Harris, Acting Deputy Director, Division of Medication Error Prevention and Analysis (DMEPA)

MEETING RECORDER: Darrell Lyons, Safety Regulatory Project Manager, Project Management Staff (PMS)

FDA ATTENDEES

Office of Surveillance and Epidemiology

Danielle Harris, Deputy Director (Acting), Division of Medication Error Prevention and Analysis
Chi-Ming (Alice) Tu, Team Leader, Division of Medication Error Prevention and Analysis
Mishale Mistry, Associate Director, Division of Medication Error Prevention and Analysis
Sarah Thomas, Safety Evaluator, Division of Medication Error Prevention and Analysis
Darrell Jenkins, Chief Project Manager Staff, Project Management Staff
Vasanth Ayalasomayajula, Team Leader, Project Management Staff
Darrell Lyons, Safety Regulatory Project Manager, Project Management Staff

SPONSOR ATTENDEES

La Jolla Pharmaceutical Company

Jennifer Carter, Chief Operating Officer
Doranne Frano, Vice President, Regulatory Affairs
Patti Ryan, Associate Director, Regulatory Affairs

MEETING OBJECTIVES

The purpose of this teleconference is to notify La Jolla Pharmaceutical Company of DMEPA's preliminary findings for the proposed proprietary name, (b) (4) and provide the applicant with regulatory options to address the Agency's concerns.

BACKGROUND

La Jolla Pharmaceutical Company submitted a Request for Proprietary Name Review on December 6, 2017, to review the proposed proprietary name, (b) (4)

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA notified the Applicant of our preliminary safety concerns with the proposed proprietary name, (b) (4) submitted under NDA 209360.

DMEPA finds the proposed proprietary name unacceptable based on 21CFR201.10(c)(5) because of similarity in pronunciation to the currently marketed proprietary name, (b) (4). (b) (4) is a currently marketed lidocaine injectable product. The similarity of this name pair is supported by FDA's Phonetic and Orthographic Computer Analysis (POCA), which calculates a combined score of 62%, indicating the names are moderately similar. Therefore, DMEPA intends to issue a denial letter for (b) (4)

In light of La Jolla Pharmaceutical Company's application action date, we informed the applicant that we expedited our review of the proposed name with intent to work with the applicant to obtain a viable proprietary name for the proposed product. Given our findings, we asked the applicant if they had considered proposing (b) (4). We acknowledged that we previously reviewed the name (b) (4) for this product and found the name unacceptable due to presence of the USAN stem (b) (4) in the name and due to a conflict with another pending name under review. However, given the application goal date for the proposed product, we anticipate that the application action date would precede that of the conflicting application.

REGULATORY OPTIONS FOR THE PROPOSED PROPRIETARY NAME

DMEPA presented the Applicant with the following options:

1. Request that DMEPA finalize the current name review 2018.
2. The Applicant can withdraw the proposed proprietary name, (b) (4) and submit an alternate name. Although a 90 day PDUFA proprietary name review goal would be invoked, DMEPA will expedite the review to the extent possible with the goal of having an acceptable proprietary name prior to the application goal date.

DISCUSSION

The applicant will withdraw the proposed name, (b) (4) and submit an alternate name for proprietary name review.

POST MEETING ACTIONS

On December 11, 2017, La Jolla Pharmaceutical Company withdrew the proposed proprietary name, (b) (4). Also on December 11, 2017, the Applicant submitted the proposed proprietary name, Giapreza, for review.

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/s/

DARRELL LYONS
12/14/2017

DANIELLE M HARRIS
12/14/2017

From: [Doranne Frano](#)
To: [Soukehal, Sabry](#)
Cc: [Megan Eddleman](#)
Subject: Re: NDA 209360 (angiotensin II) Late Cycle Meeting
Date: Thursday, December 14, 2017 12:04:09 PM

Hi Sabry, I discussed this with the La Jolla Team and we would like to cancel the Late Cycle PDUFA V meeting scheduled for Dec 21, 2017.

Thank you,
Doranne Frano
Regulatory Affairs
La Jolla Pharmaceutical Company
San Diego CA 92121

From: "Soukehal, Sabry" <Sabry.Soukehal@fda.hhs.gov>
Date: Thursday, December 14, 2017 at 8:42 AM
To: Doranne Frano <dfrano@ljpc.com>
Subject: NDA 209360 (angiotensin II) Late Cycle Meeting

Hello Doranne,

I have a quick question regarding our planned Late Cycle Meeting.

As you know, this meeting scheduled on December 21, 2017, is one of the milestone meetings under the PDUFA V program. Given our recent communications and our intent to take an early action on your NDA, would you like to keep this meeting or may we cancel it?

Thank you,

Sabry Soukehal
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
sabry.soukehal@fda.hhs.gov
p: (240) 402 6187
f:(301) 796-9838

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/s/

SABRY SOUKEHAL
12/14/2017



NDA 209360

**PROPRIETARY NAME REQUEST
WITHDRAWN**

La Jolla Pharmaceutical Company
4550 Towne Centre Ct.
San Diego, CA 92121

ATTENTION: Doranne Frano
Vice President, Regulatory Affairs

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) dated and received June 29, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Angiotensin II Injection for Infusion, 2.5 mg/mL.

We also refer to:

- Your correspondence, dated and received November 21, 2017, requesting review of your proposed proprietary name, (b) (4)
- Our December 4, 2017, teleconference
- Your correspondence, dated and received on December 4, 2017, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4)

This proprietary name request is considered withdrawn as of December 4, 2017.

We note that you have proposed an alternate proprietary name in your submission dated November 21, 2017. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Sabry Soukehal, Regulatory Project Manager in the Office of New Drugs, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Darrell Lyons
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DARRELL LYONS
12/12/2017

MEMORANDUM of TELECONFERENCE

MEETING DATE: December 4, 2017

TIME: 1:30 P.M. EST

LOCATION: Teleconference

APPLICATION: NDA 209360

DRUG NAME: (b) (4) (Angiotensin II) Injection, 2.5 mg/mL and 5 mg/2 mL (2.5 mg/mL)

TYPE OF MEETING: Proprietary Name Review

MEETING CHAIR: Chi-Ming (Alice) Tu, Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)

MEETING RECORDER: Darrell Lyons, Safety Regulatory Project Manager, Project Management Staff (PMS)

FDA ATTENDEES

Office of Surveillance and Epidemiology

Danielle Harris, Deputy Director (Acting), Division of Medication Error Prevention and Analysis
Chi-Ming (Alice) Tu, Team Leader, Division of Medication Error Prevention and Analysis
Sarah Thomas, Safety Evaluator, Division of Medication Error Prevention and Analysis
Darrell Jenkins, Chief Project Manager Staff, Project Management Staff
Darrell Lyons, Safety Regulatory Project Manager, Project Management Staff

Office of New Drugs

Sabry Soukehal, Regulatory Project Manager, Division of Cardiovascular and Renal Products

SPONSOR ATTENDEES

La Jolla Pharmaceutical Company

George Tidmarsh, Chief Executive Officer
Patti Ryan, Associate Director, Regulatory Affairs
Doranne Frano, Vice President Regulatory Affairs

MEETING OBJECTIVES

The purpose of this teleconference is to notify La Jolla Pharmaceutical Company of DMEPA's preliminary findings for the proposed proprietary name, (b) (4) and provide the applicant with regulatory options to address the Agency's concerns.

BACKGROUND

La Jolla Pharmaceutical Company submitted a Request for Proprietary Name Review on Tuesday, November 21, 2017, to review the proposed proprietary name, (b) (4)

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA requested this teleconference to notify the Applicant of their preliminary safety concerns with the proposed proprietary name, (b) (4) submitted under NDA 209360.

DMEPA finds the proposed proprietary name unacceptable based on 21CFR201.10(c)(5) because of similarity in spelling and orthographic similarity to the currently marketed proprietary name, (b) (4). (b) (4) is a currently marketed (b) (4). The orthographic similarity of this name pair is supported by FDA's Phonetic and Orthographic Computer Analysis (POCA), which calculates a combined score of 70%, indicating the names are highly similar. Therefore, DMEPA intends to issue a denial letter for (b) (4).

In the interest of transparency and in light of La Jolla Pharmaceutical Company's application action date of February 28, 2018, DMEPA wanted to inform the Applicant of these findings in advance of the NDA goal date.

REGULATORY OPTIONS FOR THE PROPOSED PROPRIETARY NAME

DMEPA presented the Applicant with the following options:

1. Request that DMEPA finalize the current name review by the proprietary name PDUFA date of February 19, 2018.
2. The Applicant can withdraw the proposed proprietary name, (b) (4) and submit an alternate name. Although a 90 day PDUFA proprietary name review goal would be invoked, DMEPA will expedite the review to the extent possible with the goal of having an acceptable proprietary name prior to the application goal date.

DISCUSSION

La Jolla Pharmaceutical Company will withdraw the current proposed proprietary name, (b) (4) and submit a new proprietary name for the Agency's review.

POST MEETING ACTIONS

On December 4, 2017, La Jolla Pharmaceutical Company withdrew the proposed proprietary name, (b) (4). Subsequently on December 6, 2017, the Applicant submitted the proposed proprietary name, (b) (4) for review.

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/s/

DARRELL LYONS
12/11/2017

CHI-MING TU
12/11/2017



NDA 209360

LABELING PMR/PMC DISCUSSION COMMENTS

La Jolla Pharmaceutical Company
Attention: Doranne Frano
Vice President, Regulatory Affairs and Quality Assurance
4550 Towne Centre Court
San Diego, CA 92121

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) dated June 29, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LJPC-501 (angiotensin II) Injection 2.5mg/vial and 5.0 mg/vial.

We also refer to our August 25, 2017, letter in which we notified you of our target date of November 29, 2017 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On September 8, 2017, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by **December 1, 2017**. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

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

These revisions have been reviewed and cleared to the level of Division Director.

If you have any questions, please call me at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Sabry Soukehal
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE: Prescribing Information

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

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/s/

SABRY SOUKEHAL
11/21/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209360

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

La Jolla Pharmaceutical Company
Attention: Doranne Frano
VP, Regulatory Affairs
4550 Towne Centre Court
San Diego, CA 92121

Dear Ms. Frano:

We acknowledge receipt on October 27, 2017, of your October 27, 2017 correspondence notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from

10182 Telesis Court, 6th Floor
San Diego, CA 92121

to

4550 Towne Centre Court
San Diego, CA 92121

for the following new drug application (NDA):

NDA 209360 for LJPC-501 (angiotensin II) Injection for Infusion.

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call Sabry Soukehal, Regulatory Project Manager, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
11/17/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209360

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

La Jolla Pharmaceutical Company
4550 Towne Centre Ct.
San Diego, CA 92121

ATTENTION: Doranne Frano
Vice President, Regulatory Affairs

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) dated and received June 29, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Angiotensin II Injection, 2.5 mg/mL.

We also refer to your correspondence, dated and received August 17, 2017, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Sabry Soukehal, Regulatory Project Manager in the Office of New Drugs at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
11/14/2017



NDA 209360

INFORMATION REQUEST

La Jolla Pharmaceutical Company
Attention: Doranne Frano
Vice President, Regulatory Affairs and Quality Assurance
10182 Telesis Court, 6th Floor
San Diego, CA 92121

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) dated and received June 29, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LJPC-501 (angiotensin II) Injection 2.5mg/vial and 5.0 mg/vial.

We are reviewing your labeling submitted on June 29, 2017 and September 8, 2017. We acknowledge the literature you cited regarding use in Pregnancy and Lactation in Section 5.4 of your Summary of Clinical Safety. To support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling, we have the following additional requests:

- Please clarify that a thorough literature review was conducted to verify that no reproductive and developmental toxicology studies have been performed with angiotensin II. Please include a description of your search parameters and a copy of each relevant publication.
- Please provide a comprehensive review and summary of all available published literature regarding angiotensin II (human or bovine) use in pregnant and lactating women and the effects of angiotensin on male and female fertility (include search parameters and a copy of each relevant publication),
- Please provide revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the Selected Requirements for Prescribing Information checklist to

correct any formatting errors to ensure conformance with the format items in regulations and guidances.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues **by October 30, 2017**. The resubmitted labeling will be used for further labeling discussions.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
10/23/2017



NDA 209360

MID-CYCLE COMMUNICATION

La Jolla Pharmaceutical Company
Attention: Doranne Frano
Vice President, Regulatory Affairs and Quality Assurance
10182 Telesis Court, 6th Floor
San Diego, CA 92121

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LJPC-501 (angiotensin II) Injection 2.5 mg/vial and 5.0 mg/vial.

We also refer to the teleconference between representatives of your firm and the FDA on October 10, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Martin Rose, MD, JD
Clinical Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 10, 2017; 3:30pm – 4:30pm (Eastern Time)

Application Number: NDA 209360
Product Name: LJPC-501 (angiotensin II)
Indication: Treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy
Applicant Name: La Jolla Pharmaceutical

Meeting Chair: Martin Rose, MD, JD
Meeting Recorder: Sabry Soukehal

FDA ATTENDEES

*Office of Drug Evaluation I

Ellis Unger, MD	Director
Robert Temple, MD	Deputy Director

*Division of Cardiovascular and Renal Products

Stephen Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Michael Monteleone, MS, RAC	Associate Director for Labeling
Martin Rose, MD, JD	Clinical Team Leader
Fred Senatore, MD, PhD, FACC	Clinical Reviewer
Tzu-Yun McDowell, MD	Clinical Reviewer
Thomas Papoian, PhD, DABT	Non-Clinical Team Leader
Gowra Jagadeesh, PhD	Non-Clinical Reviewer
Sabry Soukehal	Regulatory Health Project Manager

*Office of Clinical Pharmacology

Venkateswaran Chithambaram Pillai, PhD	Clinical Pharmacology Reviewer
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*Office of Pharmaceutical Quality

Mohan Sapru, PhD	CMC Team Leader
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*Office of Surveillance and Epidemiology, Division of Risk Management

Theresa Ng, PharmD, BCPS, CDE	Risk Management Analyst
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APPLICANT ATTENDEES

George Tidmarsh, MD, PhD
Lakhmir Chawla, MD
Stew Kroll
Luke Seikkula
Patricia Ryan, PhD
Doranne Frano
Steen Ottosen, MD

Chief Executive Officer
Chief Medical Officer
Sr. Vice President, Biostatistics
Vice President, Pharmaceutical Operations
Associate Director, Regulatory Affairs
Vice President, Regulatory Affairs
Sr. Director, Medical Safety and Pharmacovigilance

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

CMC: Drug product stability - Increasing levels of degradation impurity on storage

Regarding product stability, especially under in-use conditions, the Division expressed concern with increasing levels of (b) (4), a degradation impurity, which has not been systematically monitored under room temperature storage conditions. The applicant was asked to address this issue by providing in-use stability data for the final drug product.

3.0 INFORMATION REQUESTS

The Applicant was informed that the following information requests will be sent:

CMC:

Provide all available drug product stability data to adequately support proposed expiration period of (b) (4) months, including in-use stability data at room temperature to support the proposed product excursion period and labeling instructions for administration of the product.

Labeling:

Submit additional information regarding literature relevant to use in Pregnancy and Lactation.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

a) Major Safety Concerns: The potential risk of thrombosis

The following comment was sent to the Applicant on October 6, 2017:

We observed a higher incidence of embolic and thrombotic -related AEs in the LJPC-501 arm compared to placebo. Although the clinical data are too limited to draw any firm conclusion, this potential risk is plausible given that animal and human studies have shown that angiotensin II has prothrombotic effects through various mechanisms. In addition, the proposed indicated patient population is at high risk for thrombosis. Hence, this safety concern is likely to be addressed in labeling. We are exploring this signal further. You should submit any relevant assessments and/or your plan to address this safety concern.

During the meeting, the Division clarified that assessments on this potential risk should be done considering all thrombotic events and any exploratory analyses should be performed in both arms including the background risk at baseline. The analyses should not be limited to patients with DVTs. In addition, the Division pointed out that there were few fatal ischemia events in the CNS that could be potentially related to the risk of thrombosis. The applicant should take this into consideration when they conduct their analyses.

b) Risk Management

The following comment was sent to the Applicant on October 6, 2017:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

No further discussion occurred during the meeting.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee Meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The LCM is scheduled for December 21, 2017. We intend to send you the LCM background package approximately 10 days in advance of the scheduled meeting.

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/s/

MARTIN ROSE
10/23/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209360

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

La Jolla Pharmaceutical Company
10182 Telesis Court, 6th Floor
San Diego, CA 92121

ATTENTION: Doranne R. Frano
Vice President, Regulatory Affairs

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) dated and received June 29, 2017, submitted under section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act for LJPC-501 (angiotensin II) Injection, 2.5mg/vial and 5.0 mg/vial

We acknowledge receipt of your correspondence, dated and received August 17, 2017, requesting a review of your proposed proprietary name, (b) (4)

If the application is filed, the user fee goal date will be November 15, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Sabry Soukehal, Regulatory Project Manager, in the Office of New Drugs at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DARRELL LYONS
09/01/2017



NDA 209360

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

La Jolla Pharmaceutical Company
Attention: Doranne Frano
Vice President, Regulatory Affairs and Quality Assurance
10182 Telesis Court, 6th Floor
San Diego, CA 92121

Dear Ms. Frano:

Please refer to your New Drug Application (NDA) dated and received June 29, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for LJPC-501 (angiotensin II) Injection 2.5 mg/vial and 5.0 mg/vial.

We also refer to your amendments dated July 7, July 18, July 27, July 28, and August 24, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is February 28, 2018. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V. Please refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 29, 2017.

In addition, the planned date for our internal mid-cycle review meeting is October 3, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the "paragraph IV acknowledgment letter" described in 21 CFR 314.52(b) and the "postmark" is 4 calendar days after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

At this time, we are notifying you that we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites, which include:

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

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

1. The length of Highlights must be one-half page or less unless a waiver has been granted. Please reduce the Highlights section of labeling to one-half page or less.

2. When clinical trials adverse reactions data are included, 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.”

This statement is currently missing. Please include in section 6.1.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **September 8, 2017**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
08/25/2017



NDA 209360

NDA ACKNOWLEDGMENT

La Jolla Pharmaceutical Company
Attention: Doranne Frano
Vice President, Regulatory Affairs and Quality Assurance
10182 Telesis Court, 6th Floor
San Diego, CA 92121

Dear Ms. Frano:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: LJPC-501 (angiotensin II) Injection 2.5mg/vial and 5.0 mg/vial

Date of Application: June 29, 2017

Date of Receipt: June 29, 2017

Our Reference Number: NDA 209360

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
07/12/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122708

MEETING MINUTES

La Jolla Pharmaceutical Company
Attention: Ms. Doranne Frano
10182 Telesis Court
Suite 600
San Diego, CA 92121

Dear Ms. Frano:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LJPC-501(angiotensin II) Injection.

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on May 9, 2017. The purpose of the meeting was to discuss the content and format of the proposed 505(b)(2) NDA submission and to seek agreement on the clinical, regulatory, and chemistry, manufacturing and controls (CMC) sections of the proposed NDA.

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

If you have any questions, please contact:

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

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 9, 2017 at 3:30 – 5:00 PM ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 122708
Product Name: LJPC-501 (angiotensin II) Injection
Indication: To increase blood pressure in adults with distributive shock who remain hypotensive despite fluid therapy and vasopressor therapy.
Sponsor/Applicant Name: La Jolla Pharmaceutical Company

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

FDA ATTENDEES

Center for Drug Evaluation and Research

Robert Temple, M.D.

Deputy Director for Clinical Science

Office of Drug Evaluation I

Ellis Unger, M.D.

Director

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

Norman Stockbridge, M.D., Ph.D.

Director

Michael Monteleone, M.S., RAC

Associate Director for Labeling

Martin Rose, M.D.

Clinical Team Leader

Fortunato Fred Senatore, M.D., Ph.D., FACC

Clinical Reviewer

Tzu-Yun (Z) McDowell, Ph.D.

Clinical Analyst

Thomas Papoian, Ph.D.

Pharmacology Team Leader

Gowra Jagadeesh, Ph.D.

Pharmacology Reviewer

Edward Fromm, R.Ph., RAC

Chief, Project Management Staff

Quynh Nguyen, Pharm.D., RAC

Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Sudharshan Hariharan, Ph.D.

Clinical Pharmacology Team Leader

Xiaolei Pan, Ph.D.

Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Office of New Drug Products

Wendy I. Wilson-Lee, Ph.D.

Branch Chief (Acting), Branch 1

Mohan Sapru, M.S., Ph.D.
Mariappan V. Chelliah, Ph.D.

CMC Lead for Cardiovascular and Renal
Products and Application Technical Lead
Drug Product Reviewer

Office of Process and Facilities
Anitha Govada, Ph.D.

Process and Controls Reviewer

Office of Surveillance and Epidemiology, Division of Risk Management
Ameet Joshi, Pharm.D.

Risk Management Analyst

SPONSOR ATTENDEES

Representing La Jolla Pharmaceutical Company

George F. Tidmarsh, M.D., Ph.D.
Lakhmir Chawla, M.D.
Stew Kroll, M.A.
Doranne Frano, M.S.

Patricia Ryan, Ph.D.

Chief Executive Officer
Chief Medical Officer
Senior Vice President of Biometrics
Vice President, Regulatory Affairs and Quality
Assurance
Associate Director, Regulatory Affairs

1.0 BACKGROUND

La Jolla Pharmaceutical Company is developing LJPC-501 (angiotensin II) Injection to increase blood pressure in adults with distributive shock who remain hypotensive despite fluid therapy and vasopressor therapy. Angiotensin II is a peptide hormone naturally produced by the body that regulates blood pressure via vasoconstriction and sodium reabsorption.

A Pre-IND Meeting was held on June 30, 2014. La Jolla submitted IND 122708 for LJPC-501 for the treatment of catecholamine-resistant hypotension (CRH) on October 17, 2014. The IND contained the Phase 3 protocol entitled “*A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)*” (Protocol LJ501-CRH01). This same protocol was also submitted along with a Statistical Analysis Plan under a Special Protocol Assessment on October 22, 2014. The Division issued a “Special Protocol – Agreement” Letter on February 2, 2015.

An End-of-Phase 2 (EOP2) meeting was held on August 16, 2016. During the EOP2 meeting, specific aspects of the clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) development programs for LJPC-501 were discussed. The sponsor’s plan to submit a 505(b)(2) New Drug Application (NDA) submission was also discussed during that time.

The sponsor requested this Pre-NDA meeting to discuss the content and format of the proposed 505(b)(2) NDA submission and to seek agreement on the nonclinical, clinical, regulatory, and CMC sections of the proposed NDA. FDA sent Preliminary Comments and additional CMC comments via email to La Jolla for this Pre-NDA meeting on May 8, 2017. La Jolla emailed a slide presentation containing their responses and a Word document with their responses inserted into the FDA Preliminary Comments document on May 9, 2017.

La Jolla began the Pre-NDA meeting by presenting their top-line data results after which their responses to the FDA Preliminary Comments were discussed as indicated below (see attached for the sponsor’s slides).

2.0 DISCUSSION

2.1 Regulatory

Question 1: Case Report Form Waiver for Phase 3 Study

It is La Jolla's position that individual case report forms are not necessary for proper review of the study and therefore a waiver is requested for patients who died during the study or did not complete the study because of an adverse event. Does the Agency agree?

FDA Response to Question 1:

Yes. However, you should be prepared to expeditiously provide any case report forms if requested during the review of your NDA.

Discussion:

The sponsor accepted FDA's response and agreed to provide case report forms expeditiously if requested during the NDA review.

Question 2: Priority Review

La Jolla plans to request Priority Review at the time of NDA submission. The data from the completed Phase 3 clinical trial, LJ501-CRH01, indicate that LJPC-501 has the potential to provide a significant improvement in safety and effectiveness over standard of care treatments for severe hypotension due to distributive shock in adults who do not respond adequately to fluid and vasopressor therapy. Does the Agency agree with this approach?

FDA Response to Question 2:

Determination of review designation is made at the time an NDA is filed. Our preliminary assessment is that it is likely your NDA will be designated priority.

Discussion:

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

Question 3: Environmental Assessment

La Jolla believes LJPC-501 falls under the categorical exclusion category as FDA approval of the application for LJPC-501 will not significantly affect the environment. Does the Agency agree?

FDA Response to Question 3:

This substance likely is in accordance with a categorical exclusion from an environmental assessment (EA) and will not significantly affect the environment. Ensure that the specific claim is cited (e.g., whether 21 CFR 25.31(b) or (c), or both), and that a statement regarding extraordinary circumstances is provided, per 21 CFR 25.15 and 25.21.

Discussion:

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

Question 4: Risk Evaluation and Mitigation Strategies

La Jolla plans to provide a Risk Management Plan (RMP) as part of the proposed NDA submission. Based on the risks assessed as part of the completed Phase 3 clinical study, La Jolla does not believe that any post-marketing Risk Evaluation and Mitigation Strategies will be required. Does the Agency agree?

FDA Response to Question 4:

Our preliminary assessment based on the information you have provided is that a REMS is unlikely to be required.

Discussion:

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

Question 5: 120 Day Safety Update

The original 505(b)(2) NDA will contain a complete and comprehensive review of safety information related to LJPC-501. La Jolla does not anticipate the need to submit a 120-day safety update. Does the Agency agree?

FDA Response to Question 5:

Yes.

Discussion:

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

2.2 Chemistry, Manufacturing, and Controls (CMC)

Question 6: (b) (4)

(b) (4)

FDA Response to Question 6:

Yes.

Discussion:

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

Question 7: Shelf-life and Bridging of Product Presentations

La Jolla plans to submit in the NDA two commercial presentations for the LJPC-501 drug product consisting of two different strengths: 2.5 mg/vial (2.5 mg/mL) and 5 mg/vial (2.5 mg/mL). There will be no differences in the formulation or container closure system for the two presentations. In the 505(b)(2) NDA, La Jolla plans to rely on the long-term stability data for 3 registration batches of drug product to support a proposed expiration dating period for the 5 mg/vial (2.5 mg/mL) presentation. La Jolla will present stability data for 3 registration batches produced in the 2.5 mg/vial (2.5 mg/mL) presentation consisting of accelerated and long-term stability data. La Jolla plans to rely on the 5 mg/vial (2.5 mg/mL) long-term stability data to establish a proposed expiration dating period for the 2.5 mg/vial (2.5 mg/mL) presentation and will present bridging data to support equivalence of the stability profile, manufacturing process, site of manufacture and controls for the two presentations in the application. Does the Agency agree with this approach?

FDA Response to Question 7:

Shelf-life for the drug product will be determined during review of your NDA. However, your proposed stability and "bridging study" plan for the two packaging configurations of the drug product appear reasonable. We note that you plan to provide up to 6 months of accelerated stability data for the 2.5 mg/vial configuration to bridge the stability of this batch to the 5 mg/^{(b)(4)} configuration. At the time of the NDA review, if we deem that the stability profile of the drug product in the 5 mg/vial presentation is similar to that in the 2.5 mg/vial presentation, then similar drug product expiration may be assigned for both the configurations.

In addition, we recommend that you ensure that the two proposed packaging configurations meet USP <1151> for excess volume. Furthermore, per 21 CFR 201.51(g), for drugs in ampules or vials that are intended for injection, the declaration of net quantity of contents on the label is considered to express the minimum quantity of contents and further requires that variation above the stated measure must comply with the excess volumes set forth in USP.

Discussion:

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

Question 8: Batch Records

La Jolla plans to include the proposed commercial scale LJPC-501 drug product master batch records and an executed LJPC-501 drug product batch record from one representative registration stability batch for each strength of drug product in the NDA. In the case of the 5 mg/vial (2.5 mg/mL) presentation, the representative batch was also used in the pivotal Phase 3 clinical trial. Does the Agency agree with this plan?

FDA Response to Question 8:

In general, your proposal to include only one representative executed batch record (total two batch records out of seven executed batches) for each strength of the registration stability batches is acceptable. However, the information available at this time is insufficient to comment on the adequacy of your scale-up strategy and determination of the appropriateness of in-process specifications. Therefore, we recommend that data from a minimum of three executed batches should be included in the submission to determine if the executed batches are representative of proposed commercial scale manufacturing capability. Alternatively, you may submit a summary report of process parameters and control strategies used for all seven executed batches.

Discussion:

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

Additional CMC Comments:

In preparation for your upcoming NDA, we have the following additional comments:

- We recommend that you implement a quantitative elemental impurities test, method, and acceptance criteria in accordance with ICH Q3D and USP <232>/<233>. As a reminder, Class 1 (As, Cd, Pb, Hg), Class 2A (Co, V, Ni), and certain Class 3 (Li, Sb, Cu) elements should be monitored for parenteral dosage forms. A risk assessment may be conducted (per ICH Q3D) using six representative pilot-scale batches or three representative production-scale batches to determine that the elemental impurity levels are below the control threshold (30% of the PDE) and that no additional controls are necessary.

- USP salt policy requires that when the active ingredient in a drug product is a salt, the name and strength of the drug product shall be expressed in terms of the active moiety and its corresponding strength on the label. Therefore, ensure that the drug product labeling adheres to the USP salt policy. Refer to USP <7> and USP <1121> for further details.

La Jolla Response to Additional CMC Comments (emailed on May 9, 2017):

La Jolla has validated the elemental impurities test (b) (4) for drug substance and has established acceptance criteria in accordance with ICH Q3D and USP <232>/<233>.

Testing:

7 batches of drug substance (registration and validation).

7 registration batches of drug product.

Results:

(b) (4)

Conclusion:

(b) (4)

Does the Agency agree with this approach?

Discussion:

FDA agreed with the sponsor's approach regarding the elemental impurities test. In addition, FDA requested that the sponsor provide the risk assessment with their NDA submission; the sponsor agreed to do so.

Regarding the USP salt policy, the sponsor accepted FDA's response; no discussion occurred.

Additional CMC Comments (emailed separately to La Jolla on May 8, 2017):

1. When preparing your NDA, please review the Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. The document can be found here:
<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>

2.

(b) (4)

(b) (4)

(b) (4)

3. Provide extractables and leachables data for any elastomeric component that are used in the proposed container closure system that comes in contact with the drug product. Please refer to USP <1663>, USP <1664>, and FDA's '[Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics](#)' for further details.
4. Provide a risk assessment for the potential for delamination in the Type (b) (4) glass vials as a result of the manufacture and storage of the drug product. Please refer to USP <160> and the FDA advisory on glass lamellae for your risk assessment report, <http://www.fda.gov/drugs/drugsafety/ucm248490.htm>.
5. Compatibility of the drug product with reconstitution diluents and dosing device (e.g., precipitation, stability, adsorption to saline bag or PVC tubing) should be addressed to provide appropriate and supportive information for the labeling.
6. Provide data from freeze thaw study (at least three cycles) to show whether the critical quality attributes of the drug product will be affected if the vials are accidentally subjected to freezing.
7. If the proposed shelf-life of the drug product is greater than the real-time long term stability data available at the time of submission, provide statistical evaluation of the stability data to support any proposed shelf-life extension.

Discussion:

The sponsor accepted FDA's comments; no discussion occurred.

2.3 Nonclinical

Question 9: Comparability of LJPC-501 to other forms of Angiotensin II

Does the Agency agree that the described cellular functional studies demonstrating similar potency between LJPC-501 and the bovine form of angiotensin II are sufficient to satisfy the request by FDA to provide these data as part of the LJPC-501 bridging justification to Hypertensin and bovine forms of angiotensin II?

FDA Response to Question 9:

Yes.

Discussion:

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

2.4 Clinical

Question 10: Population

Does the FDA agree that a representative patient population was included in the Phase 3 study (LJ501-CRH01) to support the proposed indication?

FDA Response to Question 10:

Based on the information you have provided, the study population appears to be representative.

Discussion:

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

Question 11: Patient Narratives

Does the FDA agree with the proposal for submission of narratives?

FDA Response to Question 11:

Yes.

Discussion:

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

Question 12: Datasets

Does the FDA agree that the proposed plan for the submission of safety and efficacy datasets and to provide SAS programs upon request is acceptable for the submission of the NDA?

FDA Response to Question 12:

No. In addition to the SDTM and ADaM datasets, please also submit the tabulation/case report form datasets as SAS transport files, and their associated define files as XML and pdf. Please also submit all SAS codes (and macros) used to produce the tables and figures in the main section (not in the Appendix) of your CSR. See also the list of **"Additional Pre-NDA Requests"** below.

La Jolla Response for Question 12 (emailed on May 9, 2017):

La Jolla will provide tabulation/CRF, SDTM and ADaM datasets as SAS transport files and the associated define files and users guides for the SDTM and ADaM datasets. In addition, La Jolla will provide all SAS codes (and macros) used to produce the tables and figures in the main section of the CSR.

For clarity, La Jolla has applied CDISC standards in the creation of datasets and the generation of tables, listings and figures (TLFs) for the pivotal study. In particular, the tabulation/CRF datasets were converted to SDTM datasets and the SDTM datasets were used to generate the ADaM datasets, which were used for the generation of all TLFs.

Define files and users guides have been created for both the SDTM and ADaM datasets. The SDTM define package contains variable-level links to the CRF pages used for mapping the CRF/tabulation data to SDTM. The ADaM define package includes discussion on the complex algorithms used for creating the variables (e.g., achievement of the targeted MAP at Hour 3) utilized in the statistical analyses.

Does the FDA agree with the proposal?

Discussion:

FDA agreed with the sponsor's proposal.

Question 13: Summary Level Clinical Site Data

Does the FDA agree with the proposed submission of summary level clinical site data in the original NDA submission?

FDA Response to Question 13:

Yes. Please also refer to the "Office of Scientific Investigations (OSI) Requests" below.

Discussion:

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

Question 14: Omission of ISS and ISE

La Jolla does not plan to prepare integrated efficacy or safety datasets or integrated summary documents (ISE and ISS). As agreed during the Pre-IND meeting (Reference ID: 3600727), data from the Phase 3 trial would provide an adequate safety database for LJPC-501. Data from the single Phase 3 study, LJ501-CRH01, will be presented in a full clinical study report, and efficacy and safety results will be summarized in Modules 2.7.3 and 2.7.4, respectively. Support of pharmacokinetics, efficacy, and safety of angiotensin II from the medical literature will be summarized briefly in Module 2.7 documents, and PDFs of all referenced articles will be provided in Module 5.4 with a tabular summary in Module 5.2. Does the Agency agree with this approach to the organization of the safety and efficacy data in this 505(b)(2) application?

FDA Response to Question 14:

We agree that an ISE is not required. However, you should prepare the equivalent of an ISS based on the publications you intend to submit to support safety. You should extract serious adverse events from each publication and create tables that sum the number of these serious adverse events coded using MedDRA (i.e., system organ class incorporating high-level group terms, high level terms and preferred terms). You should also include denominators (i.e., total number of patients from the publications and calculate percentages.

La Jolla Response for Question 14 (emailed on May 9, 2017):

La Jolla will prepare an equivalent of an ISS based on the publications that will be submitted in the NDA. La Jolla has reviewed the literature and extracted any mention of adverse events, interruption of infusions or other safety, or tolerability information. La Jolla will review all safety information, identify the serious adverse events and code the events using MedDRA.

For summarizing serious adverse events from the literature, the denominators will be calculated based on the total number of subjects from the studies reporting safety. The ISS will be comprised of a summary of safety data from the pivotal study and, separately, a summary of data from the studies from the literature that report safety events. The text of the ISS will be submitted in Module 2, Section 2.7.4. ISS Tables and appendices will be submitted in Module 5, Section 5.3.5.3.

La Jolla does not plan to integrate safety of angiotensin II from the literature with the LJ501-CRH01 clinical trial data.

Does FDA agree with this approach?

Discussion:

FDA agreed with the sponsor's proposal. In addition, FDA requested that for the ISS prepared from the literature, the sponsor add a column in the table for each system organ class (SOC) term with a hyperlink to the publications from which the adverse events were derived. This hyperlink should allow ready access to the individual publications to facilitate review.

Given that the sponsor had reviewed 1,124 literature articles, they noted they would focus on the subset of articles that appear to be of higher quality for inclusion in the table. The sponsor plans to integrate safety data of angiotensin II across the studies, but not across the literature.

2.5 Additional Pre-NDA Requests

Protocol

1. Please submit all versions of the protocol for LJ501-CRH01 and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
2. Please submit all versions of the Statistical Analysis Plan (SAP) for LJ501-CRH01. Please ensure that a Summary of Changes for each version is included. Also include the number of subjects enrolled in the trial at the time the change was made.
3. Please submit all versions of the CRF used in the study, including both annotated and un-annotated versions of each CRF version.

Clinical Trial Materials

4. Please submit all informed consent document(s). Please describe any country- or region-specific variations.
5. Please provide sample clinical trial kits, from both arms, identical to those used during LJ501-CRH01. Ship them to the desk address of Quynh M. Nguyen (RPM) in the same packaging as will be used for shipping to investigative sites.
6. Please submit all of your data management plans and cite and all amendments for LJ501-CRH01, including all manual and programmatic checks.
7. Please submit your site monitoring plan and all amendments along with applicable dates for LJ501-CRH01. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, please explain the process for amending.

Post-Meeting Note:

Please submit all monitoring reports and site audits reports.

8. Please submit a description of the responsibilities of each ARO or CRO used in LJ501-CRH01.
9. At the time of the NDA submission, please include all meeting minutes of all groups with any responsibility for the management of the trial. Please include agendas and all data/slides presented at each meeting. Please indicate if the meeting was opened or closed. For those

meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

10. Please submit all newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trials. Please bookmark the newsletters by date.

General Data and Analyses

11. Please submit a table detailing all of the tables and figures featured in the pivotal trial. The table should contain the following:
 - a. title of the table or figure in NDA
 - b. a page number hyperlink to the location of the table or figure
 - c. a name hyperlink to the SAS code (and/or macros) used to create the table or figure
 - d. names of the datasets used to create the table or figure (hyperlinks are useful, but not necessary)
 - e. for derived (analysis) datasets used to conduct your analyses, you should indicate the CRF pages and tabulation datasets from which the information was derived

La Jolla Response to General Data Analysis Request 11 (emailed on May 9, 2017):
The CSR will include a table detailing all of the tables and figures featured in the pivotal trial. For clarity, La Jolla Question 12 asked specifically for SAS codes for tables and figures in the main section (not in the Appendix) of the CSR. The CSR appendices include a table of all SAS tables and a table of all SAS figures including those not reported in the main section of the CSR. For this request, would FDA like the requested table and links for these tables from appendices as well?

Discussion:

FDA responded that it would be sufficient to provide the requested tables and links from the main section of the CSR (not in the Appendix).

12. Please submit any other datasets used to conduct your key analyses (e.g., analyses related to efficacy, safety, subject disposition) that are not included in the previous request.
13. For all derived datasets included in requests #11 and 12, please submit all scripts/programs used to create the analysis datasets. The scripts and define files should be sufficient to facilitate understanding of how the analysis datasets were created. If variables are inadequately described in the define files, you may need to also submit all datasets (and associated define files) used to derive your analysis datasets.

La Jolla Response to General Data Analysis Request 13 (emailed on May 9, 2017):
Does the plan (see response to La Jolla Question 12) of providing tabulation/CRF, SDTM and ADaM datasets with the associated define files adequately address the request? In particular, the SAS programs converting the tabulation/CRF datasets to SDTM datasets are not included in the proposed submission. Does the Agency agree?

Discussion:

The sponsor should also submit the SAS programs that converted the tabulation/CRF datasets to SDTM datasets, as well as the programs used to convert SDTM and ADaM.

14. Please include a list of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for NDA review. Submit SAS code that was used to create or clean up your analyses datasets.

La Jolla Response to General Data Analysis Request 14 (emailed on May 9, 2017):

All of the tabulation/CRF, SDTM and ADaM datasets are of high quality for review. The tabulation/CRF datasets underwent 100% source data verification along with Data Management, Biostatistics and Medical review. Much of the data review was done without SAS codes. The generation of ADaM datasets and analyses were done with SAS double programming.

Are these the SAS codes for generating the ADaM datasets and SAS tables that are being requested?

Discussion:

FDA explained that the purpose of this request is to understand the methods and programs that were used by the sponsor to clean up their analyses datasets and the quality control used in the process. The sponsor acknowledged their understanding of the FDA's request.

15. Please submit a dataset that contains all subjects that were unblinded. The dataset should include the unique subject ID, the treatment received, who requesting unblinding, date of unblinding, and the reason for unblinding.
16. Please provide a dataset that contains a list of all subjects for whom you submitted a narrative. Please provide a table that lists the IDs for subjects who died, who had SAEs, who discontinued due to an AE, and who experienced AEs of special interest (i.e., arrhythmias, ischemia). The subject IDs in those tables should hyperlink to the respective narratives.
17. For the pivotal study, please list in one table the following:
 - Dates of first patient and last patient visits
 - Dates of data lock
 - Dates for each interim analysis
 - Dates of all versions of the SAP (with a hyperlink to each SAP)
 - Dates of the initial protocol and all revisions (with a hyperlink to the protocol and each revision).

Other

18. Please provide a statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC) which we agreed maintain the same oversight responsibilities as IRBs, please reference the waiver and include the date.

19. Please submit a completed Clinical Pharmacology Summary Aid document (see attachment). You should only answer the questions that are relevant to your particular NDA.

La Jolla Clarification Question on Request 19 (emailed on May 9, 2017):

In regards to the Pharmacology Summary Aid request, will section NDA 2.7.2 (Summary of Clinical Pharmacology Studies) suffice to address this need?

The Summary Aid you provided seems to be an old format and the new guidance contains a different format. Would it be acceptable to use the new format if this standalone document is required?

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm073007.pdf>

FDA Response to Clarification Question on Request 19 (refer to email on May 9, 2017):

The review aid is aimed at addressing key clinical pharmacology information that will help the reviewer during review documentation. That is why this is a standalone document in addition to the 'Summary of Clinical Pharmacology Studies' usually submitted by the sponsor. Since there is a new QBR format for the clinical pharmacology review, we agree that the review aid can be prepared based on the new review format as reference.

Discussion:

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

20. Please submit the coding dictionary used for mapping investigator verbatim terms to preferred terms as SAS transport files. The file should consist of a list of all investigator verbatim terms and the preferred terms to which they were mapped.
21. Please provide your rationale for assuaging the applicability of foreign data to U.S. population/practice of medicine in the submission.

There are two major pieces to this applicability of foreign data issue as follows:

- Are the patients the same (US versus rest of the world)?
- Are the medical systems treating the disease the same way with respect to interventions and background therapy on a region-specific basis?

La Jolla Response to Other Request 21 (emailed on May 9, 2017):

La Jolla will provide a rationale for the applicability of foreign data. La Jolla proposes to provide a summary of patient demographics and baseline characteristics by region (North America [US, Canada], Europe [UK, Belgium, Germany, Finland, France], and Australasia [New Zealand, Australia]) from the pivotal study in Module 5 as an appendix to the CSR and referenced in Section 2.7.3.

All patients were treated in the intensive care unit. A discussion of the medical systems and interventions for treating CRH across regions will be included in Section 2.7.3. A relevant method to compare medical practice is to compare vasopressors used prior to and during study drug administration across regions by generic drug name and number (percentage) of patients.

Is this approach acceptable?

Discussion:

FDA stated that this approach was acceptable.

22. In the NDA, please submit an annotated version of requests listed in these Pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document can be placed in the reviewer's aid.

ISS

23. Please prepare the equivalent of an ISS based on the publications you intend to submit to support safety. You should extract serious adverse events from each publication and create tables that sum the number of these serious adverse events coded using the same MedDRA version used in your pivotal trial (i.e., system organ class incorporating high-level group terms, high level terms and preferred terms). You should also include denominators (i.e., total number of patients from the publications) and calculate percentages.

La Jolla Response to ISS Request 23 (emailed on May 9, 2017):

See Question 14: Omission of ISS and ISE.

Other datasets

24. Please submit a dataset (SAS transport file) for all randomized subjects with the following attributes:
- There should be one row of data per subject.
 - Please note that if the requested variable also appears in another dataset, the variable name and format should be the same as that used in other datasets in your application.
 - Variables should include:
 - Unique subject ID (This should be in the format as in other datasets.)
 - Randomized arm
 - As-treated arm
 - Age
 - Gender
 - Death flag (patient died during the study period)
 - BP response flag (patient had a protocol-specified BP response)
 - Norepinephrine dose rate at enrollment
 - Epinephrine dose rate at enrollment
 - Norepinephrine equivalent rate (based on epinephrine rate)
 - Similar information as for epinephrine for each other vasopressor (dopamine, phenylephrine, vasopressin) described in Appendix D of the protocol for LJ501-CRH01
 - Sum of norepinephrine equivalent rates
 - Flag if patient met norepinephrine equivalent dose rate requirement for enrollment
 - MAP at enrollment
 - Flag if patient met MAP criteria for enrollment
 - Flag if patient qualified for enrollment on the basis of both norepinephrine equivalent dose rate and MAP

Discussion:

Regarding the “Death flag (patient died during the study period)” under request #24, FDA clarified that it would be acceptable to provide more than one flag indicating deaths occurring in the different study periods.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

If, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

Discussion:

- The content of a complete application was discussed. See above for the discussion and agreements.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS. As stated in FDA’s Response to Question 4, FDA’s preliminary assessment is that a REMS is unlikely to be required, based on the information provided.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The sponsor intends to submit a complete application; therefore, there are no agreements for late submission of application components.

4.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its

October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

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

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

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

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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

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

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

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

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

5.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

6.0 PRESCRIBING INFORMATION

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

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

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

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

7.0 SUBMISSION FORMAT REQUIREMENTS

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

8.0 SECURE EMAIL COMMUNICATIONS

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

9.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

10.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the

background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

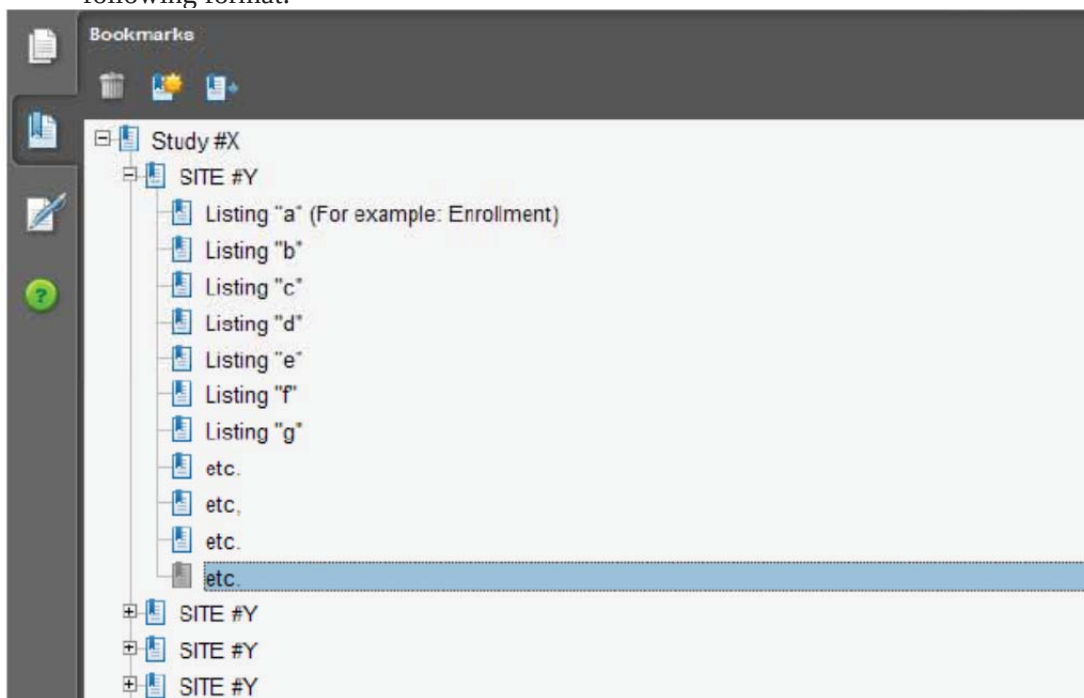
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

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

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



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

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

References:

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

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

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

11.0 ATTACHMENTS AND HANDOUTS

Clinical Pharmacology Summary Aid document

Sponsor's presentation slides "ATHOS-3 (LJPC-501-CRH01) Top Line Data"

Sponsor's presentation slides "LJPC-501 (angiotensin II) Pre-NDA Meeting"

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug

products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal $t_{1/2}$ and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex,

race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C_{max} or C_{min} is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C_{max} and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max}, t_{max}, AUC, C_{max,ss}, C_{min,ss}, C_{max,ss}/C_{min,ss}, t_{max,ss}, AUC_{0-τ}, CL/F, V/F and t_{1/2} (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max}, C_{min}, CL/F and t_{1/2} of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, t_{max}, t_{max,ss}, C_{max}, C_{max,ss} and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for $\geq 90\%$ of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to

be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m²) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether C_{max} and C_{min} of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target

population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C_{max} and CL/F on Cl_{cr} for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly

altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C_{max}, t_{max} and t_{1/2} of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C_{max}, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the

rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to K_m , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for K_i , IC_{50} and V_{max} for each

relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/K_i ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t_{1/2}, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C_{max} after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and

efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C_{max}, AUC and C_{min} of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in C_{max}, AUC and C_{min} than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report

indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}\text{C}$.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

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

/s/

ELLIS F UNGER
06/06/2017



IND 122708

MEETING MINUTES

La Jolla Pharmaceutical Company, Inc.
Attention: George F. Tidmarsh, M.D., Ph.D.
4660 La Jolla Village Drive
Suite 1070
San Diego, California 92122-1249

Dear Dr. Tidmarsh:

Please refer to your Pre-Investigational New Drug Application (PIND) file for LJPC-501 (angiotensin II acetate for injection).

We also refer to the meeting between representatives of your firm and the FDA on August 16, 2016. The purpose of the meeting was to seek agreement on the strategic and specific aspects of the clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) development programs for LJPC-501 in the treatment of catecholamine-resistant hypotension (CRH). La Jolla would also like to discuss moving forward with a 505(b)(2) New Drug Application (NDA) submission. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

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

If you have any questions, please contact:

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: August 16, 2016 at 9:00 – 10:00 AM ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 122708
Product Name: LJPC-501(Angiotensin II Acetate Injection)
Indication: Treatment of catecholamine-resistant hypotension (CRH)
Sponsor/Applicant Name: La Jolla Pharmaceutical Company

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Quynh Nguyen, Pharm.D., RAC

FDA ATTENDEES

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

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Martin Rose, M.D.	Clinical Team Leader
Fortunato Fred Senatore M.D., Ph.D., FACC	Clinical Reviewer
Thomas Papoian, Ph.D.	Pharmacology Team Leader
Gowra Jagadeesh, Ph.D.	Pharmacology Reviewer
Maryam Changi, Pharm.D.	Regulatory Project Manager
Quynh Nguyen, Pharm.D., RAC	Regulatory Project Manager

Office of Biostatistics, Division of Biometrics I

Fanhui Kong, Ph.D.	Statistical Reviewer
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Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Sudharshan Hariharan, Ph.D.	Clinical Pharmacology Team Leader
Xiaolei Pan, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Office of New Drug Products, Branch I

Mohan Sapru, Ph.D.	CMC Lead for Cardiovascular and Renal Products (Acting)
Charles Jewell, Ph.D.	Quality Reviewer

Office of New Drug Products, Division of Biopharmaceutics

Elsbeth Chikhale, Ph.D.

Biopharmaceutics Team Leader

SPONSOR ATTENDEES

Representing La Jolla Pharmaceutical Company, Inc.

George F. Tidmarsh, M.D., Ph.D.

Lakhmir Chawla, M.D.

Doranne Frano, M.S.

Patricia Ryan, Ph.D.

Luke Seikkula

(b) (4)

Chief Executive Officer

Chief Medical Officer

Sr. Director, Regulatory Affairs and Quality Assurance

Sr. Manager, Regulatory Affairs

Sr. Director, Pharmaceutical Operations

(b) (4)

Consultant,

(b) (4)

1.0 BACKGROUND

La Jolla Pharmaceutical Company is developing LJPC-501 (Angiotensin II Acetate Injection) for the treatment of catecholamine-resistant hypotension (CRH). Angiotensin II is a peptide hormone naturally produced by the body that regulates blood pressure via vasoconstriction and sodium reabsorption.

A Pre-IND Meeting was held on June 30, 2014. La Jolla submitted IND 122708 for LJPC-501 for the treatment of CRH on October 17, 2014. The IND contained the Phase 3 protocol entitled "*A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)*" (Protocol LJ501-CRH01). This same protocol was also submitted along with a Statistical Analysis Plan under a Special Protocol Assessment on October 22, 2014. A "Special Protocol – Agreement" Letter was issued on February 2, 2015. Study LJ501-CRH01 is currently ongoing. An "Agreed Initial Pediatric Study Plan – Agreement" Letter was issued on June 1, 2015. LJPC-501 is also being investigated for the treatment of hepatorenal syndrome (HRS) under IND (b) (4).

La Jolla requested this EOP2 meeting to seek agreement on the strategic and specific aspects of the clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) development programs for LJPC-501 in the treatment of catecholamine-resistant hypotension (CRH). The sponsor would also like to discuss moving forward with a 505(b)(2) New Drug Application (NDA) submission and plans to rely on the published literature to provide additional support for the toxicology, safety and efficacy of LJPC-501 in the proposed 505(b)(2) NDA.

FDA sent Preliminary Comments to the sponsor on August 11, 2016. The sponsor provided a Discussion Points document and Powerpoint slides on August 15, 2016 in response to the Division's Preliminary Comments for Questions 1e and 1f, 3 and 12 which were discussed during the meeting as indicated below (see attachments).

2. DISCUSSION

2.1 Regulatory

Question 1: *Regulatory Pathway*

La Jolla Plans to submit a 505(b)(2) New Drug Application providing support from literature in addition to the data derived from the ongoing Phase 3 study LJ501-CRH01, "A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant

Hypotension (CRH)”, conducted under a Special Protocol Assessment (SPA) agreement. As part of the marketing application, La Jolla plans to rely on clinical research studies and nonclinical research studies using angiotensin II that are described in the literature. Does the Agency agree that the 505(b)(2) approach is an acceptable regulatory pathway for obtaining marketing approval for LJPC-501 for the treatment of CRH? Refer to [Section 10.1 Overview](#) and [Section 10.2.1 Regulatory Pathway](#) for additional details.

FDA Response to Question 1:

A 505(b)(2) application appears acceptable, at this time, based on the available information. The regulatory decision, however, will be based on 1) the outcome of your ongoing Phase 3 trial, and 2) the appropriateness of bridging scientific information/data demonstrating that the proposed LJPC-501 product and the products manufactured by (b) (4) and Ciba-Geigy are equivalent and can interchangeably be referred to as angiotensin II acetate. The supporting information/data should contain enough details to allow us to evaluate the bridging of the products. For this purpose, provide a table with columns describing the following:

- a. Each cited study critical to demonstrating the safety and efficacy of your proposed drug product.
- b. Each cited study critical to describe the PK, metabolism, PD, drug-drug interactions, etc. of the proposed drug product.
- c. Precise composition of administered drug product in the cited study, that is, whether it is identical to the human amino acid sequence on Ang-II or to another sequence, such as bovine.
- d. Administered dose (and duration of delivery, where relevant) in the cited study.
- e. Comparative chemical, physical, analytical measurements of the products; such as assay, pH, osmolality, etc. (proposed vs. those used in the cited published literature articles), if known.
- f. Bridging justification: Where the administered drug product in your cited study differs from your proposed drug product, such as in amino acid sequence, provide a justification why you can extrapolate their results to the expected clinical response from the administration of your proposed drug product. This may include comparative AT₁ receptor binding and/or cellular functional studies showing similar potency (IC₅₀) or functional effects (EC₅₀) between the different forms of Ang-II (i.e., human, bovine, etc.) reported in the literature.

Please note that if a 505(b)(2) applicant intends to rely, in part, on literature or other studies for which the applicant has no right of reference, but that are necessary for approval, the 505(b)(2) applicant should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

For additional information for sponsors considering the submission of an application through the 505(b)(2) pathway, see section 8.0 of this document.

La Jolla Points for Discussion on Comment 1e (emailed on August 15, 2016):

When known, La Jolla will provide the requested information, however, in the majority of cited clinical studies, this information was not provided. Additionally, Ciba-Geigy material (val-5 angiotensin II, bovine sequence) used in many of the cited studies is no longer available for testing.

It is La Jolla’s position that the requested information in comment 1 part e may not be required to assess comparability for the following reason:

From a physicochemical perspective, LJPC-501 and other angiotensin II products used in the literature reports are diluted ~1:1000 into a saline bag prior to administration. The differences between formulations are negligible once diluted. Therefore, the results of pH and osmolality aren’t clinically meaningful indicators of comparability between LJPC-501

and other sources of angiotensin II (ile-5 human or val-5 bovine). Does FDA agree with these points?

Discussion during Meeting on Comment 1e:

Dr. Chikhale acknowledged that the Sponsor will submit the comparative information on the (b) (4) and Ciba-Geigy forms of Ang-II when available. However, when the information is not available, a statement indicating the unavailability will be included. The FDA confirmed that the comparative information on the diluted drug product is relevant. The FDA stated that for the diluted solution, a thorough justification is needed on why the LJPC-501 product and other referenced sources of angiotensin II (ile-5 human or val-5 bovine) have similar chemical, physical, analytical measurements; such as assay, pH, and osmolality.

Dr. Sapru stated that pH and osmolality of the undiluted solution should also be part of the drug product specifications because the proposed drug product is an intravenous formulation and requested that the Sponsor provide this information in the NDA. La Jolla responded that they would do so.

La Jolla Points for Discussion on Comment 1f (emailed on August 15, 2016):

Based on the suggestion from FDA, La Jolla will conduct side-by-side in vitro experiments to demonstrate the comparability of the human ile-5 angiotensin II acetate in LJPC-501 to the bovine val-5 bovine sequence of angiotensin II. As the product (Ciba-Geigy) cited in many clinical and nonclinical studies is no longer manufactured, La Jolla plans to use the val-5 version of angiotensin II currently manufactured by (b) (4) or another representative supplier for these studies. These data will be included in the NDA.

Does the FDA agree with this approach?

La Jolla believes these data will also cover situations in which the source of angiotensin II used in the cited literature study is unknown since historically, the only two forms of angiotensin II available were the val-5 bovine and ile-5 human form. Does FDA agree?

Discussion during Meeting on Comment 1f:

Dr. Papoian stated it would be acceptable for the Sponsor to use the human-specific version of angiotensin II currently manufactured by (b) (4) or another representative supplier, since the Ciba-Geigy or bovine-specific product is no longer available.

Regarding the sponsor's plan to conduct side-by-side *in vitro* experiments to demonstrate the similarity of the human ile-5 angiotensin II acetate in LJPC-501 to the bovine val-5 bovine sequence of angiotensin II, Dr. Papoian commented that the sponsor should assess receptor pharmacology via receptor binding assays with IC₅₀ values to Ang-II receptor subtypes, AT1 and AT2. In addition, the sponsor should assess functional activity to both Ang-II receptor subtypes by using at least two of the commonly used functional assays for each of the AT1 and AT2 receptor subtypes, such as inositol tris phosphate (IP3), diacylglycerol (DAG, and protein kinase C (PKC) for AT1 receptors, and cGMP production, MAP kinase, and phospholipase A2 for AT2 receptors (see de Gasparo M, et al.; Pharmacol. Rev., 52:415-472, 2000).

2.2 Chemistry, Manufacturing, and Controls

Question 2: Comparability

La Jolla executed an analytical comparability assessment in order to rely on nonclinical and clinical research studies conducted using angiotensin II manufactured by (b) (4) in support of LJPC-501 in the proposed NDA (refer to Table 2 for a summary of the elements of the comparability assessment). The results of the comparability assessment are presented in Section 10.3.1.2 Comparability of (b) (4) Angiotensin II Acetate to (b) (4) Angiotensin II Acetate and in Section 10.3.2.2.2 Comparability of LJPC-501 Drug Product to (b) (4) Angiotensin II Drug Product. Does the Agency agree that comparability has been sufficiently demonstrated to support reliance on studies from the literature (conducted using angiotensin II drug product produced by (b) (4) to support the 505(b)(2) NDA for LJPC-501?

FDA Response to Question 2:

Yes, the comparison data between the (b) (4) manufactured Angiotensin II acetate to (b) (4) Angiotensin II acetate seems to demonstrate they are equivalent in terms of analytical chemistry characterization and properties. The comparison was done using only one batch of the (b) (4) material. (b) (4) since the actual (b) (4) drug substance is not available to you. This comparability does not carry over to the formerly marketed version of Hypertensin which is the bovine peptide amide of Angiotensin II.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

Question 3: Drug Substance Specifications

The planned drug substance test attributes and acceptance criteria for the commercial angiotensin II acetate to be used for production of commercial drug product are presented in Section 10.3.1.4 Control of Drug Substance of this briefing document.

- Does the Agency agree with the test attributes included in the proposed commercial angiotensin II acetate specifications to be submitted in the marketing application?
- Does the Agency have comments on the proposed acceptance criteria for each test attribute in the proposed commercial drug substance specifications?

FDA Response to Question 3:

Your proposed test attributes for the drug substance are acceptable (b) (4). Without these, sequence is not verified specifically for each batch. We recommend you also include elemental impurities testing in the specification as a control for (b) (4). While your acceptance criteria appear to be reasonable, their final adequacy will be determined in the context of the demonstrated batch analysis data and manufacturing capability demonstrated in your marketing application. The data you have presented thus far are not clearly representative of your commercial scale capability.

La Jolla Points for Discussion Comment 3 (emailed on August 15, 2016):

In accordance with the Agency suggestion, La Jolla agrees to maintain the ID tests for sequence and amino acid content in the specification. Additionally, La Jolla will implement elemental impurities testing for (b) (4). The specification will be supported based on analysis of our 3 registration lots. The method will be validated (b) (4) for the NDA. The method and validation report will be submitted in the NDA. Does the FDA agree with this approach?

La Jolla understands the adequacy of the specifications is a review issue. Three (3) of the

four (4) lots manufactured to date are at pilot scale and La Jolla believes these lots and process used to manufacture are representative of the commercial scale. The registration lots to be provided in the NDA are listed below (Table 13 of briefing package). No additional batch analysis information is planned to be included in the proposed NDA.

Table 13: Lots of Angiotensin II Acetate Drug Substance

Lot Number	Lot Size (grams)	Date of Manufacture
2K13048	(b) (4)	September 2013
2K14017 ^a		June 2014
2K15023 ^a		May 2015
2K15056 ^a		September 2015

^aRegistration stability lots of drug substance. Intended commercial scale is approximately (b) (4) grams per lot.

Discussion during Meeting on Comment 3:

Dr. Jewell stated that the Sponsor's strategy to use pilot scale batch data was acceptable in the absence of commercial scale data. The Agency pointed out that determining the adequacy of acceptance limits for the drug substance is a review issue and will be evaluated in the context of entirety of information and data provided in the regulatory submission.

Question 4: Drug Product Comparability

La Jolla plans to demonstrate equivalence of LJPC-501 drug product manufactured at sites used for clinical supplies during development and LJPC-501 drug product manufactured at the proposed commercial site. To support equivalence, La Jolla will compare manufacturing unit operations and product quality (batch analysis data) for drug product manufactured at each site used in La Jolla clinical studies during development and for the registration stability batches of drug product manufactured at the intended commercial production site. Does the Agency agree with La Jolla's plan to demonstrate comparability of drug product lots produced at different sites during development in support of the NDA? Refer to [Section 10.3.2.2.1 Comparability of LJPC-501 Across Manufacturing Sites](#).

FDA Response to Question 4:

Yes, we agree.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

Question 5: Drug Product Specifications

The planned drug product test attributes and acceptance criteria for the intended commercial drug product are presented in [Section 10.3.2.3 Control of Drug Product](#) of this briefing document.

- Does the Agency agree with the test attributes included in the proposed commercial LJPC-501 drug product specifications for the intended commercial drug product?
- Does the Agency have comments on the proposed acceptance criteria for each test attribute in the proposed commercial drug product specifications?

FDA Response to Question 5:

- a. The proposed tests in the drug product specification seem reasonable.
- b. Adequacy of the acceptance limits will be determined after a complete review of the data submitted in the NDA submission.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

Question 6: Drug Product Container Closure System

La Jolla does not intend to conduct product-specific leachables and extractables testing of the glass vials and stoppers that are the intended container closure system for the commercial drug product. La Jolla plans to submit the vendor's extractables information for the drug product stopper and a risk assessment performed by La Jolla for the leachables in the NDA. Refer to [Section 10.3.3.2 Container Closure](#) for more details on La Jolla's plans. Does the Agency agree with La Jolla's plans for supporting the drug product container closure system?

FDA Response to Question 6:

In general, your proposal is acceptable. Please provide justification in the NDA concerning suitability of the container closure system for the proposed formulation based on all available data.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

2.3 Nonclinical

Question 7: Safety Pharmacology

The cardiovascular effects of angiotensin II are well documented in multiple preclinical species, however no full GLP compliant safety pharmacology studies have been conducted with LJPC-501 drug product. Therefore, La Jolla initiated a hERG study to ensure angiotensin II does not inhibit hERG currents and a full GLP cardiovascular safety pharmacology study in dogs with LJPC-501 drug product. The blood brain barrier excludes access of polar peptides to the central nervous system, obviating the value of a nonclinical CNS study. When coupled with the extensive clinical knowledge of elevated endogenous angiotensin II levels in human disease states, does the Agency agree that there are no further Safety Pharmacology studies needed for the NDA? Refer to [Section 10.4.2 Pharmacology](#) for more details.

FDA Response to Question 7:

Yes, we agree.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

Question 8: Nonclinical Studies

Extensive nonclinical (and clinical) studies are reported in the literature on angiotensin II that provide a full understanding of its pharmacological actions that directly support the safety of LJPC-501. Therefore, La Jolla does not plan to conduct additional nonclinical toxicology studies on LJPC-501 and will provide a summary of relevant nonclinical studies from the literature in the NDA. Does the Agency agree that the information in the literature is sufficient for the NDA? Refer to [Section 10.4.4 Toxicology](#) for more details.

FDA Response to Question 8:

Yes, we agree.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

2.4 Clinical

Question 9: PK/PD Studies

Serum angiotensin I and angiotensin II are measured at Screening and the 3-hour time point (at the time of the primary efficacy assessment) in the ongoing Phase 3 study in CRH; summary statistics will be presented in the clinical study report. The PK/PD profile of angiotensin II is well established and therefore La Jolla does not plan to conduct further PK/PD studies in support of the NDA. Does the Agency concur? Refer to [Section 10.5.1.2 Pharmacokinetics and Metabolism](#) and [Section 10.5.1.3 Pharmacodynamics](#) for more details.

FDA Response to Question 9:

Yes, we agree that additional PK/PD studies may not be required. The data collected in the ongoing Phase 3 study will inform the PK/PD response of angiotensin II.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

Question 10: Drug-Disease & Drug-Drug Interaction Studies

As outlined in the Briefing Document and discussed at the PIND meeting, there is extensive literature available on the safety and efficacy of angiotensin II that supports the safe use of many concurrent medications in treating patients with distributive shock, therefore La Jolla does not plan to conduct drug-disease or drug-drug interaction studies. La Jolla will summarize the relevant literature in the LJPC-501 NDA. Does the Agency agree with this approach? Refer to [Section 10.5.1.3.1 Intrinsic Factors and Response to Intravenous Angiotensin II](#) and [Section 10.5.1.3.2 Concomitant Drugs and Pharmacodynamics Interactions](#) for more details.

FDA Response to Question 10:

Yes, we agree. Drug-drug or drug-disease interactions should not limit the use of LJPC-501 because LJPC-501 will be administered in a controlled clinical setting where hemodynamic variables are frequently monitored to capture changes in sensitivity to angiotensin II response due to co-medications or co-morbidities.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

Question 11: Renal & Hepatic Studies

The patient population that will receive treatment with LJPC-501 may have renal or hepatic impairment, however LJPC-501 is titrated to effect and is rapidly degraded in plasma (half-life of less than one minute) so specific renal and/or hepatic studies are not planned to support the NDA. Does the Agency concur? Refer to the subsection on Hepatic and Renal impairment in [Section 10.5.1.3.1 Intrinsic Factors and Response to Intravenous Angiotensin II](#) and [Section 10.5.1.3.2 Concomitant Drugs and Pharmacodynamics Interactions](#) for more details.

FDA Response to Question 11:

Yes, we agree. The pharmacokinetics of LJPC-501 may not be influenced by hepatic or renal impairment because LJPC-501 is a naturally occurring peptide that is metabolized rapidly in the plasma by aminopeptidase A and ACE2 with a plasma half-life of less than 1 minute. Moreover, any changes in angiotensin II response in these patients will be appropriately accounted, as LJPC-501 is titrated to effect.

Discussion during Meeting

The Sponsor accepted the FDA's response; no discussion occurred.

Question 12: *Clinical QT_c Studies*

LJPC-501 has been shown to increase blood pressure in patients who are hypotensive. La Jolla believes that it would be unethical to conduct a thorough QT study in normal healthy volunteers due to the risk to patient safety presented by therapeutic dosing of LJPC-501. The doses of LJPC-501 used in the Phase III trial are for patients with severe shock and hypotension; these doses of LJPC-501 would induce severe hypertension in healthy volunteers. Tolerable subtherapeutic doses are unlikely to be informative about QT intervals. Furthermore, data from preclinical studies and existing literature suggest that there is low risk of QT_c prolongation. La Jolla will collect data from 12-lead ECGs at baseline and at 48 hours in the ongoing clinical study which will allow La Jolla to rule out large QT effects. QT interval change from baseline will be summarized for placebo and for treatment groups in the NDA. Finally, given the proposed patient population is subjected to continuous ECG as a part of their standard of care, La Jolla believes that, absent a large effect on QT interval, LJPC-501 can be administered safely. Therefore, no further QT testing need be done prior to the NDA. Does the Agency agree with this approach? Refer to [Section 10.5.1.4.3 Cardiovascular Safety](#) for more details.

FDA Response to Question 12:

Yes. In your Phase 3 study, you should report QT prolongation or arrhythmias as an adverse event of special interest for a separate safety review and analysis.

La Jolla Points for Discussion Question 12 (emailed on August 15, 2016):

As described in the briefing package, La Jolla is collecting data from 12-lead ECGs at baseline and at 48 hours in the ongoing clinical study which will allow La Jolla to rule out large QT effects. QT interval and QT interval change from baseline will be summarized for placebo and for treatment groups in the NDA.

QT prolongation and arrhythmias will be included as adverse events of special interest for a separate safety review and analysis.

La Jolla proposes to make modifications to the Statistical Analysis Plan (SAP) to explicitly capture QT prolongation and arrhythmias as adverse events of special interest and will include the proposed plan for analyzing this safety parameter. Additional clarity will also be provided in the revised SAP for other exploratory and safety analyses. As there will be no changes to the primary or secondary efficacy endpoints, La Jolla believes these modifications to the SAP will not affect the Special Protocol Assessment (SPA) agreement with FDA.

Does FDA agree?

Discussion during Meeting on Comment 12:

FDA agreed.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

4.0 DATA STANDARDS FOR STUDIES

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

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

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

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

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

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

6.0 SUBMISSION FORMAT REQUIREMENTS

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

7.0 SECURE EMAIL COMMUNICATIONS

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

8.0 505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

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

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

9.0 Office of Scientific Investigations (OSI) Requests

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

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

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

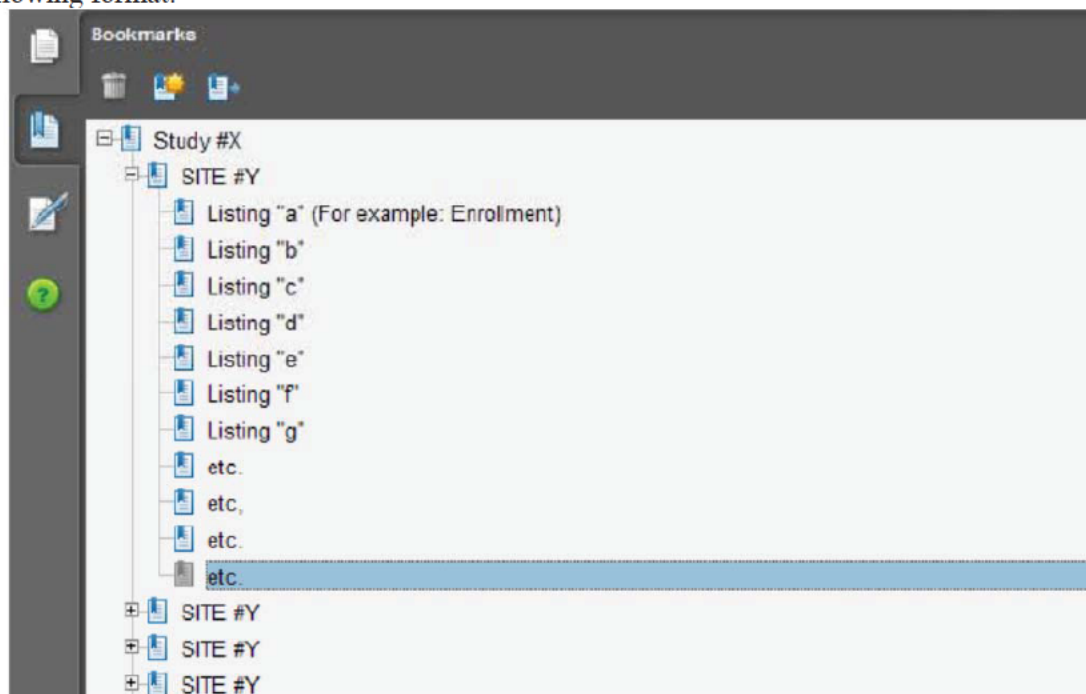
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates

- g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

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

10.0 PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

11.0 NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

12.0 ATTACHMENTS AND HANDOUTS

Sponsor's Points for Discussion document and PowerPoint slides emailed on August 15, 2016.



La Jolla Pharmaceutical Company, Inc.
10182 Telesis Court, Suite 600
San Diego, CA 92121

August 15, 2016

Quynh M. Nguyen, PharmD, RAC
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I

Center for Drug Evaluation and Research

Re: MEETING PRELIMINARY COMMENTS

La Jolla makes reference to the Preliminary Meeting Comments dated 11 Aug 2016 (Reference ID 3971100). La Jolla hereby provides an electronic version of our responses for discussion and the slides to be presented at the meeting.

If there are any questions regarding this document or if you require further information, please contact me by telephone at 858-433-6908 or by email at dfrano@ljpc.com.

Sincerely,

Doranne Frano
Sr. Director Regulatory and Quality Assurance
La Jolla Pharmaceutical Company, Inc.

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	End-of-Phase 2 (EOP2)
Meeting Date and Time:	August 16, 2016 at 9:00 – 10:00 AM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 122708
Product Name:	LJPC-501 (Angiotensin II Acetate Injection)
Indication:	Treatment of catecholamine-resistant hypotension (CRH)
Sponsor/Applicant Name:	La Jolla Pharmaceutical Company

1.0 BACKGROUND

La Jolla Pharmaceutical Company is developing LJPC-501 (Angiotensin II Acetate Injection) for the treatment of catecholamine-resistant hypotension (CRH). Angiotensin II is a peptide hormone naturally produced by the body that regulates blood pressure via vasoconstriction and sodium reabsorption.

A Pre-IND Meeting was held on June 30, 2014. La Jolla submitted IND 122708 for LJPC-501 for the treatment of CRH on October 17, 2014. The IND contained the Phase 3 protocol entitled “*A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)*” (Protocol LJ501-CRH01). This same protocol was also submitted along with a Statistical Analysis Plan under a Special Protocol Assessment on October 22, 2014. A “Special Protocol – Agreement” Letter was issued on February 2, 2015.

Study LJ501-CRH01 is currently ongoing. An “Agreed Initial Pediatric Study Plan – Agreement” Letter was issued on June 1, 2015. LJPC-501 is also being investigated for the treatment of hepatorenal syndrome (HRS) under IND (b) (4)

La Jolla requested this EOP2 meeting to seek agreement on the strategic and specific aspects of the clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) development programs for LJPC-501 in the treatment of catecholamine-resistant hypotension (CRH). The sponsor would also like to discuss moving forward with a 505(b)(2) New Drug Application (NDA) submission and plans to rely on the literature to provide additional support for the toxicology, safety and efficacy of LJPC-501 in the proposed 505(b)(2) NDA.

2.1 DISCUSSION

2.2 Regulatory

Question 1: *Regulatory Pathway*

La Jolla Plans to submit a 505(b)(2) New Drug Application providing support from literature in addition to the data derived from the ongoing Phase 3 study LJ501-CRH01, “A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)”, conducted under a Special Protocol Assessment (SPA) agreement. As part of the marketing application, La Jolla plans to rely on clinical research studies and nonclinical research studies using angiotensin II that are described in the literature. Does the Agency agree that the 505(b)(2) approach is an acceptable regulatory pathway for obtaining marketing approval for LJPC-501 for the treatment of CRH? Refer to Section 10.1 Overview and Section 10.2.1 Regulatory Pathway for additional details.

FDA Response to Question 1:

A 505(b)(2) application appears acceptable, at this time, based on the available information. The regulatory decision, however, will be based on 1) the outcome of your ongoing Phase 3 trial, and

2) the appropriateness of bridging scientific information/data demonstrating that the proposed LJPC-501 product and the products manufactured by (b) (4) and Ciba-Geigy are equivalent and can interchangeably be referred to as angiotensin II acetate. The supporting information/data should contain enough details to allow us evaluate the bridging of the products. For this purpose, provide a table with columns describing the following:

- a. Each cited study critical to demonstrating the safety and efficacy of your proposed drug product.
- b. Each cited study critical to describe the PK, metabolism, PD, drug-drug interactions, etc. of the proposed drug product.
- c. Precise composition of administered drug product in the cited study, that is, whether it is identical to the human amino acid sequence on Ang-II or to another sequence, such as bovine.
- d. Administered dose (and duration of delivery, where relevant) in the cited study.
- e. Comparative chemical, physical, analytical measurements of the products; such as assay, pH, osmolality, etc. (proposed vs. those used in the cited published literature articles), if known.
- f. Bridging justification: Where the administered drug product in your cited study differs from your proposed drug product, such as in amino acid sequence, provide a justification why you can extrapolate their results to the expected clinical response from the administration of your proposed drug product. This may include comparative AT1 receptor binding and/or cellular functional studies showing similar potency (IC50) or functional effects (EC50) between the different forms of Ang-II (i.e., human, bovine, etc.) reported in the literature.

Please note that if a 505(b)(2) applicant intends to rely, in part, on literature or other studies for which the applicant has no right of reference, but that are necessary for approval, the 505(b)(2) applicant should include a copy of such published literature in the 505(b)(2)

application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

For additional information for sponsors considering the submission of an application through the 505(b)(2) pathway, see section 8.0 of this document.

No further discussion required for items a. b. c. or d.

La Jolla Points for Discussion Comment 1e:

When known, La Jolla will provide the requested information, however, in the majority of cited clinical studies, this information was not provided. Additionally, Ciba-Geigy material (val-5 angiotensin II, bovine sequence) used in many of the cited studies is no longer available for testing.

It is La Jolla's position that the requested information in comment 1 part e may not be required to assess comparability for the following reason:

From a physicochemical perspective, LJPC-501 and other angiotensin II products used in the literature reports are diluted ~1:1000 into a saline bag prior to administration. The differences between formulations are negligible once diluted. Therefore, the results of pH and osmolality aren't clinically meaningful indicators of comparability between LJPC-501 and other sources of angiotensin II (ile-5 human or val-5 bovine).

Does FDA agree with these points?

La Jolla Points for Discussion Comment 1f:

Based on the suggestion from FDA, La Jolla will conduct side-by-side *in vitro* experiments to demonstrate the comparability of the human ile-5 angiotensin II acetate in LJPC-501 to the bovine val-5 bovine sequence of angiotensin II. As the product (Ciba-Geigy) cited in many clinical and nonclinical studies is no longer manufactured, La Jolla plans to use the val-5 version of angiotensin II currently manufactured by (b) (4) or another representative supplier for these studies. These data will be included in the NDA.

Does the FDA agree with this approach?

La Jolla believes these data will also cover situations in which the source of angiotensin II used in the cited literature study is unknown since historically, the only two forms of angiotensin II available were the val-5 bovine and ile-5 human form.

Does FDA agree?

2.3 Chemistry, Manufacturing, and Controls

Question 2: Comparability

La Jolla executed an analytical comparability assessment in order to rely on nonclinical and clinical research studies conducted using angiotensin II manufactured by (b) (4) in support of LJPC-501 in the proposed NDA (refer to Table 2 for a summary of the elements of the comparability assessment). The results of the comparability assessment are presented in Section 10.3.1.2 Comparability of (b) (4) Angiotensin II Acetate to (b) (4) Angiotensin II Acetate and in Section 10.3.2.2.2 Comparability of LJPC-501 Drug Product to (b) (4)

Angiotensin II Drug Product. Does the Agency agree that comparability has been sufficiently demonstrated to support reliance on studies from the literature (conducted using angiotensin II drug product produced by (b) (4) to support the 505(b)(2) NDA for LJPC-501?

FDA Response to Question 2:

Yes, the comparison data between the (b) (4) manufactured Angiotensin II acetate to (b) (4) Angiotensin II acetate seems to demonstrate they are equivalent in terms of analytical chemistry characterization and properties. The comparison was done using only one batch of the (b) (4) material, (b) (4) since the actual (b) (4) drug substance is not available to you. This comparability does not carry over to the formerly marketed version of Hypertensin which is the bovine peptide amide of Angiotensin II.

No further discussion needed.

Question 3: Drug Substance Specifications

The planned drug substance test attributes and acceptance criteria for the commercial angiotensin II acetate to be used for production of commercial drug product are presented in Section 10.3.1.4 Control of Drug Substance of this briefing document.

- a. Does the Agency agree with the test attributes included in the proposed commercial angiotensin II acetate specifications to be submitted in the marketing application?*
- b. Does the Agency have comments on the proposed acceptance criteria for each test attribute in the proposed commercial drug substance specifications?*

FDA Response to Question 3:

Your proposed test attributes for the drug substance are acceptable except that we do not agree with dropping the ID tests for sequence and amino acid content. Without these, sequence is not verified specifically for each batch. We recommend you also include elemental impurities testing in the specification as a control for (b) (4)

While your acceptance criteria appear to be reasonable, their final adequacy will be determined in the context of the demonstrated batch analysis data and manufacturing capability demonstrated in your marketing application. The data you have presented thus far are not clearly representative of your commercial scale capability.

La Jolla Points for Discussion Comment 3:

In accordance with the Agency suggestion, La Jolla agrees to maintain the ID tests for sequence and amino acid content in the specification. Additionally, La Jolla will implement elemental impurities testing for (b) (4). The specification will be supported based on analysis of our 3 registration lots. The method will be validated (b) (4) for the NDA. The method and validation report will be submitted in the NDA. **Does the FDA agree with this approach?**

La Jolla understands the adequacy of the specifications is a review issue. Three (3) of the four (4) lots manufactured to date are at pilot scale and La Jolla believes these lots and process used to manufacture are representative of the commercial scale. The registration lots to be provided in the NDA are listed below (Table 13 of briefing package). No additional batch analysis

information is planned to be included in the proposed NDA.

Table 13: Lots of Angiotensin II Acetate Drug Substance

Lot Number	Lot Size (grams)	Date of Manufacture
2K13048	(b) (4)	September 2013
2K14017 ^a		June 2014
2K15023 ^a		May 2015
2K15056 ^a		September 2015

^aRegistration stability lots of drug substance. Intended commercial scale is approximately (b) (4) grams per lot.

Question 4: Drug Product Comparability

La Jolla plans to demonstrate equivalence of LJPC-501 drug product manufactured at sites used for clinical supplies during development and LJPC-501 drug product manufactured at the proposed commercial site. To support equivalence, La Jolla will compare manufacturing unit operations and product quality (batch analysis data) for drug product manufactured at each site used in La Jolla clinical studies during development and for the registration stability batches of drug product manufactured at the intended commercial production site. Does the Agency agree with La Jolla's plan to demonstrate comparability of drug product lots produced at different sites during development in support of the NDA? Refer to Section 10.3.2.2.1 Comparability of LJPC-501 Across Manufacturing Sites.

FDA Response to Question 4:

Yes, we agree.

No further discussion needed.

Question 5: Drug Product Specifications

The planned drug product test attributes and acceptance criteria for the intended commercial drug product are presented in Section 10.3.2.3 Control of Drug Product of this briefing document.

- Does the Agency agree with the test attributes included in the proposed commercial LJPC-501 drug product specifications for the intended commercial drug product?*
- Does the Agency have comments on the proposed acceptance criteria for each test attribute in the proposed commercial drug product specifications?*

FDA Response to Question 5:

- The proposed tests in the drug product specification seem reasonable.
- Adequacy of the acceptance limits will be determined after a complete review of the data submitted in the NDA submission.

No further discussion needed.

Question 6: *Drug Product Container Closure System*

La Jolla does not intend to conduct product-specific leachables and extractables testing of the glass vials and stoppers that are the intended container closure system for the commercial drug product. La Jolla plans to submit the vendor's extractables information for the drug product stopper and a risk assessment performed by La Jolla for the leachables in the NDA. Refer to Section 10.3.3.2 Container Closure for more details on La Jolla's plans. Does the Agency agree with La Jolla's plans for supporting the drug product container closure system?

FDA Response to Question 6:

In general, your proposal is acceptable. Please provide justification in the NDA concerning suitability of the container closure system for the proposed formulation based on all available data.

No further discussion needed.

2.4 Nonclinical

Question 7: *Safety Pharmacology*

The cardiovascular effects of angiotensin II are well documented in multiple preclinical species, however no full GLP compliant safety pharmacology studies have been conducted with LJPC-501 drug product. Therefore, La Jolla initiated a hERG study to ensure angiotensin II does not inhibit hERG currents and a full GLP cardiovascular safety pharmacology study in dogs with LJPC-501 drug product. The blood brain barrier excludes access of polar peptides to the central nervous system, obviating the value of a nonclinical CNS study. When coupled with the extensive clinical knowledge of elevated endogenous angiotensin II levels in human disease states, does the Agency agree that there are no further Safety Pharmacology studies needed for the NDA? Refer to Section 10.4.2 Pharmacology for more details.

FDA Response to Question 7:

Yes, we agree.

No further discussion needed.

Question 8: *Nonclinical Studies*

Extensive nonclinical (and clinical) studies are reported in the literature on angiotensin II that provide a full understanding of its pharmacological actions that directly support the safety of LJPC-501.

Therefore, La Jolla does not plan to conduct additional nonclinical toxicology studies on LJPC-501 and will provide a summary of relevant nonclinical studies from the literature in the NDA. Does the Agency agree that the information in the literature is sufficient for the NDA? Refer to Section 10.4.4 Toxicology for more details.

FDA Response to Question 8:

Yes, we agree.

No further discussion needed.

2.5 Clinical**Question 9:** *PK/PD Studies*

Serum angiotensin I and angiotensin II are measured at Screening and the 3-hour time point (at the time of the primary efficacy assessment) in the ongoing Phase 3 study in CRH; summary statistics will be presented in the clinical study report. The PK/PD profile of angiotensin II is well established and therefore La Jolla does not plan to conduct further PK/PD studies in support of the NDA. Does the Agency concur? Refer to Section 10.5.1.2 Pharmacokinetics and Metabolism and Section 10.5.1.3 Pharmacodynamics for more details.

FDA Response to Question 9:

Yes, we agree that additional PK/PD studies may not be required. The data collected in the ongoing Phase 3 study will inform the PK/PD response of angiotensin II.

No further discussion needed.

Question 10: *Drug-Disease & Drug-Drug Interaction Studies*

As outlined in the Briefing Document and discussed at the PIND meeting, there is extensive literature available on the safety and efficacy of angiotensin II that supports the safe use of many concurrent medications in treating patients with distributive shock, therefore La Jolla does not plan to conduct drug-disease or drug-drug interaction studies. La Jolla will summarize the relevant literature in the LJPC-501 NDA. Does the Agency agree with this approach? Refer to Section 10.5.1.3.1 Intrinsic Factors and Response to Intravenous Angiotensin II and Section 10.5.1.3.2 Concomitant Drugs and Pharmacodynamic Interactions for more details.

FDA Response to Question 10:

Yes, we agree. Drug-drug or drug-disease interactions should not limit the use of LJPC-501 because LJPC-501 will be administered in a controlled clinical setting where hemodynamic variables are frequently monitored to capture changes in sensitivity to angiotensin II response due to co-medications or co-morbidities.

No further discussion needed.

Question 11: *Renal & Hepatic Studies*

The patient population that will receive treatment with LJPC-501 may have renal or hepatic impairment, however LJPC-501 is titrated to effect and is rapidly degraded in plasma (half-life of less than one minute) so specific renal and/or hepatic studies are not planned to support the NDA. Does the Agency concur? Refer to the subsection on Hepatic and Renal impairment in Section 10.5.1.3.1 Intrinsic Factors and Response to Intravenous Angiotensin II and Section 10.5.1.3.2 Concomitant Drugs and Pharmacodynamic Interactions for more details.

FDA Response to Question 11:

Yes, we agree. The pharmacokinetics of LJPC-501 may not be influenced by hepatic or renal impairment because LJPC-501 is a naturally occurring peptide that is metabolized rapidly in the plasma by aminopeptidase A and ACE2 with a plasma half-life of less than 1 minute. Moreover, any changes in angiotensin II response in these patients will be appropriately accounted, as LJPC-501 is titrated to effect.

No further discussion needed.

Question 12: *Clinical QT_c Studies*

LJPC-501 has been shown to increase blood pressure in patients who are hypotensive. La Jolla believes that it would be unethical to conduct a thorough QT study in normal healthy volunteers due to the risk to patient safety presented by therapeutic dosing of LJPC-501. The doses of LJPC-501 used in the Phase III trial are for patients with severe shock and hypotension; these doses of LJPC-501 would induce severe hypertension in healthy volunteers. Tolerable subtherapeutic doses are unlikely to be informative about QT intervals. Furthermore, data from preclinical studies and existing literature suggest that there is low risk of QT_c prolongation. La Jolla will collect data from 12-lead ECGs at baseline and at 48 hours in the ongoing clinical study which will allow La Jolla to rule out large QT effects. QT interval change from baseline will be summarized for placebo and for treatment groups in the NDA. Finally, given the proposed patient population is subjected to continuous ECG as a part of their standard of care, La Jolla believes that, absent a large effect on QT interval, LJPC-501 can be administered safely. Therefore, no further QT testing need be done prior to the NDA. Does the Agency agree with this approach? Refer to Section 10.5.1.4.3 Cardiovascular Safety for more details.

FDA Response to Question 12:

Yes. In your Phase 3 study, you should report QT prolongation or arrhythmias as an adverse event of special interest for a separate safety review and analysis.

La Jolla Points for Discussion Question 12:

As described in the briefing package, La Jolla is collecting data from 12-lead ECGs at baseline and at 48 hours in the ongoing clinical study which will allow La Jolla to rule out large QT effects. QT interval and QT interval change from baseline will be summarized for placebo and for treatment groups in the NDA.

QT prolongation and arrhythmias will be included as adverse events of special interest for a separate safety review and analysis.

La Jolla proposes to make modifications to the Statistical Analysis Plan (SAP) to explicitly capture QT prolongation and arrhythmias as adverse events of special interest and will include the proposed plan for analyzing this safety parameter. Additional clarity will also be provided in the revised SAP for other exploratory and safety analyses. As there will be no changes to the primary or secondary efficacy endpoints, La Jolla believes these modifications to the SAP will not affect the Special Protocol Assessment (SPA) agreement with FDA.

Does FDA agree?

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

/s/

NORMAN L STOCKBRIDGE
09/09/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 122,708

MEETING MINUTES

La Jolla Pharmaceutical Company, Inc.
Attention: George F. Tidmarsh, MD, PhD
4660 La Jolla Village Drive
Suite 1070
San Diego, California 92122-1249

Dear Dr. Tidmarsh:

Please refer to your Pre-Investigational New Drug Application (PIND) file for LJPC-501 (angiotensin II acetate for injection).

We also refer to the Pre-IND meeting between representatives of your firm and the FDA on June 30, 2014. The purpose of the meeting was to obtain FDA feedback on the drug product and nonclinical testing program, and to discuss moving forward with clinical testing under an IND.

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

If you have any questions, please contact:

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

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Pre-IND

Meeting Date and Time: June 30, 2014 at 1:00 – 2:00 PM ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: Pre-IND 122,708
Product Name: LJPC-501
Indication: Treatment of catecholamine-resistant hypotension
Sponsor/Applicant Name: La Jolla Pharmaceutical Company, Inc.

Meeting Chair: Ellis F. Unger, MD
Meeting Recorder: Quynh Nguyen, PharmD, RAC

FDA ATTENDEES

Center for Drug Evaluation and Research

Robert Temple, MD Deputy Director for Clinical Science (CDER)

Office of Drug Evaluation I

Ellis Unger, MD Director

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

Norman Stockbridge, MD, PhD	Director
Shari Targum, MD	Clinical Team Leader
Thomas Marciniak, MD	Clinical Team Leader
Fortunato Senatore, MD, PhD	Clinical Reviewer
Thomas Papoian, PhD	Pharmacology Team Leader
Gowra Jagadeesh, PhD	Pharmacology Reviewer
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Quynh Nguyen, PharmD, RAC	Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics I

James Hung, PhD	Director
Fanhui Kong, PhD	Biometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Sreedharan Sabarinath, PhD	Clinical Pharmacology Reviewer
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SPONSOR ATTENDEES

Representing La Jolla Pharmaceutical Company, Inc.

George F. Tidmarsh, MD, PhD

James M. Rolke

Lakhmir S. Chawla, MD

CEO, La Jolla Pharmaceutical Company

VP, La Jolla Pharmaceutical Company

Associate Professor of Anesthesiology and Critical Care
Medicine and of Medicine, George Washington

University Hospital

Regulatory Consultant, SciLucent, LLC

Beth Silverstein, M.S. RAC

1.0 BACKGROUND

LJPC-501 (angiotensin II acetate for injection) is being developed by La Jolla Pharmaceutical Company, Inc. Angiotensin II is a peptide hormone naturally produced by the body that regulates blood pressure via vasoconstriction and sodium reabsorption. The sponsor requested this Pre-IND meeting to obtain FDA feedback on the drug product and nonclinical testing program, and to discuss moving forward with clinical testing under an IND for the treatment of catecholamine-resistant hypotension (CRH). The sponsor intends to conduct a multicenter, Phase 3 study to examine the safety and efficacy of LJPC-501 in the treatment of CRH. The sponsor currently has an open IND for LJPC-501 under IND (b) (4) for the treatment of hepatorenal syndrome (HRS). The Division's Preliminary Comments were sent to the sponsor on June 20, 2014. In response, the sponsor provided via email a brief set of presentation slides on June 25, 2014, including two questions on slide 8, which were discussed during the meeting as indicated under **2.3 Clinical Questions 2, 3 and 4** below.

2.0 DISCUSSION

2.1 Chemistry, Manufacturing, and Controls

La Jolla does not have any questions regarding chemistry, manufacturing, and controls.

2.2 Nonclinical

On the basis of the significant clinical experience with angiotensin II, LJPC does not intend to conduct nonclinical safety studies on LJPC-501. A pharmacology study of angiotensin II performed in rabbits, along with extensive clinical data on the safety of intravenously administered angiotensin II, support the safety of the proposed clinical dose of angiotensin II (5 – 40 ng/kg/min). (b) (4)

Question 1. Does the Agency agree that no additional toxicology testing is needed to support the safety of the drug for proposed clinical study?

FDA Response to Question 1:

We agree.

2.3 Clinical

No clinical safety studies have been completed using LJPC-501. (b) (4)

Question 2. Does FDA agree

(b) (4)

FDA Response to Question 2:

(b) (4)

Safety of LJPC-501 will mostly be evaluated in your proposed Phase 3 trial.

Discussion during Meeting

See Questions 3 and 4.

FDA's response was

(b) (4)

that the Phase 3 study, properly designed, could do so. FDA believed available data do support clinical testing.

La Jolla intends to conduct a multicenter Phase 3 study to examine the safety and efficacy of LJPC-501 in the treatment of CRH. Patients will be eligible for randomization if they are older than 18 years of age and have been diagnosed with CRH. The dose of angiotensin II will be titrated

(b) (4)

Drug will continue to be administered for 4 days to examine safety.

Safety will be assessed by monitoring adverse events. A protocol synopsis is provided in this meeting package (Appendix 1).

Question 3. *Does FDA agree that the proposed endpoints described in this study are appropriate for evaluating the safety and efficacy of the drug in Phase 3 testing to support a new drug application (NDA) for the treatment of CRH?*

FDA Response to Question 3:

Your proposed primary endpoint (b) (4)

As such, this endpoint could not provide evidence of effectiveness for LJPC-501 in the treatment of CRH. Demonstration of maintenance of some minimum blood pressure would suffice as a primary endpoint, as long as the study shows that the effect is attributable to LJPC-501. A number of study designs could achieve this goal, and we can discuss these at the meeting.

Because the mortality rate is high ($\approx 50\text{-}60\%$) in this patient population, we suggest you consider making mortality a primary or secondary endpoint, rather than blood pressure.

We recommend that all clinical trials be conducted double-blinded. Because we may have additional recommendations after we review the complete protocol, we also recommend that you submit the protocol for a special protocol assessment.

Discussion during Meeting

The sponsor provided a brief presentation (see attached sponsor slides) and noted the following:

- There is a distinction in the definition of “hypotension” versus “shock.”
- Short periods of hypotension are associated with serious adverse events, e.g., acute kidney injury and myocardial injury.
- The duration of hypotension impacts patient outcomes independent of shock.

The sponsor summarized their originally proposed study protocol:

- **Subject population and size:** 200-300 subjects (b) (4)
- **Treatment:** (b) (4)
- **Endpoints:**
 - (b) (4)
 - (b) (4)
 - (b) (4)

Dr. Unger indicated that we did not believe the sponsor’s proposed primary endpoint (b) (4) represented a clinical

benefit. He suggested that the sponsor make mortality the primary endpoint. The sponsor, however, replied that it was not feasible to have mortality as a primary endpoint.

Dr. Stockbridge suggested that showing that angiotensin II can raise blood pressure would be an acceptable endpoint. After further discussion, the Agency agreed that the primary endpoint should be the number of patients with CRH that achieve a MAP of 75 mmHg on angiotensin II versus placebo.

Dr. Temple suggested inclusion of both patients who have CRH with a MAP >65 mmHg on high doses of vasopressors and patients who cannot be maintained at a MAP of 65 mmHg. The results would be analyzed by these subgroups, i.e., patients receiving high doses of vasopressin, patients unable to be maintained at a MAP of 65 mmHg. Patients with a recent exposure to ACEi or ARB would also be analyzed.

Question 4. Does FDA agree that the design of the proposed Phase 3 clinical study described in the enclosed protocol synopsis will generate the data necessary to support FDA review and consideration for marketing approval?

FDA Response to Question 4:

In general, the design seems adequate. You restricted the SOFA score to the cardiovascular system. In an ICU setting, SOFA scores for other systems (e.g., respiratory, neurological, renal, and coagulation) should be considered. Improvement of SOFA scores is clinically meaningful and should be considered as potential secondary endpoints.

Discussion during Meeting

After further discussion, the following revised study design for the Phase 3 clinical study was proposed:

- Patients will be included in the study if they require an excessive dose of vasopressors to maintain a MAP of 65 mmHg or if they remain hypotensive (MAP <65 mmHg) despite high dose vasopressors.
- Patients with CRH will be defined as those with a CV SOFA ≥ 4 plus the need for vasopressin, or a high dose of catecholamines (e.g., NE) alone. Patients will be stratified by vasopressin exposure and MAP <65 mmHg versus >65 mmHg.
- Patients who meet entry criteria will be randomly assigned to placebo or angiotensin II, with continuation of standard-of-care vasopressor therapy as dictated by their treating clinician. The trial will be double-blind. **(Post-meeting note:** It may be advisable to use a double dummy design to maintain blinding.)
- Placebo or angiotensin II will be titrated to achieve a MAP of 75 mmHg. During the titration period, the dose of vasopressors that the patient was previously receiving will be held constant so that the effect of angiotensin II can be assessed. For safety reasons, if the MAP drops during that study period despite upward titration of angiotensin II (or placebo), the baseline vasopressors will be allowed to be titrated up. Data on fluid administration during the infusion will also be collected.
- Once a MAP of 75 mmHg is achieved, the angiotensin II or placebo will be titrated to maintain the MAP for 3 hours.
- The primary endpoint measure will be the fraction of patients who achieve a MAP of 75 mmHg at 3 hours.

- Other assessments will include whether the MAP of 75 mmHg was attained at hours 1, 2, and 3, the dose of angiotensin II that was required to achieve a MAP of 75 mmHg, and the dose of other vasopressors during the study period.
- At the end of the 3-hour assessment period, patients will continue on angiotensin II or placebo at the dose found to achieve a MAP of 75 mmHg. If the dose of 20 ng/kg/min results in a MAP >75 mmHg, the dose can be titrated down per a predefined protocol to achieve a CV SOFA score < 4. The patients will continue to receive angiotensin II for 48 hours, at which time angiotensin II will be withdrawn. Blood pressures will be collected during and after discontinuation of angiotensin II or placebo to assess durability of effect and monitor for possible hypotension. During this period, patients will remain on standard-of-care vasopressors.

The Division recommended seeking a waiver for expedited reporting of expected serious adverse events related to the underlying disease as these are actually study endpoints or are expected. The sponsor will systematically collect information on adverse events that are most relevant to the vasoconstrictive properties of the drug, such as renal failure and mesenteric ischemia.

Regarding the size of the safety database, the Division agreed that 200-300 patients in the study would be sufficient.

2.4 Regulatory

LJPC plans to submit the IND for LJPC-501 for the treatment of CRH in electronic common technical document (eCTD) format. (b) (4)

The electronic IND will provide hypertext links to the location of the information being cross-referenced in a summary table in Section 1.1.4.

Question 5. Does FDA agree that LJPC (b) (4)

FDA Response to Question 5:
We agree.

2.5 Additional FDA Preliminary Comments

Please provide the criteria to be used for dose-titration with LJPC-501 and catecholamines to obtain the target MAP in your proposed study. Also explain the schedule for reducing the maintenance dose of catecholamines once the target MAP is achieved.

3.0 PREA REQUIREMENTS

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

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

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

4.0 DATA STANDARDS FOR STUDIES

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

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

6.0 ATTACHMENTS AND HANDOUTS

La Jolla presentation slides.

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

/s/

ELLIS F UNGER
07/29/2014