

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200671Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Department of Health and Human Services  
Food and Drug Administration

Form Approved: OMB No. 0910-0513  
Expiration Date: 10/31/2016  
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER

200671

NAME OF APPLICANT/NDA HOLDER

New Haven Pharmaceuticals, Inc  
965 West Main Street, Branford, CT 06405

*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)

DURLAZA pending FDA Approval

ACTIVE INGREDIENT(S)

Acetylsalicylic acid (aspirin)

STRENGTH(S)

162.5 mg

DOSAGE FORM

Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, 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 approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration 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 all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5603957

b. Issue Date of Patent

February 18, 1997

c. Expiration Date of Patent

February 18, 2014

d. Name of Patent Owner

New Haven Pharmaceuticals, Inc.

Address (of Patent Owner)

965 West Main Street

City/State

Branford, CT

ZIP Code

06405

FAX Number (if available)

Telephone Number

(203) 488-4620 or 676-3676

E-Mail Address (if available)

hpenner@newhavenpharma.com

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/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

6 White Pine Lane

City/State

Guilford, CT

ZIP Code

06437

FAX Number (if available)

Telephone Number

(203) 676-3676

E-Mail Address (if available)

hpenner@newhavenpharma.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

<b>2. Drug Substance (Active Ingredient)</b>	
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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes <input type="checkbox"/> 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.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>3. Drug Product (Composition/Formulation)</b>	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. 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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
<b>5. No Relevant Patents</b>	
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.	<input type="checkbox"/> 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/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed

June 12, 2014

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder 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/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

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

Name

New Haven Pharmaceuticals, Inc.

Address

965 West Main Street

City/State

Branford, CT

ZIP Code

06405

Telephone Number

(203) 488-4620 or 676-3676

FAX Number (if available)

E-Mail Address (if available)

hpenner@newhavenpharma.com

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 20 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 Chief Information Officer  
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

Form Approved: OMB No. 0910-0513  
Expiration Date: 10/31/2016  
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER

200671

NAME OF APPLICANT/NDA HOLDER

New Haven Pharmaceuticals, Inc  
965 West Main Street, Branford, CT 06405

*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)

DURLAZA pending FDA Approval

ACTIVE INGREDIENT(S)

Acetylsalicylic acid (aspirin)

STRENGTH(S)

162.5 mg

DOSAGE FORM

Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, 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 approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration 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 all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5846566

b. Issue Date of Patent

December 8, 1998

c. Expiration Date of Patent

April 13, 2014

d. Name of Patent Owner

New Haven Pharmaceuticals, Inc.

Address (of Patent Owner)

965 West Main Street

City/State

Branford, CT

ZIP Code

06405

FAX Number (if available)

Telephone Number

(203) 488-4620 or 676-3676

E-Mail Address (if available)

hpenner@newhavenpharma.com

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/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

6 White Pine Lane

City/State

Guilford, CT

ZIP Code

06437

FAX Number (if available)

Telephone Number

(203) 676-3676

E-Mail Address (if available)

hpenner@newhavenpharma.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**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?  Yes  No

2.2 Does the patent claim 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? (An answer is required only if the patent is a product-by-process patent.)  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? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

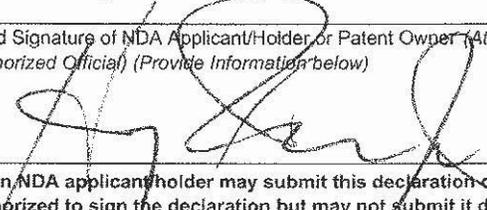
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent)	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? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
---	--

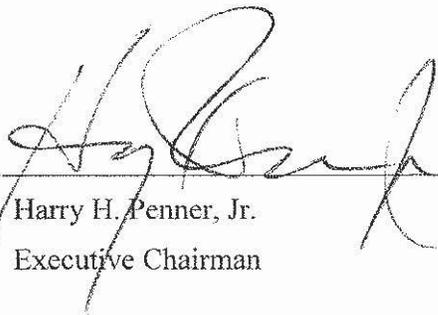
**5. No Relevant Patents**

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

<b>6. Declaration Certification</b>	
<p>6.1 <i>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.</i></p> <p><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></p>	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	June 12, 2014
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
Check applicable box and provide information below.	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name New Haven Pharmaceuticals, Inc.	
Address 965 West Main Street	City/State Branford, CT
ZIP Code 06405	Telephone Number (203) 488-4620 or 676-3676
FAX Number (if available)	E-Mail Address (if available) hpenner@newhavenpharma.com
<p>This section applies only to requirements of the Paperwork Reduction Act of 1995.</p> <p><b>*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*</b></p> <p>The burden time for this collection of information is estimated to average 20 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:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer Paperwork Reduction Act (PRA) Staff PRAStaff@fda.hhs.gov</p> <p style="text-align: center;"><i>"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."</i></p>	

## PATENT CERTIFICATIONS

New Haven Pharmaceuticals, Inc., 965 West Main Street, Branford, CT 06405 hereby certifies US Patent No. (s): US 5603957 and US 5846566 covers: Microcapsules for Controlled release of acetylsalicylic acid (aspirin). This product is the subject of this application (NDA: 200671) for which approval is being sought.



---

Harry H. Penner, Jr.  
Executive Chairman

August 14, 2014

---

Date

Confidential and Proprietary Property  
of  
New Haven Pharmaceuticals, Inc.  
965 West Main Street  
Branford, CT 06405

1

## EXCLUSIVITY SUMMARY

NDA # 200671

SUPPL # n/a

HFD # 110

Trade Name: DURLAZA

Generic Name: (aspirin) Extended Release Capsules

Applicant Name: New Haven Pharmaceuticals

Approval Date, If Known: TBD

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

**505(b)(2)**

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

**n/a**

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

**n/a**

c) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

**FIVE**

d) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

**n/a**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# n/a

Aspirin monograph - 21 CFR, Part 343.80

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

n/a

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not

essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

**n/a**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

**n/a**

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

**n/a**

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

The sponsor conducted study NHP-ASA-01 which was a pivotal dose-response study that was performed to choose a dose of NHP-55C that is pharmacodynamically equivalent to controlled release aspirin 81 mg. The response measures selected were inhibition of serum TxB<sub>2</sub>, inhibition of urinary 11-dehydro-TxB<sub>2</sub>, and inhibition of platelet aggregation. Based on the data from that study, the clinical pharmacology reviewer determined that based on a 2-fold lower ED50, NHP-554C 162.5 mg should be pharmacodynamically equivalent to IR aspirin 81 mg. Please see the finalized clinical pharmacology review by Sudharshan Hariharan for a more in depth review of this study.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

NHP-ASA-01

YES

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

n/a

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

NHP-ASA-01

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

**n/a**

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

NHP-ASA-01

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

NHP-ASA-01

IND # 116348

YES

NO

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

**n/a**

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

**n/a**

---

Name of person completing form: Alison Blaus, RAC  
Title: Senior Regulatory Project Manager  
Date: 15 September 2015

Name of Division Director signing form: Norman Stockbridge, MD, PhD  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/  
-----

ALISON L BLAUS  
09/15/2015

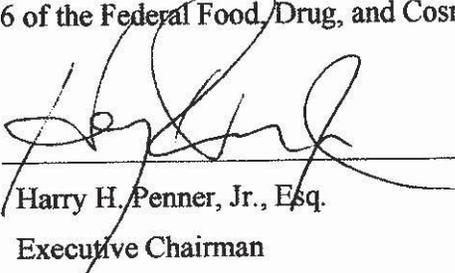
NORMAN L STOCKBRIDGE  
09/15/2015

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

1.3. Administrative Information

**3. DEBARMENT CERTIFICATION**

New Haven Pharmaceuticals, Inc., 965 West Main Street, Branford, CT 06405 hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

  
\_\_\_\_\_  
Harry H. Penner, Jr., Esq.  
Executive Chairman

6-3-13  
Date

Confidential and Proprietary Property  
of  
New Haven Pharmaceuticals, Inc.  
965 West Main Street  
Branford, CT 06405

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 200671 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: DURLAZA Established/Proper Name: aspirin Dosage Form: Extended Release Capsules		Applicant: New Haven Pharmaceuticals Agent for Applicant (if applicable): n/a
RPM: Alison Blaus, RAC		Division: Division of Cardiovascular & Renal Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:</p> <p><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></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>5 October 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain		<input type="checkbox"/> Received

<sup>1</sup> 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.

<sup>2</sup> 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).

❖ Application Characteristics <sup>3</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority          Chemical classification (new NDAs only): SE2  <i>(confirm chemical classification at time of approval)</i></p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  <input type="checkbox"/> Breakthrough Therapy designation         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p>           REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input checked="" type="checkbox"/> REMS not required         </p> <p>Comments:</p>	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

<sup>3</sup> 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.

<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s): Approval on 4Sep15
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	21Nov14 6Nov14
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 4Sep15, 14Nov14 DMEPA: <input type="checkbox"/> None 16Mar15 and 15Jun15 DMPP/PLT (DRISK): <input type="checkbox"/> None 25Jun15 OPDP: <input type="checkbox"/> None 22Jun15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None

Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	14Nov14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 8 June 15 and 21Jul15
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ 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> )	<input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	
• Date reviewed by PeRC <u>13 May 15</u> If PeRC review not necessary, explain: <u>n/a</u>	
❖ 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, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	Included
❖ 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)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 10 Dec 2009 & 10Sep13
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Mid-cycle Communication ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A
• Late-cycle Meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) ( <i>indicate dates of mtgs</i> )	12Nov12 (OCP Guidance)
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	n/a
Decisional and Summary Memos	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4Sep15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 28Aug15
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None

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

<b>Clinical</b>	
<b>❖ Clinical Reviews</b>	
• Clinical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)	28Oct14 & 30Apr15
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR</b> If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	See 30Apr15 Clinical Review
<b>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</b>	<input checked="" type="checkbox"/> None
<b>❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</b>	<input checked="" type="checkbox"/> N/A
<b>❖ Risk Management</b>	
• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))	n/a
• REMS Memo(s) and letter(s) (indicate date(s))	n/a
• Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	<input checked="" type="checkbox"/> None
<b>❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)</b>	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
<b>❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)</b>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
<b>❖ Statistical Division Director Review(s) (indicate date for each review)</b>	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<b>❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)</b>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 4Nov14, 2Jun15, & 8Aug15
<b>❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)</b>	<input type="checkbox"/> None requested 5Feb15 & 18Jun15

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 28Oct14 & 24Apr15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 29Apr15 (two), 4May15 & 21May15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See 29Apr15 Quality Review (titled R1)
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable - See 21May15 Quality Review Re-evaluation date: (b) (4) <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input checked="" type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> 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	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/  
-----

ALISON L BLAUS  
09/15/2015

1.3. Administrative Information

**2. FIELD COPY CERTIFICATION**

New Haven Pharmaceuticals, Inc., 965 West Main Street, Branford, CT, 06405, hereby certifies that Margaret Sands of the FDA's New England District (NEW-DO) Office, One Montvale Avenue, 4<sup>th</sup> Floor, Stoneham, MA 02180 was notified on June 2, 2014 by Letter (copy attached) that New Haven Pharmaceuticals, Inc. is submitting an eCTD (NDA) to the FDA's Division of Cardiovascular and Renal Drug on or about September 5, 2014, and that the electronic archival copy of NDA#200671 would be accessible through the FDA's electronic network for the field copy technical sections described in 21 CFR 314.50 (1)(3).



Arthur D. Edwards  
Vice President, Administration  
New Haven Pharmaceuticals, Inc.  
965 West Main Street  
Branford, CT 06405  
Phone: (203) 233-8517  
[aedwards@newhavenpharma.com](mailto:aedwards@newhavenpharma.com)

06-June-2014  
Date

Confidential and Proprietary Property  
of  
New Haven Pharmaceuticals, Inc.  
965 West Main Street  
Branford, CT 06405



June 2, 2014

Food and Drug Administration  
New England District (NEW-DO) Office,  
One Montvale Avenue, 4<sup>th</sup> Floor,  
Stoneham, MA 02180  
Attention: Margaret Sands

Dear Ms. Sands:

As discussed with you on May 28, 2014, this letter will serve as notification to the New England District (NEW-DO) Office that New Haven Pharmaceuticals, Inc. 965 West Main Street, Branford, CT 06405 is submitting an e-CTD (NDA) to the FDA's Division of Cardiovascular and Renal Drug on or about September 5, 2014, and that the electronic archival copy of NDA#200671 would be accessible through the FDA's electronic network for the field copy technical sections described in 21 CFR 314.50 (1)(3).

In addition, as discussed on May 28, 2014, I did contact Michael Monteleone, MS, Senior Regulatory Health Project Manager, FDA, Division of Cardiovascular and Renal Drug on May 29, 2014, to confirm with him that he is in agreement with the New England District (NEW-DO) Office that it is not necessary for New Haven Pharmaceuticals, Inc. to provide the field copy technical sections of the NDA to the New England District (NEW-DO) Office as the electronic archival copy of the NDA will be available via the FDA's network.

Thank you and if you have any questions regarding this matter, please do not hesitate to contact the undersigned.

Sincerely,

A handwritten signature in cursive script that reads "Arthur D. Edwards".

Arthur D. Edwards  
VP Administration  
New Haven Pharmaceuticals, Inc.  
965 Main Street  
Branford, CT 06405  
Cell: (b) (6)  
[aedwards@newhavenpharma.com](mailto:aedwards@newhavenpharma.com)

New Haven Pharmaceuticals, Inc., 965 West Main Street, Branford, Ct 06405

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

/s/  
-----

MARY GRACE LUBAO  
09/22/2015



NDA 200671

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

New Haven Pharmaceuticals, Inc.  
Attention: Larry M. Dillaha, M.D.  
Chief Operations Officer  
116 Washington Avenue, 4th Floor  
North Haven, CT 06473

Dear Dr. Dillaha:

Please refer to your New Drug Application (NDA) dated September 5, 2014, received September 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DURLAZA (aspirin) Extended Release 162.5 mg Capsules..

On June 26, 2015, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **October 5, 2015**.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by 7 July 2015.

If you have any questions, please call:

Alison Blaus, RAC  
Senior Regulatory Project Manager  
(301) 796-1138

Sincerely,

*{See appended electronic signature page}*

Stephen M. Grant, M.D.  
Deputy Director  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/  
-----

STEPHEN M GRANT  
06/30/2015



NDA 200671

**INFORMATION REQUEST**

New Haven Pharmaceuticals, Inc.  
Attention: Larry M. Dillaha, M.D.  
Executive Vice President, Operations  
116 Washington Avenue, 4th Floor  
North Haven, CT 06473

Dear Dr. Dillaha:

Please refer to your New Drug Application (NDA) dated September 5, 2014, received September 5, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for DURLAZA (aspirin) Extended Release 162.5 mg Capsules.

We also refer to the form FDA-483, issued by the Office of Scientific Investigations (OSI) to (b) (4) (b) (4) on (b) (4), containing a list of observations made during the inspection of this laboratory regarding study NHP-ASP-01.

The above referenced FDA-483 identified bioanalytical issues pertaining to pharmacodynamic data (serum Tx<sub>B2</sub> and urinary 11-dehydro-Tx<sub>B2</sub>) with respect to cross-reactivity and matrix effect. These issues affect interpretation of dose-response findings and may affect the ability to bridge DURLAZA® 162.5 mg to Aspirin immediate release 81mg from study NHP-ASP-01 and so affect the approvability of your NDA. Please submit to your NDA a discussion of the findings and your interpretation of them.

As this information is critical for regulatory action, please provide a response to the above request for information no later than **June 26, 2015**.

If you have any questions, please call:

Alison Blaus, RAC  
Senior Regulatory Project Manager  
(301) 796-1138

Sincerely,

{See appended electronic signature page}

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

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

/s/  
-----

ALISON L BLAUS  
06/23/2015

NORMAN L STOCKBRIDGE  
06/23/2015

**PeRC Meeting Minutes**  
**May 13, 2015**

**PeRC Members Attending:**

Lynne Yao

Robert "Skip" Nelson

Wiley Chambers

Rosemary Addy

George Greeley

Peter Starke

Daiva Shetty **NON-RESPONSIVE**

Freda Cooner

Tom Smith

Karen Davis-Bruno

Daiva Shetty

Andrew Mulberg

Greg Reaman **NON-RESPONSIVE**

Adrienne Hornatko-Munoz

Andrew Mosholder **NON-RESPONSIVE**

Hari Cheryl Sachs

Julia Pinto

Shrikant Pagay

Lily Mulugeta

Kevin Krudys

Rachel Witten

Dianne Murphy

Maura O'Leary

Kristiana Brugger

Agenda

NON-RESPONSIVE

NDA 200671

Durlaza (Full Waiver) \*Agreed iPSP

(b) (4) myocardial infarction

(b) (4)

NON-RESPONSIVE

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

NON-RESPONSIVE

**Durlaza Full Waiver**

- Proposed Indication: (b) (4) myocardial infarction (b) (4)
- PeRC Recommendations:
  - The PeRC agreed with the Division to grant a full waiver because studies would be impossible or highly impracticable.

NON-RESPONSIVE

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

/s/  
-----

GEORGE E GREELEY  
05/26/2015

**From:** Knight, Yvonne  
**To:** [Dillaha, Larry](#)  
**Cc:** [Edwards, Art \(aedwards@newhavenpharma.com\)](#); [Blaus, Alison](#)  
**Subject:** Information Request for NDA 200671 (Prompt Response)  
**Date:** Wednesday, May 13, 2015 7:28:00 AM  
**Importance:** High

---

Good morning Dr. Dillaha,

We have an information request concerning New Haven's New Drug Application (NDA) for NDA 200671. We request a prompt response to this IR request no later than COB Thursday May 14, 2015.

1. Confirm that the drug product capsules are imprinted with the name DURLAZA on each capsule. If so, include this description in the Appearance parameter of the drug product specification, provide the revised drug product specification, and confirm that (b) (4) is used for imprinting".

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
FDA/CDER/OPQ/OPRO  
10903 New Hampshire Avenue  
Bldg. 75, Room 4664  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)



**From:** Knight, Yvonne  
**To:** Edwards, Art (aedwards@newhavenpharma.com); Dillaha, Larry  
**Cc:** Blaus, Alison  
**Subject:** Information Request for NDA 200671 (Prompt Response)  
**Date:** Tuesday, March 17, 2015 9:34:00 AM  
**Importance:** High

---

Good morning Dr. Dillaha,

We have an information request concerning New Haven's New Drug Application (NDA) for NDA 200671. We request a prompt response to this IR request no later than **Monday COB March 23, 2015**.

1. The DMF (b) (4) that you are referencing for (b) (4) is currently deficient. A Deficiency Letter dated March 06, 2015 was sent to DMF holder. In order to have an approval of the submitted NDA, the DMF (b) (4) should receive an adequate status.
2. Provide revised drug substance specification aligned with that of the updated release specification by the holder of DMF (b) (4) in response to the Deficiency Letter dated 06-Mar-2015.
3. Confirm that the same commercial grade of ethylcellulose and povidone that was used in manufacture of drug product registration batches, (b) (4) and Grade (b) (4) will be used to manufacture all future drug product lots to ensure the lot to lot consistency of these excipients that impact drug release.
4. Provide complete drug product specification that includes all revisions made to date.
5. Provide a post-approval stability protocol for the commitment production batches that will include testing at the intermediate condition.
6. Revise the side panel of the carton and container labels as follows: "Each capsule contains 162.5 mg of aspirin", i.e., remove the (b) (4) definition from the panel.
7. In your Amendment dated 02/23/2015 you have submitted a revised Annotated Package Insert but a complete updated SPL file with the revised Product Data Element (PDE) was not submitted. Submit the complete updated SPL file with revised title of the Product Data Element (PDE).

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
FDA/CDER/OPQ/OPRO  
10903 New Hampshire Avenue  
Bldg. 21, Room 2667  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)



**OFFICE OF  
PHARMACEUTICAL QUALITY**

**From:** Knight, Yvonne  
**To:** Edwards, Art (aedwards@newhavenpharma.com); Dillaha, Larry  
**Cc:** [Blaus, Alison](#)  
**Subject:** Additional Information Request for NDA 200671 (Prompt Response)  
**Date:** Tuesday, March 17, 2015 6:39:00 PM  
**Importance:** High

---

Good afternoon Dr. Dillaha,

We have an information request concerning New Haven's New Drug Application (NDA) for NDA 200671. We request a prompt response to this IR request no later than **Tuesday COB March 24, 2015**.

1. Your response received on Jan 30, 2015, did not include the requested SAS transport files. Submit for bioequivalence (BE) study PKFT 9542, the individual and mean data for plasma concentration, period, sequence, etc. as SAS transport files using the following format:

SUBJ SEQ PER TRT C1 C2 C3...Cn KE\_FIRST KE\_LAST T1 T2 T3...Tn

Where KE\_FIRST and KE\_LAST are the first and last time points, respectively, used to estimate the elimination constant (Kel) for each subject/period. Also submit the pharmacokinetic dataset using the following format:

SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf

2. Include the individual dissolution data in tabular and graphical format and provide the dissolution profile comparisons (e.g.,  $f_2$  testing) for the two batches (b)(4) 589-95, (b)(4) 599-95) tested in BE study PKFT 9542.
3. The drug substance particle size distribution for the batches tested in pivotal PK and clinical trials (FT02 589-95, FT03 599-953, 106284R, 3113896R, 311444R, Batch 0001, Batch 0002 and Batch 0003) in terms of  $D_{10}$ ,  $D_{50}$ , and  $D_{90}$ .
4. The dissolution profiles as a function of drug substance particle size distribution in terms of  $D_{10}$ ,  $D_{50}$  and  $D_{90}$ .

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
FDA/CDER/OPQ/OPRO  
10903 New Hampshire Avenue

Bldg. 21, Room 2667  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)





NDA 200671

**GENERAL ADVICE**

New Haven Pharmaceuticals, Inc.  
Attention: Larry M. Dillaha, M.D.  
Executive Vice President, Operations  
965 West Main Street  
Branford, CT 06405

Dear Dr. Dillaha:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DURLAZA (Extended Release Acetylsalicylic Acid) Capsules.

We also refer to your 24 February 2015 submission containing revised carton and container labeling.

We have reviewed the referenced material and have the following comments:

**Container Label and Carton Labeling (including professional sample)**

1. Remove the (b) (4) from the principal display panel (PDP). Critical information such as the proprietary name, established name, and strength should be the most prominent information on the PDP. Other information such as the (b) (4) should not compete in size and prominence with critical product information.
2. The established name lacks prominence commensurate with the proprietary name. Thus we request you revise the presentation of the entire established name “(Aspirin) Extended Release Capsules” to be at least half as large as the letters comprising the proprietary name such that the established name shall have a prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).
3. Relocate the product strength statement away from the net quantity statement to appear immediately beneath the established name. From post marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
4. Add the statement “Swallow capsules whole. Do not crush or chew.” to the Dosage section on the side panel of the container label and the carton labeling.

If you have any questions, please contact:

Alison Blaus, RAC  
Senior Regulatory Project Manager  
(301) 796-1138

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

ALISON L BLAUS  
03/16/2015

NORMAN L STOCKBRIDGE  
03/16/2015



IND 116348

**ADVICE LETTER**

New Haven Pharmaceuticals, Inc.  
Attention: Larry M. Dillaha, M.D.  
Executive Vice President, Operations  
965 West Main Street  
Branford, CT 06405

Dear Dr. Dillaha:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DURLAZA (Controlled Release Acetylsalicylic Acid) Capsules.

We also refer to your submission dated December 19, 2014, received December 23, 2014, containing your Agreed-Upon Initial Pediatric Study Plan (iPSP).

We have completed our review of the submission, and we confirm our agreement to your Agreed iPSP. We have no further comments on your PSP. A clean copy of the Agreed iPSP is attached for your reference.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto: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).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, please contact:

Alison Blaus, RAC  
Senior Regulatory Project Manager  
(301) 796-1138

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Agreed-Upon PSP

ATTACHMENT: A

AGREED-UPON PEDIATRIC STUDY PLAN (PSP)

IND#: 116348

NHP-554 CAPSULES, 162. MG

1. OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION:

Acute myocardial infarction (AMI) is rare in childhood and adolescence. Although adults acquire coronary artery disease (CAD) from lifelong buildup of plaque, which can rupture leading to thrombosis formation and occlusion of blood flow to the cardiac muscle, the cause of AMI in children are usually due to an anomalous origin of the left coronary artery such as ALCAPA (Anomalous Left Coronary Artery from the Pulmonary Artery), or an acute inflammatory condition of the coronary arteries, such as Kawasaki's disease. Regardless of the etiology, the final common pathway of AMI includes myocardial ischemia leading to cell death.

Per statistics from the CDC, the mortality from Acute Myocardial Infarction is 0.2 deaths per 100,000 population in persons aged 15-24 years and fewer than 0.2 deaths per 100,000 in infants younger than 1 year. By comparison, mortality from AMI in persons aged 65-74 years is 262 deaths per 100,000. One study published in 2007 in the Journal of Pediatrics reported an estimated incidence of AMI in adolescents as 157 per year or 6.6 events per 1 million patient-years.

As mentioned above, when MIs do occur in children, the most common cause is a congenital abnormality of the coronary artery called ALCAPA (Anomalous Left Coronary Artery from the Pulmonary Artery). Normally, the coronary arteries originate from the base of the aorta. With ALCAPA, the left coronary artery originates from the base of the pulmonary artery. A combination of low oxygen blood and decreased perfusion pressure results in inadequate blood and oxygen delivery to the heart muscle. This then causes a myocardial infarction, or heart attack. Babies with this problem typically require surgery to reimplant the left coronary artery to its normal location.

A second cause of heart attacks in children involves an anomalous origin of the coronary artery. Some children are born with a coronary artery originating from the incorrect sinus. The left coronary artery may originate from the right sinus of Valsalva, or the right coronary artery may originate from the left sinus of Valsalva. As the coronary artery travels between the aorta and pulmonary artery, it may become compressed or take off at an acute angle. During exercise, this may result in inadequate delivery of blood and oxygen to the heart muscle and a subsequent myocardial infarction, or heart attack.

In teenagers, a heart attack can occasionally occur because of coronary artery vasospasm. This is most often triggered by drug use or smoking. With coronary artery vasospasm, the

coronary artery squeezes down and insufficient blood gets through. In addition, a blood clot may be formed at the location where the coronary artery squeezes down.

Cardiomyopathy and Hypertrophic Cardiomyopathy are yet other causes of AMI and sudden death in a pediatric population as reported in a 2003 issue of New England Journal of Medicine and a 2010 issue of Heart Failure Clinic respectively, but again the incidence is extremely low when compared to the adult population.

Other, even more rare, causes for AMI in a pediatric population include; other abnormalities of the coronary vasculature, traumatic MI, and use of drugs of abuse to mention just a few.

The signs and symptoms of AMI in a pediatric population are similar to that of an adult population. Mainly, chest pain, dyspnea, palpitation, etc...

The incidence of strokes in children has been stable over the last 10 years according to the Statistical Fact Sheet published in 2014 by the American Heart Association. (approx. 1.3 per 100,000 children) The leading cause of stroke in a previously healthy child is a cerebral arteriopathy. This accounts for more than half of all cases. Children with sickle cell disease and congenital heart defects are at increased risk of stroke.

In the adult population, approximately 795,000 new and recurrent strokes were reported in 2010 according to the same source cited above.

## 2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT:

The mechanism of action of aspirin is well understood.

Aspirin, which is the active ingredient in DURLAZA (Pending FDA approval), NHP-554C Capsules, 162.5 mg, is the most widely studied antiplatelet drug. Aspirin exerts its effect mainly by interfering with the biosynthesis of cyclic prostanoids, ie, thromboxane A<sub>2</sub> (TxA<sub>2</sub>), prostacyclin, and other prostaglandins. Specifically, aspirin causes irreversible acetylation of the enzyme cyclooxygenase, consequently inhibiting the production of TxA<sub>2</sub>, a vasoconstrictor and promoter of platelet aggregation, as well as prostacyclin (PGI<sub>2</sub>), an inhibitor of platelet aggregation and vasodilator, in platelets and vascular endothelial cells, respectively.

DURLAZA, NHP-554C Capsules, 162.5 mg, was developed with a unique delivery mechanism a prolonged, gradual release of aspirin so as to achieve TxA<sub>2</sub> inhibition equivalent to low-dose, immediate release aspirin while not suppressing PGI<sub>2</sub> to an appreciable extent.

The use of DURLAZA, NHP-554C Capsules, 162.5 mg, like immediate release aspirin, is intended as secondary prevention of cardiovascular events, not for primary prevention.

New Haven Pharmaceuticals, Inc. • 965 West Main Street • Branford, Connecticut 06405

Because of the extremely low incidence of thrombus mediated CV events in a pediatric population, it is impractical to determine the efficacy and safety of the product in this group.

3. OVERVIEW OF EXTRAPOLATION TO SPECIFIC PEDIATRIC POPULATIONS:

As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to extrapolate efficacy from an adult population to a pediatric population.

4. REQUEST FOR PRODUCT SPECIFIC WAIVER:

New Haven Pharmaceuticals, Inc. is formally requesting a waiver to the Pediatric Research Equity Act (PREA) requirement for the subject IND#: 116348 and pending NDA#: 200671 regarding DURLAZA, NHP-554C Capsules, 162.5 mg, which is a modified release form of Aspirin. We are requesting this waiver based on the fact that carrying out any pediatric study within the label indication would be highly impractical.

As Hew Haven Pharmaceuticals, Inc. NDA#200671 is a 505(b)(2) submission we will inherit the current label indication for the Reference Listed Drug, conventional or immediate release aspirin, which is:

(b) (4)

- Reduce the (b) (4) risk of death and (b) (4) stroke in patients who have had ischemic stroke or transient (b) (4)
- Reduce the (b) (4) risk of death and (b) (4) MI in patients with a (b) (4) MI or unstable angina pectoris
- (b) (4) with chronic stable angina (b) (4)

(b) (4)

The pathophysiology of cardiovascular events, which is usually plaque buildup leading to rupture and thrombus formation with vessel occlusion, is a process that takes years to evolve. While the trend has been to see children with more CVD risk factors at an earlier

age, the rate of events in a pediatric population is still very low. It is so low, in fact to make doing a meaningful clinical trial in this group impractical.

Additionally, because of the risk of Reye's Syndrome, many providers and guideline committees urge against the use of aspirin in the pediatric population except in certain conditions like Kawasaki's Disease or after cardiac surgery.

5. SUMMARY TABLE OF PLANNED NONCLINICAL AND CLINICAL STUDIES:

As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to conduct Nonclinical and Clinical Studies to generate a Table of Nonclinical and Clinical Studies.

6. PEDIATRIC FORMULATION DEVELOPMENT:

As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to develop a Pediatric Formulation.

7. NONCLINICAL STUDIES:

As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to conduct Nonclinical Studies.

8. ADDITIONAL DATA TO SUPPORT STUDIES IN CHILDREN:

As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to conduct Clinical Studies in Children; no additional data is available.

9. CLINICAL STUDIES:

- a. Pediatric Pharmacokinetic Studies: As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to conduct Pediatric Pharmacokinetic Studies.
- b. Clinical Effectiveness and Safety Studies Planned: As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to conduct Clinical Effectiveness and Safety Studies in Children.

10. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN:

New Haven Pharmaceuticals, Inc. • 965 West Main Street • Branford, Connecticut 06405

As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to conduct Pediatric Clinical Studies; thus there are no timelines.

11. PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES:

As New Haven Pharmaceuticals, Inc. is requesting a Full Waiver, NHP has no plans to extrapolate efficacy from an adult population to a pediatric population.

12. AGREEMENT FOR PEDIATRIC STUDIES WITH OTHER REGULATORY AUTHORITIES:

New Haven Pharmaceuticals, Inc. has no Agreements with any Regulatory Authority to conduct Pediatric Studies.

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

/s/  
-----

ALISON L BLAUS  
02/09/2015

NORMAN L STOCKBRIDGE  
02/09/2015

**From:** Knight, Yvonne  
**To:** Edwards, Art (aedwards@newhavenpharma.com); "Larry Dillaha"  
**Subject:** RE: Information Request for NDA 200671 (Prompt Response)  
**Date:** Friday, January 30, 2015 1:02:00 PM  
**Importance:** High

---

Please Respond to IR by Monday COB February 16, 2015.

Yvonne Knight

---

**From:** Knight, Yvonne  
**Sent:** Friday, January 30, 2015 12:59 PM  
**To:** Edwards, Art (aedwards@newhavenpharma.com); Larry Dillaha  
**Cc:** Knight, Yvonne  
**Subject:** Information Request for NDA 200671 (Prompt Response)  
**Importance:** High

Good afternoon Dr. Dillaha,

We have an information request concerning New Haven's New Drug Application (NDA) for NDA 200671. We request a prompt response to this IR request no later than **Monday COB February 16, 2014**.

1. The DMF (b)(4) that you are referencing for (b)(4) is currently deficient. We communicated these deficiencies to the DMF holder. In order to have an approval of the submitted NDA, the DMF (b)(4) should receive an adequate status.
2. Specify the drug substance acceptance criteria for Identification A, Identification B, for (b)(4) substances and for Substances (b)(4)
3. Confirm the commercial grade of the (b)(4) (b)(4) Provide information demonstrating whether any lot to lot variability of these excipients has an impact on drug release.
4. Include a test and acceptance criterion for (b)(4) content at release and stability in the drug product specification, or justify its absence.
5. Include a limit for (b)(4) in the drug product specification.
6. Provide justification for not including a (b)(4) in the container/closure system since it is known that aspirin is susceptible to (b)(4)
7. Provide 12 months stability data for three batches of the physician samples packaged in 30 count HDPE bottles. Provide this data not later than March 5, 2015.
8. Provide a comparison of the headspace for packaging configuration in 100 ml bottle and 30 cc bottle.
9. Include testing at the intermediate condition through 12 months (four time points) in the post-approval stability protocol for the commitment production batches and for the registration batches to be consistent with ICH Q1A (R2).
10. Revise a name of the drug on the carton and container labels to DURLAZA™ (aspirin) Extended Release Capsules
11. Explain the meaning of the equivalency statement (b)(4) on the carton and container labels.

12. Revise the title of the Product Data Element (PDE) in the SPL to DURLAZA (aspirin) Extended Release Capsules according to that in the revised carton and container labels.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS  
Regulatory Health Project Manager  
Division of New Drug Quality Assessment  
FDA/CDER/OPS/ONDQA  
10903 New Hampshire Avenue  
Bldg. 21, Room 2667  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)



IND 116348

## ADVICE/INFORMATION REQUEST

New Haven Pharmaceuticals, Inc.  
Attention: Larry M. Dillaha, M.D.  
Executive Vice President, Operations  
965 West Main Street  
Branford, CT 06405

Dear Dr. Dillaha:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DURLAZA (Controlled Release Acetylsalicylic Acid) Capsules.

We also refer to your amendment dated 20 October 2014, containing your initial Pediatric Study Plan (iPSP). In this submission, you request a full waiver from the Pediatric Research Equity Act (PREA) because studies would be impossible or highly impractical. We agree that a waiver is appropriate for this indication.

Please submit a letter within 90 days of receipt of this communication, stating your agreement or disagreement with our understanding of the initial Pediatric Study Plan.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as “Duplicate.”
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto: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).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, please contact:

Alison Blaus, RAC  
Regulatory Project Manager  
(301) 796-1138

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

NORMAN L STOCKBRIDGE  
12/10/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 200671

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

New Haven Pharmaceuticals, Inc.  
965 West Main Street  
Branford, Ct. 06405

ATTENTION: Arthur D. Edwards  
Vice President, Administration

Dear Mr. Edwards:

Please refer to your New Drug Application (NDA) dated and received September 5, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetylsalicylic Acid Capsules 162.5 mg.

We also refer to your, correspondence, dated and received September 25, 2014, requesting review of your proposed proprietary name, Durlaza.

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

If any of the proposed product characteristics as stated in your September 25, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Alison Blaus, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1138.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
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/  
-----

KELLIE A TAYLOR  
11/21/2014



NDA 200671

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

New Haven Pharmaceuticals, Inc.  
Attention: Mr. Arthur D. Edwards  
Vice President, Administration  
965 West Main Street  
Branford, CT 06405

Dear Mr. Edwards:

Please refer to your New Drug Application (NDA) dated 5 September 2014, received 5 September 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DURLAZA (Controlled Release Acetylsalicylic Acid) Capsules.

We also refer to your amendments dated 25 September, 16 and 21 October, and 10 November 2014.

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 **Standard**.

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 commitment requests by 7 June 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please 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.

We request that you submit the following information:

Chemistry, Manufacturing, and Controls (CMC)

1. Master Batch Records
2. DMF references for packaging components

### Biopharmaceutics

1. The dissolution method development report including:
  - a. Dissolution validation methodology report
  - b. Justification of the medium, pH, speed, use of enzymes etc.
2. Data demonstrating the discriminating ability of the proposed QC method.
3. Particle size distribution for batches GAFT04, 382-92, 599-95 and 589-95 before and after coating.
4. Data on the effect of granule particle size distribution on dissolution.
5. Data on the effect of granule coating size on dissolution.
6. Individual and mean values for all batches used in setting the dissolution acceptance criteria
7. Revise the acceptance criteria based on the following:
  - a. The first point should be based on the mean value of the clinical trial batches  $\pm 10\%$  variation rather than NLT  $(b)(4)\%$ .
  - b. The last time point should be the time point where at least  $(b)(4)\%$  of drug has been released.
8. Information on the dissolution methods used throughout the phases of product's development.
9. The individual and mean plasma concentration, period, sequence from BE study PKFT 9542 as SAS transport files.
10. Information on the batch number and manufacturing site for the batch tested in PK/PD study ASA-001.
11. Bridging information/data between the batches manufactured at the final commercial site,  $(b)(4)$  and the site used to manufactured formulation  $(b)(4)$   $(b)(4)$ .
12. Information/data supporting the controlled release designation claim such as the following:
  - a. The drug product's steady-state performance is comparable (e.g. degree of fluctuation is similar or lower) to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
  - b. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units

### Regulatory

1. You indicate that this application relies on the aspirin final OTC monograph, that is, the Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the Counter Human Use monograph at 21 CFR Part 343, but cite only a part of the aspirin final OTC monograph in your submission (i.e., on your Form FDA 356h). Please submit a revised Form FDA 356h that reflects your reliance on the aspirin final OTC monograph.

### **PRESCRIBING INFORMATION**

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

1. Please remove the (b) (4) in the footer.
2. For clarity, please define all abbreviations and acronyms upon its first appearance in the Full Prescribing Information (FPI).
3. Prescribing Information (FPI).
4. The beginning of the ADVERSE REACTIONS (AR) section (before the subsection 6.1) should identify the most clinically significant AR and direct practitioners to more detailed information about those reactions, if any. For example, the section should first identify and cross-reference all serious and otherwise potentially important AR described in greater detail in other labeling sections, especially WARNINGS AND PRECAUTIONS.
5. Per 21 CFR 201.57, please amend Section 8.4, **Pediatric Use**, to read, “Safety and effectiveness have not been established in pediatric patients.”
6. Please delete (b) (4). This section should only be included when there is information to convey.
7. (b) (4)
- 8.
9. There is no horizontal line between the TOC and FPI. Please add a line.
10. Please include pharmacologic class. The first sentence should read, "DURLAZA is a Nonsteroidal Anti-inflammatory Drug indicated (b) (4)....".
11. Please add bullets for each population to help differentiate the groups.
12. Please include your company name and the contact information under the Adverse Reactions section of the Highlights.
13. In the Highlights, please change (b) (4) TO "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling".
14. Throughout the FPI, in your cross-reference, please included the referenced subsection when appropriate as well (e.g., [see Warnings and Precautions (5.2)]).
15. Please include a subsection under Section 6 entitled, "Clinical Trials Experience". Per 21 CFR 201.57(c)(7), the first statement in this subsection should be, "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.".
16. Please include Section 17 in the FPI and include the important information that the physician should communicate to the patient.
17. Please make the (b) (4) a standalone page (either within the same file or a separate file).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **10 December 2014**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

**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) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, 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**

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call:

Alison Blaus, RAC  
Regulatory Project Manager  
(301) 796-1138.

Sincerely,

*{See appended electronic signature page}*

Stephen Grant, M.D.  
Deputy Director  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/  
-----

ALISON L BLAUS  
11/19/2014

STEPHEN M GRANT  
11/19/2014

**From:** Knight, Yvonne  
**To:** [ldillaha@newhavenpharma.com](mailto:ldillaha@newhavenpharma.com)  
**Cc:** Knight, Yvonne  
**Subject:** Information Request for NDA 200671 (Prompt Response)  
**Date:** Tuesday, November 04, 2014 3:40:19 PM  
**Importance:** High

---

Good afternoon Dr. Dillaha,

We have an information request concerning New Haven's New Drug Application (NDA) for NDA 200671. We request a prompt response to this IR request no later than Monday COB November 10, 2014.

In your amendment dated 10/16/2014, you mention that the (b) (4) facility will cease manufacturing operations, but will continue to serve as a stability testing site. Submit an updated list of all manufacturing and testing sites with their current responsibilities. If the (b) (4) site is no longer used for manufacturing, clarify exactly which manufacturing operations were transferred to the new site.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS  
Regulatory Health Project Manager  
Division of New Drug Quality Assessment  
FDA/CDER/OPS/ONDQA  
10903 New Hampshire Avenue  
Bldg. 21, Room 2667  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW  
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:  
**CDER-OPDP-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)  
Alison Blaus, ODE 1/DCaRP, (301)796-1138

REQUEST DATE:  
22 Sep 2014

IND NO:  
116348

NDA/BLA NO:  
200671

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:  
Controlled release ASA

PRIORITY  
CONSIDERATION:  
Standard Review

CLASSIFICATION OF  
DRUG:  
505 (b)(2)

DESIRED COMPLETION DATE:  
2 weeks after providing  
substantially complete labeling

NAME OF FIRM:  
New Haven Pharmaceuticals

PDUFA Date: 5 July 2015

**TYPE OF LABEL TO REVIEW**

**TYPE OF LABELING:**  
(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

**TYPE OF  
APPLICATION/SUBMISSION**

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

**REASON FOR LABELING CONSULT**

- INITIAL PROPOSED LABELING
- LABELING REVISION

**For OSE USE ONLY**

- REMS

**EDR link to submission:**

EDR Location: \\CDSESUB1\evsprod\NDA200671\0000

**Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.**

**OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.**

**COMMENTS/SPECIAL INSTRUCTIONS:**

Filing Meeting: 27 Oct 2014  
Mid-Cycle Meeting: TBD  
Labeling Meetings: TBD  
Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER: Alison Blaus

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

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

/s/  
-----

ALISON L BLAUS  
09/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): Mail: OSE		FROM: Alison Blaus, ODE 1/DCaRP, (301)796-1138		
DATE 22 Sep 2014	IND NO. 116348	NDA NO. 200671	TYPE OF DOCUMENT NDA Submission	DATE OF DOCUMENT 5 September 2014
NAME OF DRUG Controlled release ASA	PRIORITY CONSIDERATION Standard NDA Review	CLASSIFICATION OF DRUG 505(b)(2)	DESIRED COMPLETION DATE 5 May 2015	
NAME OF FIRM: New Haven Pharmaceuticals				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Carton/Container Labels				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review these carton/container labels for this NDA, controlled release aspirin. <b>Link to the Application</b> EDR Location: <a href="\\CDSESUB1\evsprod\NDA200671\0000">\\CDSESUB1\evsprod\NDA200671\0000</a> <b>PDUFA DATE: 5 July 2015</b> <b>ATTACHMENTS:</b> Draft Package Insert, Container and Carton Labels (please see these documents at the above EDR location). <b>CC:</b> Archival IND/NDA 200671 HFD-110/Division File HFD-110/RPM HFD-110/Reviewers and Team Leaders				
NAME AND PHONE NUMBER OF REQUESTER Alison Blaus		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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

/s/  
-----

ALISON L BLAUS  
09/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR PATIENT LABELING REVIEW CONSULTATION</b>	
TO: <b>CDER-DMPP-PatientLabelingTeam</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) Alison Blaus, ODE 1/DCaRP, (301)796-1138	
REQUEST DATE: 22 September 2014	NDA/BLA NO.: 200671	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)	
NAME OF DRUG: Controlled release ASA	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: 505(b)(2)	DESIRED COMPLETION DATE: 2 Weeks after receiving substantially complete labeling
SPONSOR: New Haven Pharmaceuticals		PDUFA Date: 5 July 2015	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> <b>(Check all that apply)</b> <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
		<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
<b>EDR link to submission:</b>			
EDR Location: <a href="\\CDSESUB1\evsprod\NDA200671\0000">\\CDSESUB1\evsprod\NDA200671\0000</a>			
<b>Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.</b>			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Filing/Planning Meeting: 27 October 2014  Mid-Cycle Meeting: TBD  Labeling Meetings: TBD  Wrap-Up Meeting: TBD			
SIGNATURE OF REQUESTER: Alison Blaus, RAC			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS	

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

/s/  
-----

ALISON L BLAUS  
09/22/2014



NDA 200671

**NDA ACKNOWLEDGMENT**

New Haven Pharmaceuticals, Inc.  
Attention: Mr. Arthur D. Edwards  
Vice President, Administration  
965 West Main Street  
Branford, CT 06405

Dear Mr. Edwards:

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

Name of Drug Product: DURLAZA, NHP-554C [Controlled Release Acetylsalicylic Acid (ASA)] Capsules, 162.5 mg

Date of Application: September 5, 2014

Date of Receipt: September 5, 2014

Our Reference Number: NDA 200671

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 November 4, 2014, 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 action 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, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Alison Blaus, RAC  
Regulatory Health Project Manager  
(301) 796-1138

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 I  
Center for Drug Evaluation and Research

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

/s/  
-----

EDWARD J FROMM  
09/15/2014

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2015. See instructions for OMB Statement, below.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

**PRESCRIPTION DRUG USER FEE COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:  
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm>

<p><b>1. APPLICANT'S NAME AND ADDRESS</b></p> <p>NEW HAVEN PHARMACEUTICALS INC Arthur Edwards 965 W Main St  Branford CT 064053431 US</p>	<p><b>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</b></p> <p>200-671</p>
<p><b>2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE</b></p> <p>203-233-8517</p>	<p><b>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</b></p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> <p>200671</p>

<p><b>3. PRODUCT NAME</b></p> <p>DURLAZA ( Aspirin )</p>	<p><b>6. USER FEE I.D. NUMBER</b></p> <p>PD3014412</p>
--	--

**7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES?  YES  NO**

PRIORITY REVIEW VOUCHER NUMBER:

**8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.**

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

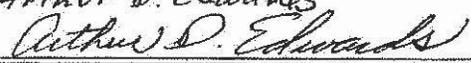
**Privacy Act Notice:**

This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: <http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm>.

**OMB Statement:**

**Public reporting burden for this collection of information** is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	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 control number.
--	--	--

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE <i>Arthur D. Edwards</i> 	TITLE <i>V-P Administration</i>	DATE <i>31-July-2014</i>
--	------------------------------------	-----------------------------

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION  
 \$0.00

Form FDA 3397 (03/12)

### INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at [https://userfees.fda.gov/OA\\_HTML/pdufaCAcdLogin.jsp](https://userfees.fda.gov/OA_HTML/pdufaCAcdLogin.jsp). If you need assistance in completing the form call 301-796-7200 or email: [userfees@fda.gov](mailto:userfees@fda.gov).

NOTE: Form FDA 3397 need not be submitted for:

**CDER**

- 505(j) applications
- Supplements to 505(j) applications
- 351(k) applications

**CDER**

Any supplement that does not require clinical data for approval.  
Applications and supplements for:

- \* Products for further manufacturing use only
- \* Whole blood or blood components for transfusion
- \* Bovine blood product for topical application licensed before September 1, 1992
- \* A crude allergenic extract product
- \* An in vitro diagnostic biological product licensed under Section 351 of the PHS Act
- \* 351(k) applications

ITEM NO.	INSTRUCTIONS
1-2.	<b>Self-explanatory</b>
3.	<b>PRODUCT NAME:</b> Include generic or proper name and trade name, as applicable.
4.	<b>BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) -</b> Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A SUPPLEMENT enter the BLA STN.  <b>FOR DRUG PRODUCTS:</b> Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm</a> .
5.	<b>CLINICAL DATA:</b> The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a> .
6.	<b>USER FEE I.D. NUMBER:</b> Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	<b>PRIORITY REVIEW VOUCHER:</b> If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA's Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA's guidance can be found on FDA's web site: <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf</a> .
8.	<b>EXCLUSIONS:</b> The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	<b>WAIVER:</b> Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.

Form FDA 3397 (03/2012)(BACK)

Close Print Cover sheet

## **1. USER FEE WAIVER EXTENSION**

Per Section 736(d)(1)(D) of the Federal Food, Drug and Cosmetic Act (the Act) a waiver of the application fee was granted on December 12, 2013 for new drug application (NDA) 200671 and an extension to the waiver on July 8, 2014 by the FDA as long as the application is received by the FDA before February 1, 2015.

Per instructed in the July 8, 2014, letter from the FDA a copy of the July 8, 2014, letter from Jane A. Axelrad, Associate Director for Policy, Center for Drug Evaluation and Research is attached regarding the details of the waiver and the extension of same.



Food and Drug Administration  
10903 New Hampshire Ave.  
Building 51, Room 6257  
Silver Spring, MD 20993

JUL 08 2014

Arthur D. Edwards  
Vice President, Administration  
New Haven Pharmaceuticals, Inc.  
965 West Main Street  
Branford, CT 06405

**RE: New Haven Pharmaceuticals, Inc., Request for Small Business Waiver Extension  
2014.062 for New Drug Application 200671, Aspirin Capsules**

Dear Mr. Edwards:

This responds to your May 28, 2014, letter requesting a waiver of an application user fee (Waiver Request 2014.062) under the small business waiver provision, section 736(d)(1)(D)<sup>1</sup> of the Federal Food, Drug, and Cosmetic Act (the Act). You request an extension of the small business waiver of the fiscal year (FY) 2014<sup>2</sup> human drug application fee for new drug application (NDA) 200671, aspirin capsules, previously granted December 12, 2013, and valid through August 16, 2014. For the reasons described below, the Food and Drug Administration (FDA) grants the New Haven Pharmaceuticals, Inc. (New Haven) request for an extension of the small business waiver of the application fee for NDA 200671, aspirin capsules.

According to your extension request, New Haven's President/CEO, Patrick P. Fourteau, and its Executive Chairman, Harry H. Penner, Jr., certified that New Haven continues to meet all of the criteria for the small business waiver that was granted on December 12, 2013.<sup>3</sup> You also state that the original submission of NDA 200671 did not occur because of feedback about the submission from the Division of Cardiovascular and Renal Drug Products. You state that New Haven now expects to submit the NDA in early September 2014, and you request that the waiver be extended for that submission.

Under section 736(d)(1)(D) of the Act, a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate<sup>4</sup> submits to the FDA for review. As outlined in section 736(d)(4) of the Act,<sup>5</sup> a small business is entitled to a waiver when the business meets the following criteria:

1. The business must employ fewer than 500 persons, including employees of its affiliates.

<sup>1</sup> 21 U.S.C. 379h(d)(1)(D).

<sup>2</sup> FY 2014 = October 1, 2013, through September 30, 2014.

<sup>3</sup> Federal law at 18 U.S.C. 1001 imposes criminal liability for knowingly and willfully falsifying or concealing a material fact from a branch of the Federal government.

<sup>4</sup> "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(11)).

<sup>5</sup> 21 U.S.C. 379h(d)(4).

2. The business does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce.
3. The marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA has reviewed available records, the Small Business Administration (SBA) size determination dated November 7, 2013,<sup>6</sup> and the additional information you submitted. Considering all the relevant factors, FDA concludes that New Haven continues to meet the statutory requirements of the Act. Consequently, your request for an extension of the small business waiver of the application fee for NDA 200671 is granted, provided the marketing application is received by FDA before February 1, 2015, 6 months after the original expiration date of the small business waiver. We have notified the FDA Office of Financial Management of this waiver decision.

FDA records show that New Haven has not yet submitted the full NDA 200671. **Please include a copy of this letter granting your waiver extension with your submission of NDA 200671.** Once submitted, if FDA refuses to file the application or if New Haven withdraws the application before it is filed by FDA, a reevaluation of the waiver will be required should the company resubmit its marketing application. If this situation occurs, New Haven should contact this office at least 90 days before it expects to resubmit its marketing application to determine whether New Haven continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Ashley Jones at 301-796-7900.

Sincerely,



*for*

Jane A. Axelrad  
Associate Director for Policy  
Center for Drug Evaluation and Research

<sup>6</sup> The SBA confirmed on August 16, 2013, that New Haven is a small business with the following affiliates: Harry Penner, Jr., and Patrick Fourteau.



IND 116348

**MEETING PRELIMINARY COMMENTS**

New Haven Pharmaceuticals  
Attention: Nancy Motola, Ph.D., RAC  
Vice President, Regulatory Affairs  
965 West Main Street  
Branford, CT 06405

Dear Dr. Motola:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Aspirin Capsules (NHP-554C).

We also refer to your 7 June 2013, correspondence requesting a meeting to discuss your planned dossier.

Our preliminary responses to your meeting questions are enclosed. Upon review of the briefing book and through internal discussion, we are cancelling the September 10<sup>th</sup> meeting, as the topics outlined in the briefing book do not merit further discussion and the preliminary responses resolve the proposed questions.

If you have any questions, please call me at (301) 796-1138.

Sincerely,

*{See appended electronic signature page}*

Alison Blaus, RAC  
Regulatory Health Project Manager  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** 10 September 2013 from 1300 – 1400 EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1313  
Silver Spring, Maryland 20903  
**Application Number:** IND 116348  
**Product Name:** (b) (4) Aspirin Capsules (NHP-554C)  
**Indication:** Secondary prevention of acute cardiovascular events  
**Sponsor Name:** New Haven Pharmaceuticals

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting previously scheduled for 10 September 2013 from 1300 – 1400 EST at FDA Headquarters in Silver Spring, MD between New Haven Pharmaceuticals and the Division of Cardiovascular & Renal Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

**1.0 BACKGROUND**

(b) (4) Aspirin is a controlled release aspirin product (b) (4) being developed in the USA by NHP. The sponsor acknowledges that prior to approval of a NDA they must conduct a dose-PD response (thromboxane B2 and platelet aggregation inhibition) study, per the discussion that took place at the 10 December 2009 pre-NDA meeting and the Agency's subsequent 17 December 2010 advice letter. In response to the Agency's request, the sponsor submitted the below study synopsis as part of a pre-IND meeting request:

“A Phase 1 Open-label, Three-way Randomized Crossover Study Comparing the

Pharmacodynamic and Pharmacokinetic Response for 24 Hours Following a Single-dose of (b) (4) Aspirin Capsules to Enteric-coated Aspirin Tablets in Healthy Volunteers”

We reviewed the sponsor’s protocol synopsis and their development plans and provided preliminary comments on 6 November 2013. The subsequent face-to-face meeting was cancelled. After taking into account our comments, the sponsor resubmitted their draft protocol for review:

“A Phase 1 Open-label, Four-way, Randomized, Crossover, Single-Dose, Dose-Response Study Comparing the Pharmacodynamic of (b) (4) Aspirin Capsules to Immediate-Release Aspirin Capsules in Healthy Volunteers”

We provided clinical pharmacology comments on the draft protocol, letter dated 17 January 2013, and these comments (along with those provided under the pre-IND meeting) have been incorporated in the final protocol submitted as part of the IND.

This pre-NDA meeting was scheduled to discuss the format and content of a potential NDA submission.

## 2.0 DISCUSSION

### 2.1 Questions for the Agency

#### **Clinical/Clinical Pharmacology**

1. The primary basis of approval of the NDA will be the ongoing dose-PD response study (NHP-ASP-01) and the Food Effect study (ASA-001). All other studies will be considered supportive studies. These supportive studies and ASA-001 will be presented individually and will not be pooled because no electronic data sets are available except for NHP-ASP-01. However, we plan to address product safety by summarizing the safety for each study, in addition to existing aspirin literature and the US OTC aspirin monograph, Professional Labeling (21 CFR Part 343.80).  
Due to the fact that the vast majority of studies in the submission are Phase 1 in nature, and there is a relatively small population for safety, it is expected that the text portion of the safety summary (Module 2.7.4) will be sufficiently detailed to serve as the ISS, yet concise enough to meet the size limitation of Module 2. Therefore, NHP will present and place all available safety information, including text, tables, and figures (when appropriate), in Module 2.7.4 as the ISS. There is nothing further to present in Module 5.3.5.3 (Reports of Analyses of Data from More than One Study) of the eCTD. Reference is made to Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, (April 2009); Section III.C. ISE- and ISS- Related Differences between Module 2 and Module 5 of the CTD and eCTD - Exceptions. For Module 2.7.4, tables and figures will be sourced and hyperlinked to the respective CSR section in Module 5.3.  
Does the Division agree with this plan?

#### **FDA Preliminary Response**

Yes. Electronic data for the food effect study (ASA-001) should also be submitted.

2. The studies conducted with NHP-554C were primarily designed to evaluate and compare PK, PD, safety, and tolerability between NHP-554C and a reference product (delayed-release or immediate-release aspirin). For this reason, an ISE will not be generated.

Does the Division agree?

**FDA Preliminary Response**

Yes.

3. Due to the nature of the studies included in this eCTD focusing on the PD, PK, safety and tolerability of NHP-554C, Module 2.7.3 will be limited to Section 2.7.3.1 (Background and Overview of Clinical Efficacy). Cross references to other sections of this eCTD will be made where necessary.

Does the Division agree?

**FDA Preliminary Response**

Yes.

4. Study NHP-ASP-01 is a dose-response study examining the relationship between PD markers (serum thromboxane B<sub>2</sub>, urine 11-dehydro-thromboxane B<sub>2</sub>, and platelet aggregation using arachidonic acid and collagen as agonists) and acetylsalicylic acid (ASA) dose following single dose, oral administration of NHP-554C to healthy volunteers. Additionally, the PD response of NHP-554C will be compared to a single dose of immediate-release aspirin. Characterization of the PK of ASA and its metabolite, salicylic acid (SA), and the safety of NHP-554C are secondary objectives of the study.

Data from this study will be summarized using descriptive statistics and appropriate analyses as described in the statistical analysis plan, and these summaries will be presented in the body of the CSR, with PK and PD data included in Module 2.7.2 and safety data included in Module 2.7.4 of the eCTD. Tables, listings and figures will also be presented in the appendix of the clinical study report (CSR).

[Appendix 8](#) includes PK and PD mock tables, listings and figures proposed for inclusion in the CSR and appendices for study NHP-ASP-01, with the CSR included in Module 5.3 of the eCTD.

Does the Division agree with the presentation of the PK and PD data in this format for the CSR and eCTD?

**FDA Preliminary Response**

Yes. We expect complete study reports for the studies conducted by New Haven Pharmaceuticals.

**Chemistry, Manufacturing, & Controls (CMC)**

1. Six months stability data for one registration/clinical batch manufactured recently in the US and equivalent to the intended launch/commercial product will be available at the time of NDA submission and will be included in the eCTD. NHP intends to submit 12 month stability data for the one registration/clinical batch manufactured as well as additional/ongoing longer term stability data on two other registration batches during the NDA review period via eCTD sequences. Stability data will continue to be collected to (b) (4) for the three registration batches. Longer-term stability data from the earlier European-approved product will be submitted to support the (b) (4) proposed expiration dating period.

Does the Division agree with this plan?

**FDA Preliminary Response**

We do not agree with this plan. We expect that long-term testing should cover a minimum of 12 months' duration on at least three primary batches at time of submission (refer to ICH Q1A(R2) guidance). Submission of a smaller stability data package, as proposed, may result in a "refuse to file" regulatory action.

**Labeling**

1. Aspirin has a long history of use in cardiac prevention indications as well as several other indications. There is an OTC monograph for which Professional Labeling clearly directs health care providers in the use of aspirin for the same cardiac prevention indications being sought for NHP-554C. Because of this, NHP does not intend to include a REMS.

Does the Division agree?

**FDA Preliminary Response**

Yes, we agree.

**2.2 Additional Comments from the Agency**

1. Since you have an extended release formulation, you must conduct an *in vitro* alcohol dose dumping study to characterize the potential for altered release profiles of aspirin. This advice was conveyed to you in an earlier meeting dated 11/23/2010. Please refer to the teleconference meeting minutes [page 6 of 7] for details about the conduct of this *in vitro* study. We expect to have the complete study report along with the NDA submission.

**3.0 OTHER IMPORTANT INFORMATION**

**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. Because none of the criteria will apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

**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. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

**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.				

**505(b)(2) REGULATORY PATHWAY**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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. trade name(s)).

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

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

We encourage you to identify each section of your proposed 505(b)(2) application that 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.

<b>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</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>

1. <i>Example: Published literature</i>	<i>Nonclinical toxicology</i>
2. <i>Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
3. <i>Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
4.	

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

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

/s/  
-----

ALISON L BLAUS  
08/30/2013

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

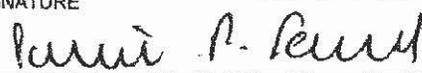
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see attachment	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Patrick Fourteau	TITLE Chief Executive Officer
FIRM/ORGANIZATION New Haven Pharmaceuticals, Inc, 965 West Main Street, Branford, CT 06405	
SIGNATURE 	DATE (mm/dd/yyyy) 06/05/2013

**This section applies only to the requirements of the Paperwork Reduction Act of 1995.**  
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 control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

**Do NOT send your completed form to the PRA Staff email address below.**  
Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
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."

1.3. Administrative Information

**4. FINANCIAL CERTIFICATION AND DISCLOSURE**

Note: The NDA (200671) contains 15 clinical studies. Fourteen (14) of the studies were conducted prior to the effective date (February 2, 1999) of 21 CFR part 54 and as such and agreed upon with the Division of Cardiovascular and Renal Drug, FDA on May 29, 2013, this Financial Disclosure document will not contain information for these fourteen (14) studies. However for the fifteenth study (NHP-ASP-01), the following information is being provided:

**Table 1: List of Investigators subjected to 21 CFR Part 54**

Name	Address	Phone Number Fax Number
Danielle Armas, M.D.	2420 West Baseline Road, Tempe, AZ 85283	T: (602) 437-0097 F: (602) 437-3386
(b) (6)		

Confidential and Proprietary Property  
of  
New Haven Pharmaceuticals, Inc.  
965 West Main Street  
Branford, CT 06405



PIND 116348

**ADVICE LETTER**

New Haven Pharmaceuticals  
Attention: Nancy Motola, Ph.D., RAC  
Vice President, Regulatory Affairs  
142 Temple Street, Suite 205  
New Haven, CT 06510

Dear Dr. Motola:

Please refer to your Pre-Investigational New Drug Application (PIND) file for (b) (4) Aspirin Capsules.

We also refer to your submission dated November 29, 2012, containing an amended protocol entitled, "A Phase 1 Open-label, Four-way, Randomized, Crossover, Single-Dose, Dose-Response Study Comparing the Pharmacodynamics of (b) (4) Aspirin Capsules to Immediate-Release Aspirin Capsules in Healthy Volunteers". This amended protocol was in response to our Pre-IND meeting preliminary comments, dated November 6, 2012, on the original version of this protocol.

Upon review of the above mentioned protocol, we find the design acceptable. However, you have not provided the details of the bioanalytical techniques that will be used for the evaluation of PK and PD. We strongly recommend that you use validated bioanalytical assays for the PK and PD evaluation. If you have any questions, please call:

Alison Blaus, RAC  
Regulatory Project Manager  
(301) 796-1138

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

NORMAN L STOCKBRIDGE  
01/17/2013



PIND 116348

**MEETING PRELIMINARY COMMENTS**

New Haven Pharmaceuticals  
Attention: Nancy Motola, Ph.D., RAC  
Vice President, Regulatory Affairs  
142 Temple Street, Suite 205  
New Haven, CT 06510

Dear Dr. Motola:

Please refer to your Pre-Investigational New Drug Application (PIND) file for (b) (4) Aspirin Capsules.

We also refer to your 7 September 2012 correspondence requesting a meeting to discuss your planned dose-PD response study.

Based on our internal discussion, we have decided that the contents of the briefing book do not warrant further discussion and are therefore cancelling the 13 November 2012 meeting. We are, however, providing our preliminary responses to your meeting questions. This response is enclosed.

If you have any questions, please call me at (301) 796-1138.

Sincerely,

*{See appended electronic signature page}*

Alison Blaus  
Regulatory Health Project Manager  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments

### PRELIMINARY MEETING COMMENTS

**Meeting Type:** C  
**Meeting Category:** Guidance  
**Meeting Date and Time:** 13 November 2012  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room 1311  
Silver Spring, Maryland 20903

**Application Number:** PIND 116348

**Product Name:** (b) (4) Aspirin Capsules

**Indication:** (1) (b) (4) the (b) (4) risk of death and (b) (4) stroke in patients who have had ischemic stroke or transient (b) (4)

(b) (4);  
(2) (b) (4) the (b) (4) risk of death and (b) (4) MI in patients with a (b) (4) MI or unstable angina pectoris;  
(b) (4) with chronic stable angina (b) (4)

**Sponsor Name:** New Haven Pharmaceuticals (NHP)

## 1.0 BACKGROUND

(b) (4) Aspirin is a controlled release aspirin product approved for marketing in Europe and being developed in the USA by NHP. The sponsor acknowledges that prior to approval of a NDA they must conduct a dose-PD response (thromboxane B2 and platelet aggregation inhibition) study, per the discussion that took place at the 10 December 2009 pre-NDA meeting and the Agency's subsequent 17 December 2010 advice letter. In response to the Agency's request, the sponsor is planning the following study:

“A Phase 1 Open-label, Three-way Randomized Crossover Study Comparing the Pharmacodynamic and Pharmacokinetic Response for 24 Hours Following a Single-dose of (b) (4) Aspirin Capsules to Enteric-coated Aspirin Tablets in Healthy Volunteers”

This meeting was scheduled to discuss various aspects of this study.

## 2. DISCUSSION

Our advice is unchanged from the advice we gave in our letter to you dated December 17, 2010 (quoted in the preamble to question 1 below). We believe that a comparison of the ID<sub>50</sub> of your product and the reference product will provide the information necessary to write adequate dosing instructions, which is the purpose of the study we suggested. (b) (4)

(b) (4)

For the assays, we recommend that you:

1. Determine thromboxane B2 in addition to its metabolite, 11-dehydro thromboxane B2 and
2. Use collagen as an agonist in addition to arachidonic acid for the platelet aggregation assay.

## 2.1. Questions for the Agency

**Question 1:** In the FDA Advice Letter of December 17, 2010, the Agency requested that NHP:

“Conduct a Dose-PD response (thromboxane B2 and platelet aggregation inhibition) study with immediate release aspirin (reference) and your product (test). The aim of this study is to define the dose of (b) (4) Aspirin that corresponds to the approved doses of immediate release aspirin. You should power the study so as to allow for the estimation of the ID50 (Dose that results in 50% of the maximal inhibition) with a relative standard error (RSE) of 20%. The PD measures should be collected following single dose administration of the aspirin products since aspirin is an irreversible platelet inhibitor and upon repeated administration the effect accumulates decreasing the ability to demonstrate dose-response.”

NHP has designed a clinical study examining the pharmacodynamic response of the (b) (4) aspirin capsule and immediate-release aspirin over a 24-hour post-dose period, in response to this request. Does the Agency agree that a single dose, cross-over study monitoring the pharmacodynamic effects of the treatments for 24 hours, as outlined in the attached protocol, is adequate to meet the objectives of the Division’s request?

**Question 2:** In the pre-meeting package there is a description of the assays that NHP plans to use for thromboxane B2 and platelet aggregation inhibition. Does the Division agree with this choice of pharmacodynamic measures?

**Question 3:** The study will characterize the area under the effect-time curve (AUEC) and the maximum response (Emax) for thromboxane B2 and platelet aggregation inhibition for the (b) (4) aspirin capsule and the immediate-release aspirin over 24 hours. Does the Agency agree with these endpoints?

**Question 4:** Eighteen subjects will be enrolled in the study, which will permit the characterization of mean area under the effect-time curve and the mean maximum response over the 24 hour period after administration of the (b) (4) aspirin capsule and immediate-release aspirin with a RSE of 20%. Does the Agency agree that the number of subjects is adequate to characterize the pharmacodynamic response of the (b) (4) aspirin capsule to immediate-release aspirin?

**Question 5:** The study will utilize the lowest (b) (4) and highest (b) (4) commercially available doses of immediate-release aspirin as comparators to the 162.5 mg dose of the (b) (4) aspirin capsule. The intent is to compare the pharmacodynamic response after a single dose of the

(b) (4) aspirin capsule to the range of pharmacodynamic response observed after a single dose with the immediate-release aspirin. Does the Division agree?

### **3.0 OTHER IMPORTANT INFORMATION**

#### **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

#### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

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

#### **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>

#### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests 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.				

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

/s/  
-----

ALISON L BLAUS  
11/06/2012



NDA 200671

**GENERAL ADVICE**

New Haven Pharmaceuticals  
Attention: Nancy Motola, Ph.D., RAC  
Vice President, Regulatory Affairs  
300 George Street, Suite 561  
New Haven, CT 06511

Dear Dr. Motola:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Aspirin Capsules, 162.5 mg.

We also refer you to our December 10, 2009 and November 23, 2010 teleconference minutes to discuss your Pre-NDA application.

We have reviewed and discussed your submission with various disciplines in the Agency and we believe the spirit of our preliminary response (communicated on 11/18/2010) still is valid. We have the following comments and/or recommendations:

Conduct a Dose-PD response (thromboxane B2 and platelet aggregation inhibition) study with immediate release aspirin (reference) and your product (test). The aim of this study is to define the dose of (b) (4) Aspirin that corresponds to the approved doses of immediate release aspirin. You should power the study so as to allow for the estimation of the ID<sub>50</sub> (Dose that results in 50% of the maximal inhibition) with a relative standard error (RSE) of 20%. The PD measures should be collected following single dose administration of the aspirin products since aspirin is an irreversible platelet inhibitor and upon repeated administration the effect accumulates decreasing the ability to demonstrate dose-response.

We feel our comments and/or recommendations have adequately answered your questions and/or concerns and we would like to proceed to cancel the meeting. If you feel the meeting would be necessary, we will proceed with the teleconference scheduled for December 21, 2010, from 10:00 AM – 11:00 AM, EST.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

NORMAN L STOCKBRIDGE  
12/17/2010

## Teleconference Minutes

**Date:** November 23, 2010  
**Application:** Pre-NDA 200671  
**Drug:** (b) (4) aspirin  
**Sponsor:** New Haven Pharmaceuticals  
**Meeting Purpose:** Pre-NDA Follow Up  
**Meeting Type:** B

### FDA /CDER Attendees:

#### *Office of New Drugs, Division of Cardiovascular and Renal Products (DCRP)*

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader
Nhi Beasley, PharmD.	Clinical Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Anna Park, R.Ph.	Regulatory Project Manager

#### *Office of Clinical Pharmacology*

Rajnikanth Madabushi, Ph.D.	Team Leader
Ju-Ping Lai, Ph.D.	Clinical Pharmacologist

#### *Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I*

Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader
Martha Heimann, Ph.D.	Team Leader
David Claffey, Ph.D.	Chemist

### New Haven Pharmaceutical Attendees:

Nancy Motola, Ph.D., RAC	Vice President, Regulatory Affairs
Scott Kozak	Vice President and Chief Business officer
William Sessa, Ph.D.	Professor of Pharmacology, Yale University School of Medicine
Harry H. Penner, Jr.	Chairrman and Chief Executive Officer
Deborah Church, M.D.	Acting Chief Medical Officer

(b) (4)

### Background:

Asacard (also known as Flamasacard and Caspac), Flamel's brand of (b) (4) aspirin capsules (162.5 mg), is a controlled release aspirin product developed by Flamel Technologies of Pessac, France. This formulation of aspirin is made up of microparticles, (b) (4). The (b) (4) acts as a semi-permeable membrane that allows aspirin to

diffuse progressively over the length of the gastrointestinal tract, resulting in prolonged absorption and a subsequently prolonged duration of action.

Asacard is approved in Europe for the following therapeutic indication: secondary prophylaxis after a first coronary (b) (4) (myocardial infarction (MI), stable and unstable angina, coronary angioplasty, (b) (4)), (b) (4) stroke and (b) (4) (b) (4)). The sponsor is proposing to develop (b) (4) aspirin as a new therapy for secondary prevention of acute cardiovascular events, similar to the OTC aspirin labeling.

Preliminary responses to the submitted questions were provided to the sponsor, and are copied below, followed by any additional discussions that took place during the meeting.

**Meeting:**

**After brief introductions, the sponsor stated the food effect study was conducted and would submit the data for review and further agreed to comply with the recommendations presented by the Office of Drug Quality Assessment. Please refer to the end of the preliminary responses for additional discussion of the meeting.**

**Preamble:**

(b) (4)

(b) (4). Hence, we recommend that you conduct a BE study with at least two dose levels whose thromboxane B2 and platelet aggregation inhibition is expected to be different from no inhibition and maximal inhibition (Example: corresponding to 20% and 80% of the maximal inhibition). Since aspirin is an irreversible platelet inhibitor, the PD parameters should be measured at 24 hours following administration of a single dose with an appropriate washout period between the two dose levels and the products. Assessment of the PD following repeat administration at steady-state is less discriminatory. You should power the study to assess BE at both dose levels for both PD parameters. In addition, we recommend that you collect plasma samples to determine the Cmax and AUC of acetyl salicylic acid.

***From the Pre-NDA Meeting (10 Dec 09) Summary of Discussions:***

1. NHP has presented a rationale for use of thromboxane inhibition, as employed in the (b) (4) Aspirin development program. We believe this is an appropriate PD measurement for assessment of bioequivalence of (b) (4) Aspirin to conventional immediate release aspirin. Does the Division agree?

**Preliminary FDA Response:** No. We recommend you conduct a single-dose study that measures both thromboxane B2 inhibition and platelet inhibition. Please see preamble above.

2. NHP has presented the rationale for selection of the criteria used in the (b) (4) Aspirin clinical program for determining bioequivalence. Does the Division agree?

**Preliminary FDA Response:** See the preamble above.

3. NHP has presented the protocol and validation report for the Enzyme Immunoassay (Method ICD 52, dated December 1997 entitled EIA Analysis of Thromboxane B2 in Human Serum, completed at (b) (4).) that was used to measure thromboxane inhibition in the clinical program conducted for (b) (4) Aspirin, and an expert opinion confirming the appropriateness of this assay to measure thromboxane inhibition. Does the Division agree?

**Preliminary FDA Response:** Yes.

4. In the pre-meeting briefing package, NHP has presented CMC information and data from the most recent batches of 162.5 mg (b) (4) Aspirin, which were manufactured in 2008. These data are compared with data from batches of the same product, which were approved in the 1990s and were presented in the original Asacard MAA. These data and information demonstrate that the 162.5 mg product has maintained its integrity. Does the Division agree?

**Preliminary FDA Response:** It is unclear precisely what you mean by “integrity”. If you are asking whether the two lots manufactured in Jan 2008 are similar to those manufactured in the 1990s – the data presented indicate that they met the proposed specifications. We do note, however that one of the two recent batches had dissolution results near the proposed limits. We expect that the NDA submission will contain all (not just average) dissolution data.

5. It is NHP’s intention to produce commercial supplies of (b) (4) Aspirin for launch in the United States. The plan (b) (4) use a contract manufacturing company in the US (b) (4) (b) (4) In view of this, and, assuming agreement with (4), does the Division agree that:
  - a. Comparable data to those supplied in the briefing package from “to be manufactured” US commercial batches of (b) (4) Aspirin (as compared with older batches) will be acceptable for submission and review in the NDA?

**Preliminary FDA Response:** It is unclear what you mean by “comparable data”. We expect that the NDA will include drug product stability data from three lots of each packaging configuration. These lots should be from the proposed US drug product manufacturing site. We encourage you to include all other available supportive stability data in the application including more recent stability data from the (b) (4) manufacturing site.

- b. Specifications, assays, and stability data as presented are adequate as support for the commercial product to be produced in the US which will form the basis for approval of the product in the NDA? *(Please note that NHP acknowledges that some specifications may need to be updated to reflect conformance with USP/NF).*

**Preliminary FDA Response:** The acceptability of the 'specifications, assays and stability data' will be a review matter. An acceptance criterion for 'other related substances' will need to be added to the drug product specification.

**We have the following additional preliminary CMC comments:**

1. The drug substance particle size acceptance criteria will require justification. We expect that you will provide information on the impact of particle size on drug product performance (b) (4). Provide clarification on whether the percentages refer to percent particle counts or percent weight.

2. We recommend that you assess whether other solid state characteristics require control (b) (4). (b) (4)

3. We expect details on the steps taken to control the (b) (4) (b) (4) product and especially the (b) (4) product during shipment and storage.

4. (b) (4)

5.

6.

**Additional Preliminary Biopharmaceutics Comments:**

1. (b) (4)

2.

3. We also noted that the selected paddle rotation of speed is 100 rpm; therefore the selection of this high speed needs to be justified. Please provide dissolution method report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method. A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., selection of the equipment/apparatus,

in vitro dissolution media, agitation/rotation speed at 50, 75, and 100 rpm, pH, assay, sink conditions, etc.) that were used to identify this method as most appropriate should be included in the report. The testing conditions used for each test should be clearly specified. Also, include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). The chosen method should be discriminatory and sensitive enough to reject lots that would be expected to have less than acceptable clinical performance. Validation studies are important for identifying critical formulation and manufacturing variables during development, establishing relevant controls for the testing of the final product.

4. Provide the dissolution profile data (individual, mean, min, max, SD) from the clinical and stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values).

***Additional Questions:***

6. The pharmacodynamic bridge strategy that NHP intends to use to show “bioequivalence” of (b) (4) Aspirin to conventional immediate release aspirin depends on demonstrating (b) (4)  
(b) (4)  
(b) (4) Does the Division agree with this strategy?

**Preliminary FDA Response:** See preamble above.

7. Finally, NHP believes that adequate data and information have now been presented to the Division on (b) (4) Aspirin to allow NHP to proceed with the submission of an NDA for the 162.5 mg dose of this product. Does the Division agree?

**Preliminary FDA Response:** We do, except as noted in responses to previous questions.

**Additional preliminary comments:**

1. Since (b) (4) Aspirin is a modified release product; you need a food-effect BA study. (b) (4) to the guidance titled “Food-Effect Bioavailability and Fed Bioequivalence Studies”.
2. You should provide evidence to rule out occurrence of any dose dumping.

**Discussion during the meeting:** In the preliminary responses, the Division expressed the view that a modified-release formulation of aspirin needed to have its principal pharmacodynamic effects recalibrated to those of immediate-release aspirin. At the meeting, Dr. Madabushi explained that for a PK-PD study to show any sensitivity, it needed to be conducted at doses that were not on the flat parts of the exposure-response curve. The sponsor expressed concern about having to develop stability data on new dose strengths necessitated by such a study, but Dr. Stockbridge noted that they only needed stability data for the duration of the proposed study.

Drs. Stockbridge and Madabushi recommended the sponsor to study PD effect of more than one dose at a single time point, preferably at 24-hours, given that aspirin is an irreversible acting drug. Dr. Stockbridge further recommended stretching out the exposure-response for both PD marker and formulation to include different immediate-release strengths. Although bioequivalence may not be proven, this would define the pharmacodynamic effects after one dose for labeling purposes. It might also indicate that a higher dose than standard aspirin may be necessary to reproduce the effects of the approved doses of aspirin for secondary prevention.

A spectrum of other approaches to approval of a modified-release aspirin was discussed. (b) (4)

(b) (4)  
(b) (4)  
(b) (4) Dr. Stockbridge recommended further internal discussions would be necessary and agreed to have another follow-up discussion with the sponsor with final recommendations.

Finally, Dr. Dorantes recommended an in vitro ethanol interaction study, to rule out dose dumping. Further advice on this follows:

Initially, an in vitro dissolution testing should be conducted and depending on the result of the in vitro testing, it may have to follow-up with an in vivo study. The result of the in vitro study should be discussed with FDA prior to the NDA submission.

The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your MR product:

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the in vitro dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%. In general;
  - If the optimal dissolution medium is 0.1N HCl; dissolution profiles in this 0.1 N HCl (pH containing the above range of alcohol concentrations would be sufficient.
  - If the optimal dissolution medium is NOT 0.1N HCl; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.
  - If the optimal dissolution medium has not been identified; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
  - If the dissolution of the MR product is pH independent; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.
  - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
  - The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
- The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

Minutes preparation: *{See appended electronic signature page}*  
Anna Park, R.Ph.

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

Drafted- 11/24/10; Final- 12/2/10

Reviewed: A. Dorantes- 11/24/10  
R. Madabushi-11/28/2010  
S. Grant- 30 Nov 2010  
A. Karkowsky-30 Nov 2010  
E. Fromm-12/1/2010  
N. Stockbridge-12/2/10

-----  
**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  
12/02/2010

**Preliminary Responses**

**Application:** Pre-NDA 200671  
**Sponsor:** New Haven Pharmaceuticals  
**Drug:** (b) (4) aspirin  
**Type of Meeting:** Pre-NDA  
**Date of Internal Meeting:** November 15, 2010  
**Date of Meeting with Sponsor:** November 23, 2010

**List of Internal Meeting Participants:**

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products, DCRP
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
Stephen Grant, M.D.	Medical Team Leader, DCRP
B. Nhi Beasley, Pharm.D.	Clinical Reviewer, DCRP
Al DeFelice, Ph.D.	Pharmacology Team Leader, DCRP
Rajnikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader
Martha Heimann, Ph.D.	Product Quality Team Leader
David Claffey, Ph.D.	Product Quality Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff, DCRP
Anna Park, R.Ph.	Regulatory Project Manager, DCRP

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **November 23, 2010**, between **New Haven Pharmaceuticals** and the **Division of Cardiovascular and Renal Products**. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to the purpose of the meeting (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.*

**Preliminary Responses**

**Preamble:**

(b) (4)

(b) (4). Hence, we recommend that you conduct a BE study with at least two dose levels whose thromboxane B2 and platelet aggregation inhibition is expected to be different from no inhibition and maximal inhibition (Example: corresponding to 20% and 80% of the maximal inhibition). Since aspirin is an irreversible platelet inhibitor, the PD parameters should be measured at 24 hours following administration of a single dose with an appropriate washout period between the two dose levels and the products. Assessment of the PD following repeat administration at steady-state is less discriminatory. You should power the study to assess BE at both dose levels for both PD parameters. In addition, we recommend that you collect plasma samples to determine the Cmax and AUC of acetyl salicylic acid.

***From the Pre-NDA Meeting (10 Dec 09) Summary of Discussions:***

1. NHP has presented a rationale for use of thromboxane inhibition, as employed in the (b) (4) Aspirin development program. We believe this is an appropriate PD for assessment of bioequivalence of (b) (4) Aspirin to conventional immediate release aspirin. Does the Division agree?

**FDA Response: No. We recommend you conduct a single-dose study that measures both thromboxane B2 inhibition and platelet inhibition. Please see preamble above.**

2. NHP has presented the rationale for selection of the criteria used in the (b) (4) Aspirin clinical program for determining bioequivalence. Does the Division agree?

**FDA Response: See the preamble above.**

3. NHP has presented the protocol and validation report for the Enzyme Immunoassay (Method ICD 52, dated December 1997 entitled EIA Analysis of Thromboxane B2 in Human Serum, completed at (b) (4).) that was used to measure thromboxane inhibition in the clinical program conducted for (b) (4) Aspirin, and an expert opinion confirming the appropriateness of this assay to measure thromboxane inhibition. Does the Division agree?

**FDA Response: Yes.**

4. In the pre-meeting briefing package, NHP has presented CMC information and data from the most recent batches of 162.5 mg (b) (4) Aspirin, which were manufactured in 2008. These data are compared with data from batches of the same product, which were approved in the 1990s and were presented in the original Asacard MAA. These data and information demonstrate that the 162.5 mg product has maintained its integrity. Does the Division agree?

**FDA Response:** It is unclear precisely what you mean by “integrity”. If you are asking whether the two lots manufactured in Jan 2008 are similar to those manufactured in the 1990s – the data presented indicate that they met the proposed specifications. We do note, however that one of the two recent batches had dissolution results near the proposed limits. We expect that the NDA submission will contain all (not just average) dissolution data.

5. It is NHP’s intention to produce commercial supplies of (b) (4) Aspirin for launch in the United States. The plan is to (b) (4) (b) (4) use a contract manufacturing company in the US (b) (4) (b) (4). In view of this, and, assuming agreement with (4), does the Division agree that:

- a. Comparable data to those supplied in the briefing package from “to be manufactured” US commercial batches of (b) (4) Aspirin (as compared with older batches) will be acceptable for submission and review in the NDA?

**FDA Response:** It is unclear what you mean by “comparable data”. We expect that the NDA will include drug product stability data from three lots of each packaging configuration. These lots should be from the proposed US drug product manufacturing site. We encourage you to include all other available supportive stability data in the application including more recent stability data from the (b) (4) manufacturing site.

- b. Specifications, assays, and stability data as presented are adequate as support for the commercial product to be produced in the US which will form the basis for approval of the product in the NDA? (Please note that NHP acknowledges that some specifications may need to be updated to reflect conformance with USP/NF).

**FDA Response:** The acceptability of the ‘specifications, assays and stability data’ will be a review matter. An acceptance criterion for ‘other related substances’ will need to be added to the drug product specification.

**We have the following additional CMC comments:**

1. The drug substance particle size acceptance criteria will require justification. We expect that you will provide information on the impact of particle size on drug product performance (b) (4). Provide clarification on whether the percentages refer to percent particle counts or percent weight.
2. We recommend that you assess whether other solid state characteristics require control (b) (4)
3. We expect details on the steps taken to control the (b) (4) (b) (4) product and especially the (b) (4) product during shipment and storage.

4.

5.

6.

(b) (4)

**Additional Biopharmaceutics Comments:**

1.

2.

(b) (4)

3. **We also noted that the selected paddle rotation of speed is 100 rpm; therefore the selection of this high speed needs to be justified. Please provide dissolution method report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method. A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed at 50, 75, and 100 rpm, pH, assay, sink conditions, etc.) that were used to identify this method as most appropriate should be included in the report. The testing conditions used for each test should be clearly specified. Also, include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). The chosen method should be discriminatory and sensitive enough to reject lots that would be expected to have less than acceptable clinical performance. Validation studies are important for identifying critical formulation and manufacturing variables during development, establishing relevant controls for the testing of the final product.**
4. **Provide the dissolution profile data (individual, mean, min, max, SD) from the clinical and stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values).**

*Additional Questions:*

6. The pharmacodynamic bridge strategy that NHP intends to use to show “bioequivalence” of (b) (4) Aspirin to conventional immediate release aspirin depends on demonstrating (b) (4)
- (b) (4). Does the Division agree with this strategy?

**FDA Response:** See preamble above.

7. Finally, NHP believes that adequate data and information have now been presented to the Division on (b) (4) Aspirin to allow NHP to proceed with the submission of an NDA for the 162.5 mg dose of this product. Does the Division agree?

**FDA Response:** We do, except as noted in responses to previous questions.

**Additional comments:**

1. Since (b) (4) Aspirin is a modified release product; you need a food-effect BA study. Please refer to the guidance titled “Food-Effect Bioavailability and Fed Bioequivalence Studies”.
2. You should provide evidence to rule out occurrence of any dose dumping.

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

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

/s/  
-----

NORMAN L STOCKBRIDGE  
11/18/2010

## Meeting Confirmation

**Date:** November 23, 2010  
**Time:** 10:00 AM – 11:00 PM, EST  
**Application:** Pre-NDA 200671  
**Drug:** (b) (4) aspirin  
**Sponsor:** NewHaven Pharmaceuticals  
**Meeting Purpose:** Pre-NDA Meeting #2  
**Date of Request:** September 28, 2010  
**Date of Confirmation:** October 6, 2010  
**Meeting Type:** B

### FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Stephen Grant, M.D.	Deputy Director, DCaRP
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader
Nhi Bach Beasley, PharmD.	Clinical Reviewer
Al DeFelice, Ph.D.	Pharmacology Team Leader
Rajnikanth Madabushi, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Michael Pacanowski Pharm.D., M.P.H.	Acting Team Leader, Genomics Group
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, ONDQA
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Anna Park, R.Ph.	Regulatory Project Manager

**Location:** Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Conference Room 1415  
Silver Spring, MD 20993-0002

Our internal meeting is scheduled for November 15, 2010. We will send a written response to your questions approximately seven days after our internal meeting. You have the option of canceling your meeting if you feel our written response adequately addresses your questions.

In addition to the official copy of the briefing package that must be sent to the Ammendale Road address, please send 20 desk copies to:

**Food and Drug Administration**  
10903 New Hampshire Ave.  
ATTENTION: Anna Park  
(b) (6)  
Silver Spring, MD 20993-0002

---

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

---

/s/

---

ANNA J PARK  
10/06/2010

## Teleconference Minutes

**Date:** December 10, 2009  
**Application:** NDA 200671  
**Drug:** (b) (4) Aspirin Capsules, 162.5 mg  
**Sponsor:** New Haven Pharmaceuticals, Inc.  
**Meeting Purpose:** B  
**Meeting Type:** Pre-NDA

### **FDA/CDER Attendees:**

*Office of New Drugs, Division of Cardiovascular and Renal Products (DCaRP)*

Norman Stockbridge, M.D., Ph.D.	Director
Abraham Karkowsky, M.D., Ph.D.	Clinical Team Leader
Stephen M. Grant, M.D.	Deputy Director
Nhi Beasley, PharmD.	Clinical Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Anna Park, R.Ph.	Regulatory Project Manager

*Office of Clinical Pharmacology*

Rajnikanth Madabushi, Ph.D.	Team Leader
Islam Younis, Ph.D.	Clinical Pharmacologist

*Office of New Drug Quality Assessment, Division of Pre-marketing Assessment I*

Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead
------------------------------	--------------------------------

*Office of New Drugs, Division of Nonprescription Regulation Development*

Elaine Abraham, R.Ph.	Interdisciplinary Scientist
-----------------------	-----------------------------

*Office of Biometrics, Division of Biometrics I*

Valeria Freidlin, Ph.D.	Statistician
-------------------------	--------------

### **New Haven Attendees:**

Nancy C. Motola, Ph.D., RAC	Vice President, Regulatory Affairs
Scott Kozak	Vice President and Chief Business Officer
Harry H. Penner, Jr.	Chairman and Chief Executive Officer
Lavanya Rajachandran, Ph.D.	Executive Director, Clinical Development

(b) (4)

(b) (4)

### **Background:**

(b) (4) Aspirin is a controlled release aspirin product developed by (b) (4) that is made up of microparticles, (b) (4). The (b) (4) (b) (4) acts as a semi-permeable membrane that allows aspirin to diffuse progressively over the length of the gastrointestinal tract, resulting in a long duration of action. Asacard<sup>®</sup>, Flamel's brand of Micropump<sup>®</sup> Aspirin capsules (162.5 mg), has been approved in Europe for "behind the counter" dispensing but was never marketed in any country. The sponsor proposes to develop (b) (4) formulation for the secondary prevention of acute cardiovascular events, comparable to the OTC aspirin labeling for professionals that appear in 21 CFR 343.80.

Preliminary responses to the submitted questions were provided to the sponsor, and are copied below, followed by any additional discussions that took place during the meeting.

**Meeting:**

**Questions**

1. New Haven Pharmaceuticals intends to submit an NDA for [REDACTED] (b) (4) Aspirin for the proposed indications (mentioned above). Substantial evidence of safety and efficacy would include studies confirming the pharmacodynamic equivalence to standard immediate release aspirin in both healthy subjects and patients with atherosclerosis. New Haven Pharmaceuticals believes that an NDA as allowed under 505(b)(2) of the FDC Act consisting of this information would be sufficient to allow the Division to review [REDACTED] (b) (4) Aspirin for approval in the above mentioned indications. *Does the Division agree?*

**Preliminary FDA Response:** Yes. 21CFR 320.24 discusses the types of evidence that can establish bioequivalence. Section (b)(3) makes clear that if equivalent bioavailability of the active moiety can not be established (as can not be for your product), then demonstration of equivalence of an appropriate pharmacological effect of the active moiety is acceptable to establish bioequivalence if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. Whether the studies you plan to submit are adequate to establish bioequivalence on the basis of the effect of your product on thromboxane B2 levels and measurement of platelet aggregation is unclear. In particular, it is unclear what criteria were used to determine equivalence and whether these criteria were prespecified.

**Additional discussions during the meeting:** DCaRP stated that although it is generally preferable to establish bioequivalence based on pharmacokinetic data, it understood that New Haven would be unable to do so for their product. DCaRP indicated that it would therefore be acceptable to establish bioequivalence of their product to immediate-release aspirin via pharmacodynamic (PD) measurements. DCaRP stated that it was unaware that the USFDA had ever approved an aspirin product for marketing based on PD measurement(s) and New Haven indicated it also had not been able to find a precedent. Because there was no regulatory precedent, DCaRP suggested further discussions will be necessary to determine the appropriate PD measurement(s) and if the studies already conducted will be adequate. When asked what the appropriate PD measurement was, the sponsor acknowledged it was unclear, but did note a statistically significant increase in thromboxane level suppression when a comparison was made between day 28 and baseline (14 days of run-in period) at the 75 mg dose. In addition, it was unclear why the thromboxane level increased at the end of the run-in period but they did note this elevation was seen only with the 75 mg dose and not with their product or the 150 mg dose.

DCaRP noted that the studies summarized in the package submitted for this meeting were conducted in the 1990s and wondered if the accuracy of the thromboxane B2 assay used was comparable to present day methods. New Haven stated they believed that the methodology has not changed since the studies were conducted. They plan to provide data indicating that total exposure to salicylate was comparable to the immediate-release formulation based on AUC. Dr. Madabushi noted this to be relevant when the comparison is made across products that are all immediate-release, while [REDACTED] (b) (4) aspirin has an entirely different time course, making it difficult for a determination to be made based on salicylate levels. The sponsor said that the AUC results and the amount of aspirin absorbed in the gastrointestinal tract were similar between their product and the immediate-release aspirin.

DCaRP reminded New Haven that without clinical outcome studies, (b) (4)  
(b) (4) The sponsor acknowledged their professional labeling would be the same as the currently marketed products.

2. Although approval was sought solely for the 162.5 mg (b) (4) aspirin capsule in the MAA, and product information (in the relevant CMC sections) was provided only for the 162.5 mg capsule, the data presented in the clinical trial reports in the approved MAA appear to support a (b) (4) (b) (4) aspirin dose, (b) (4) the approved 162.5 mg dose. NHP proposes, therefore, that the dosing (b) (4) for (b) (4) aspirin, as supported by the clinical trials, (b) (4) (b) (4) 162.5 mg/day (b) (4). Assuming that NHP would submit appropriate product and biopharmaceutical data for the (b) (4) 162.5 mg capsule, NHP proposes that the NDA may support (b) (4) doses/products. *Does the Division agree?*

**Preliminary FDA Response:** Yes. Please also conduct a pharmacokinetic/pharmacodynamic study comparing lower doses of (b) (4) Aspirin to an IR formulation of aspirin. The information gained from this study will be helpful for writing instructions for use with concomitant medications such as ibuprofen.

(b) (4)

**Summary of discussions:**

1. The sponsor will suggest an appropriate PD measurement and provide their rationale.
2. The sponsor will suggest the criteria for determining bioequivalence.
3. The sponsor will provide additional information on the thromboxane B2 assay.
4. Because the CMC information provided in the briefing package was a decade old, Dr. Srinivasachar recommended the sponsor to provide updated background information and specific questions regarding the manufacturing of their product.
5. DCaRP recommended New Haven request a follow-up meeting to review their data in more detail to determine if another PD study was likely to be needed for a successful NDA submission.

Minutes preparation: *{See appended electronic signature page}*  
Anna Park

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

Drafted-12/11/09; Final- 12/25/09

Reviewed: K. Srinivasachar- 12/11/09

I. Younis- 12/13/09  
R. Madabushi- 12/22/09  
A. Karkowsky- 12-22/09  
S. Grant- 22 Dec 2009  
E. Fromm-12-23-09  
N. Stockbridge-12/23/09

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-200671

-----  
GI-1

-----  
NEW HAVEN  
PHARMACEUTICA  
LS

-----  
(b) (4)  
162.5mg Aspirin Capsules,

-----  
**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  
12/28/2009

**Preliminary Responses**

**Application:** NDA 200671  
**Sponsor:** New Haven Pharmaceuticals  
**Drug:** (b) (4) Aspirin Capsules  
**Type of Meeting:** Pre-NDA  
**Classification:** B  
**Date of Internal Meeting:** December 3, 2009  
**Date of Meeting with Sponsor:** December 10, 2009

**List of Internal Meeting Participants:**

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
Stephen Grant, M.D.	Deputy Director, DCRP
Nhi Beasley, PharmD.	Medical Reviewer, DCRP
Robert Fiorentino, M.D.	Medical Officer, DCRP
Rajnikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader
Islam Younis, Ph.D.	Clinical Pharmacology
Valeria Freidlin, Ph.D.	Statistician
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, ONDQA
Matthew Holman, Ph.D.	Deputy Director, Division of Nonprescription Regulation Development (DNRD)
Elaine Abraham, R.Ph.	Interdisciplinary Scientist, DNRD
Walt Ellenberg, Ph.D.	Regulatory Project Manager, DNRD
Edward Fromm, R.Ph., RAC	Chief Project Management, DCRP
Anna Park, R.Ph.	Regulatory Project Manager, DCRP

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **December 10, 2009**, between **New Haven Pharmaceuticals** and the **Division of Cardiovascular and Renal Products**. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to the purpose of the meeting (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or*

*additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.*

### Preliminary Responses

1. New Haven Pharmaceuticals intends to submit an NDA for (b) (4) Aspirin for the proposed indications (mentioned above). Substantial evidence of safety and efficacy would include studies confirming the pharmacodynamic equivalence to standard immediate release aspirin in both healthy subjects and patients with atherosclerosis. New Haven Pharmaceuticals believes that an NDA as allowed under 505(b)(2) of the FDC Act consisting of this information would be sufficient to allow the Division to review (b) (4) Aspirin for approval in the above mentioned indications. *Does the Division agree?*

**FDA Response:** Yes. 21CFR 320.24 discusses the types of evidence that can establish bioequivalence. Section (b)(3) makes clear that if equivalent bioavailability of the active moiety can not be established (as can not be for your product), then demonstration of equivalence of an appropriate pharmacological effect of the active moiety is acceptable to establish bioequivalence if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. Whether the studies you plan to submit are adequate to establish bioequivalence on the basis of the effect of your product on thromboxane B2 levels and measurement of platelet aggregation is unclear. In particular, it is unclear what criteria were used to determine equivalence and whether these criteria were prespecified.

2. Although approval was sought solely for the 162.5 mg (b) (4) aspirin capsule in the MAA, and product information (in the relevant CMC sections) was provided only for the 162.5 mg capsule, the data presented in the clinical trial reports in the approved MAA appear to support a (b) (4) (b) (4) aspirin dose, (b) (4) the approved 162.5 mg dose. NHP proposes, therefore, that the dosing (u) (4) for (u) (4) aspirin, as supported by the clinical trials, (b) (4) (b) (4) 162.5 mg/day (b) (4). Assuming that NHP would submit appropriate product and biopharmaceutical data for the (b) (4) 162.5 mg capsule, NHP proposes that the NDA may support (b) (4) doses/products. *Does the Division agree?*

**FDA Response:** Yes. Please also conduct a pharmacokinetic/pharmacodynamic study comparing lower doses of (b) (4) Aspirin to an IR formulation of aspirin. The information gained from this study will be helpful for writing instructions for use with concomitant medications such as ibuprofen.

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-200671

-----  
GI-1

-----  
NEW HAVEN  
PHARMACEUTICA  
LS

-----  
(b) (4)  
162.5mg Aspirin Capsules,

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

/s/  
-----

STEPHEN M GRANT

12/08/2009

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266

White Oak  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002

**This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law.** If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP; 10903 New Hampshire Ave.; Silver Spring, MD 20993-0002

**Transmitted to FAX Number:** 203-488-6552

**Attention:** Nancy C. Motola, Ph.D., RAC

**Company Name:** NewHaven Pharmaceutical

**Phone:** 860-461-5487

**Subject:** Pre-NDA meeting request

**Date:** October 22, 2009

**Pages including this sheet:** 2

**From:** Anna Park  
**Phone:** 301-796-1129  
**Fax:** 301-796-9841

## Meeting Confirmation

**Date:** December 10, 2009  
**Time:** 9:00 AM – 10:00 AM, EST  
**Application:** NDA 200671  
**Drug:** (b) (4) Aspirin Capsules 162.5 mg  
**Sponsor:** NewHaven Pharmaceutical  
**Meeting Purpose:** Pre-NDA meeting  
**Date of Request:** October 9, 2009  
**Date of Confirmation:** October 22, 2009  
**Meeting Type:** B

### FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Stephen Grant, M.D.	Deputy Director, DCRP
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
Nhi Beasley, Pharm.D.	Medical Officer, DCRP
Chuck Resnick, Ph.D.	Pharmacology Team Leader
Rajnikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader
James Hung, Ph.D.	Director, Division of Biometrics I, Office of Biostatistics (OB)
Valeria Freidlin, Ph.D.	Statistician
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-marketing Assessment I, ONDQA
Edward Fromm, R.Ph., RAC	Chief Project Management, DCRP
Anna Park, R.Ph.	Regulatory Project Manager, DCRP

**Location:** Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Conference Room 1315  
Silver Spring, MD 20993-0002

Our internal meeting is scheduled for November 18, 2009. We will send a written response to your questions approximately three days after our internal meeting. You have the option of canceling your meeting if you feel our written response adequately addresses your questions.

**Please email me in Word version the list of meeting attendees and the list of specific questions from the briefing document, when available.**

**Please notify me via email of any meeting attendees who are also Special Government Employees (SGEs) and specify the date on which they have received clearance from CDER to participate in this meeting.**

**Archival copies of the briefing document should be officially submitted in triplicate to the Document Control Room no later than 4 weeks prior to the meeting. In addition to the triplicate copies, please send 25 Desk Copies of the briefing document to the following address:**

**Food and Drug Administration**

**10903 New Hampshire Ave.**

**Attention: Anna Park**

(b) (6)

**Silver Spring, MD 20993-0002**

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-200671

-----  
GI-1

-----  
NEW HAVEN  
PHARMACEUTICA  
LS

-----  
(b) (4)  
162.5mg Aspirin Capsules,

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

/s/  
-----

ANNA J PARK  
10/22/2009