CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200671Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

NDA # 200671 (Division of Cardiovascular and Renal Products)
Date: 21-May-2015
Product Name: DURLAZA™(aspirin) Extended Release Capsules
Company Name: New Haven Pharmaceuticals, Inc.
Subject: Overall OPQ/OPF Recommendation
Updated Drug product Specification (Amendment 14-May-2015)

OPF Recommendation for Manufacturing Facilities

Pursuant the overall "**Approve" OPF Recommendation** issued on 08-May-2015 (refer to attachment to this Memo), the overall quality recommendation is for "approval".

Updated Drug Product Specification

The applicant has provided the following updated drug product specification.

Drug Product Regulatory Specification

Test	Method	Acceptance Criteria
Appearance*	(b) (4)	Size 2 capsule shell, white to off-white opaque capsule containing white (b) (4) white crystalline powder. Capsules are imprinted with the name Durlaza using (b) (4)
Identification		(b) (4)
Identification		
Dissolution*		
1 hour		(b) (4)
3 hour		
9 hour		
22 hour		
30 hour		
Disintegration Time		
(b) (4)		

Test	Method	Acceptance Criteria
Related substances*		
		(b) (4)
Assay *		(b) (4)
		(b) (4)

ASA -Acetylsalicylic Acid; (b) (4) NMT-Not more than;
NLT-Not less than; RRT-relative retention time

Evaluation: Adequate. The firm has revised the Appearance parameter to include the information on imprinting the capsules with the approved proprietary name Durlaza. This revision was done in response to IR dated 13-May-2015.

Recommendation and Conclusion on Approvability

NDA 200671 for Durlaza™ (Aspirin) Extended Release Capsules is recommended for Approval from the CMC standpoint. Based on the provided stability data, the 15 months expiration dating period is recommended for drug product stored in the 90 count HDPE bottles at the recommended storage condition, 25°C (77°F) [USP Controlled Room Temperature].

Attachment

Inspection Management Form

NDA 200671-Orig1-New/NDA(4)

(b) (4)

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Overall Application Reevaluation Date

(b) (4)

Lyudmila Soldatova -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300147892, cn=Lyudmila Soldatova -S
Date: 2015.05.21 13:55:09 -04'00'

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.05.21 15:50:34 -04'00'

NDA 200-671

Aspirin Extended Release Capsules

New Haven Pharmaceuticals, Inc.

Lyudmila N. Soldatova, Ph. D.
OPQ/OLDP/DPMA I
for
Division of Cardiovascular and Renal Products

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1. NDA 200-671

2. REVIEW #: 2

3. REVIEW DATE: March 5, 2015; Revision Date April 28, 2015

4. REVIEWER: Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	05-Sep-2014
Amendment	16-Oct-2014
Amendment	10-Nov-2014
Amendment	20-Jan-2015
Review #1	09-Feb-2015

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	30-Jan-2015
Amendment	18-Feb-2015
Amendment	24-Feb-2015
Amendment	06-Mar-2015
Amendment	27-Mar-2015
Amendment	28-Apr-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	New Haven Pharmaceuticals Inc.
Address:	965 West Main Street, Branford CT 06405

Representative: Arthur D. Edwards, VP Administration
Telephone: (203) 233-8517

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Durlaza
b) Non-Proprietary Name (USAN): Aspirin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Secondary Prevention of Acute Cardiovascular Events

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 162.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

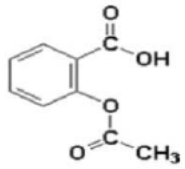
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN Name: Aspirin
Chemical Names:
Acetylsalicylic Acid
Salicylic Acid Acetate
2-(Acetyloxy) benzoic Acid
CAS: [50-78-2]



Molecular formula: $C_9H_8O_4$
Molecular weight: 180.16 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4	(b) (4)	1	Adequate	22-Apr-2015	Drug substance
	II		Aspirin	1	Adequate (b) (4)	16-Dec-2014	Drug substance
	IV		(b) (4)	4	N/A	N/A	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		Office of Compliance
Pharm/Tox	The approvability of NHP-554C control release formulation will rely on the clinical pharmacokinetic study results.	4/24/2015	Belay Tesfamariam, Ph. D.
Biopharm/ONDP/ OPQ	Pending		Sandra Suarez, Ph.D.
DMEPA	Pending		

Chemistry Review Data Sheet

DMEPA	Proprietary name: Acceptable	21-Nov-2015	Kellie A Taylor, Pharm D., MPH
Methods Validation	Adequate as per this review by Dr. Soldatova	09-Feb-2015	Lyudmila Soldatova, Ph.D.
EA	Categorical Exclusion claim is Adequate as per this Review by Dr. Soldatova	09-Feb-2015	Lyudmila Soldatova, Ph.D.
Microbiology	Acceptable from a product quality microbiology standpoint	12-Sep-2014	CDER OPS IO MICRO

The Chemistry Review for NDA 200-671

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 200671 for Aspirin Extended Release Capsules is recommended for Approval from the CMC standpoint pending the Overall recommendation for drug substance and drug product manufacturing facilities from Office of Process and Facilities (OPQ/OPF). The drug substance and drug product deficiencies summarized in the IR Letter dated 30-Jan-2015 and IR Letter dated 17-Mar-2015 have been satisfactory resolved, and the drug substance DMF (b) (4) is found to be Adequate. Based on the provided stability data, the 15 months expiration dating period is recommended for drug product stored in the 90 count HDPE bottles at the recommended storage condition, 25°C (77°F) [USP Controlled Room Temperature].

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Refer to the Review #1 dated 09-Feb-2015 for this NDA regarding the description of the Drug Product and Drug Substance.

The drug substance and drug product deficiencies presented in the IR Letter dated 30-Jan-2015 and IR Letter dated 17-Mar-2015 have been satisfactory resolved by the applicant. The most critical outstanding deficiencies were resolved as follows: 1) The drug substance specification was revised according to that revised by the holder of DMF (b) (4) as requested; 2) The applicant has confirmed that the same commercial grade of ethylcellulose and povidone that was used in manufacture of drug product registration batches will be used in manufacture of all future drug product lots to ensure the lot-to-lot consistency of these excipients; 3) The drug product specification was revised to include a limit for (b) (4), as requested, and to include the revised dissolution specification as recommended by biopharm reviewer; 4) The drug product specification limit of NMT (b) (4)% for major degradant, (b) (4) (b) (4), was accepted by a pharm/tox reviewer through discussion at the team meetings; 5) Based on the provided stability data for (b) (4) registration batches, and considering compliance of the stability data to the revised specification, the 15 months expiration dating period is granted to drug product packaged in 90 count HDPE bottles (commercial product); 6) Based on the additional 12-month stability data for one batch of physician sample packaged in 30 count 30 cc HDPE container, and considering the justification provided by the firm, the same expiry of 15 months as for the commercial product in 90 count HDPE bottles is granted; 7) The name of the

drug on the carton and container labels was revised to DURLAZA™ (aspirin) Extended Release Capsules as requested.

The drug substance DMF (b) (4) is found to be Adequate as per Review #3 by Dr. Lyudmila Soldatova; the DMF holder has addressed the identified deficiencies. The drug substance DMF (b) (4) remains Adequate. The Overall recommendation for drug substance and drug product manufacturing facilities from OPQ/OPF is currently pending.

Executive Summary Risk Assessment for Drug Product Aspirin ER Capsules					
From Initial Quality Assessment (IQA)			Review Assessment		
Product Property/ Impact of Change CQAs	Factors Affecting CQAs	*Risk Ranking	Risk Mitigation Approach in Control Strategy	Risk Evaluation	Lifecycle Consideration/ Comments
Assay, Stability	Degradation (b) (4)	Low	Control of major degradant (b) (4) in the DP specification; storage of drug product at 25ºC (b) (4)	Acceptable	(b) (4)
Physical stability (solid state)	(b) (4)	Low		Acceptable	
Content Uniformity		Low		Acceptable	
Microbial limits		Low		Acceptable	
Alcohol dose dumping	Dose dumping due to enhanced solubility of rate controlling excipients and drug in alcohol	High	About (b) (4)% of the drug is dumped within 1 hour in 40% alcohol. Biopharm reviewer recommends that the clinical and clinical pharmacology reviewer evaluate the clinical relevance of the in vitro results.	Acceptable	Comment by clinical reviewer: "Dose dumping will have the effect of attenuating the controlled release mechanism, thereby making the drug approximate the kinetics of the immediate-release formulation. The result of this from a clinical perspective is that there is no difference in benefit-risk compared to standard aspirin".
Dissolution	(b) (4)	Med	(b) (4)	Acceptable	(b) (4) Additional considerations to be determined based on biopharm evaluation of the dissolution method and acceptance criteria. The revised acceptance criteria for dissolution are accepted by the applicant, and batch analysis and stability data comply with that.

*Risk ranking is FMECA based and applies to product attribute/CQA. Low ≤25RPN, Med=25 – 60 RPN, High ≥60RPN

B. Description of How the Drug Product is Intended to be Used

NDA 200671 Aspirin Extended Release Capsules is being developed by New Haven Pharmaceuticals, Inc. for the secondary prevention of acute cardiovascular events.

Proposed Aspirin Administration (from currently proposed PI)

- (b) (4) One DURLAZA (b) (4) Capsule 162.5 mg per day. (b) (4) recommended (b) (4) the capsule is taken with a full glass of water, (b) (4), at the same time each day. (b) (4)

Do not take DURLAZA 2 hours before or 1 hour after consuming alcohol.

C. Basis for Approvability or Not-Approval Recommendation

NDA 200671 is recommended for Approval from the CMC standpoint. The outstanding issues with deficiencies in the DMF (b) (4), and with the drug substance and drug product deficiencies in the submitted NDA have been resolved. An overall recommendation from the OPF for drug substance and drug product facilities is currently pending.

III. Administrative

A. Reviewer's Signature

Lyudmila N. Soldatova

B. Endorsement Block

Chemist: Lyudmila Soldatova, Ph.D./17-April-2015
Chemistry Branch Chief: Olen Stephens, Ph.D.
CMC Lead: Kasturi Srinivasachar, Ph.D.

C. CC Block

Quality Project Manager: Yvonne Knight
Clinical Project Manager: Alison Blaus

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

Based upon an e-mail (attached) from Alison Blaus on February 3, 2015 The USPI (Annotated Package Insert and Prescribing Information will be revised to reflect the following change: **from** [redacted] (b) (4) **to** "DURLAZA™ (aspirin) Extended Release Capsules" to ensure there is alignment with the requested changes to the Carton and Container Label.

EVALUATION: The applicant has not submitted the revised Product Data Element (PDE) in the SPL file.

COMMENT

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).

RESPONSE (Amendment 27-Mar-2015)

Submitted as requested, please see Section 1.14.1

EVALUATION: Adequate. The acceptable Product Data Element is provided in the revised SPL file.

List Of Deficiencies To Be Communicated: None.

Lyudmila Soldatova -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300147892, cn=Lyudmila Soldatova -S
Date: 2015.04.29 11:00:51 -04'00'

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.04.29 11:14:44 -04'00'

NDA 200-671

Aspirin Extended Release Capsules

New Haven Pharmaceuticals, Inc.

Lyudmila N. Soldatova, Ph. D.
OPQ/OLDP/DPMA I
for
Division of Cardiovascular and Renal Products

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C. CC Block 9

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Chemistry Review Data Sheet

1. NDA 200-671

2. REVIEW #: 1

3. REVIEW DATE: February 09, 2015

4. REVIEWER: Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 116348	27-Apr-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	05-Sep-2014
Amendment	16-Oct-2014
Amendment	10-Nov-2014
Amendment	20-Jan-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	New Haven Pharmaceuticals Inc.
Address:	965 West Main Street, Branford CT 06405
Representative: Arthur D. Edwards, VP Administration	
Telephone: (203) 233-8517	

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Durlaza
b) Non-Proprietary Name (USAN): Aspirin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Secondary Prevention of Acute Cardiovascular Events

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 162.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

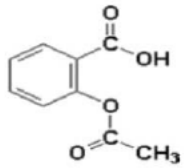
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

_x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN Name: Aspirin
Chemical Names:
Acetylsalicylic Acid
Salicylic Acid Acetate
2-(Acetyloxy) benzoic Acid
CAS: [50-78-2]



Molecular formula: $C_9H_8O_4$
Molecular weight: 180.16 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	25-Nov-2014	Drug substance
	II		Aspirin	1	Adequate (b) (4)	16-Dec-2014	Drug substance
	IV		(b) (4)	4	N/A	N/A	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		Office of Compliance
Pharm/Tox	Pending		Belay Tesfamariam, Ph. D.
Biopharm/ONDP/ OPQ	Pending		Sandra Suarez, Ph.D.
DMEPA	Pending		
DMEPA	Proprietary name: Acceptable	21-Nov-2015	Kellie A Taylor, Pharm D., MPH
Methods Validation	Adequate as per this review by Dr. Soldatova	09-Feb-2015	Lyudmila Soldatova, Ph.D.
EA	Categorical Exclusion claim is Adequate as per this Review by Dr. Soldatova	09-Feb-2015	Lyudmila Soldatova, Ph.D.
Microbiology	Acceptable from a product quality microbiology standpoint	12-Sep-2014	CDER OPS IO MICRO

The Chemistry Review for NDA 200-671

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 200671 for Aspirin Extended Release Capsules cannot be approved in its current form from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug substance DMF (b) (4) deficiencies, drug substance and drug product deficiencies summarized in the IR Letter dated 02-Feb-2015, and upon the Overall OC recommendation for drug substance and drug product manufacturing facilities.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed dosage form for NDA 200671 is Durlaza™ (aspirin) Extended Release Capsules, 162.5 mg (Durlaza is a tentatively accepted proprietary name). The drug product is intended to provide a continuous, 24-hour release of aspirin drug product. The dosage form is a size 2 white to off-white opaque (b) (4) gelatin capsule containing a white (b) (4)-white crystalline powder (b) (4) (b) (4) (b) (4) (b) (4). All excipients used in the manufacture of aspirin capsules are of compendial grade except for the (b) (4) gelatin capsules that contain titanium dioxide. The capsules excipients are used in this formulation in quantities similar to those used in the approved drugs. The formulation and manufacturing process for the drug product was developed by (b) (4) and then transferred to (b) (4), the commercial production facility for the US market. The formulation development was performed to achieve the extended release characteristic by using a (b) (4) method. The (b) (4) formulation contains the commonly used (b) (4), to obtain the desired extended release characteristics. The applicant will need to confirm the commercial grade of these excipients to ensure consistent dissolution profile of the drug product batches. Particle size of the drug substance is a critical attribute to achieve the target dissolution profile of the product. Through the manufacturing process development, after evaluating various particle size ranges it was determined that a particle size distribution in the range of (b) (4) was optimal. The manufacturing process consists of three major phases: (b) (4) (b) (4). The (b) (4) phase is the most complex. Through the process development it has been established that operating within the proposed ranges for critical parameters in the (b) (4) (b) (4) and (b) (4) processes yields product with similar dissolution profiles;

however, only three drug product batches were evaluated thus far. Standard specifications for (b) (4) have been proposed that include assay, related substances, uniformity of dosage units, appearance, identification, bioburden, dissolution (b) (4) time points), disintegration time and (b) (4) Dissolution method and acceptance criteria are being currently evaluated by OPQ/ONDP biopharm reviewer. The acceptance of limit of NMT (b) (4) % for major degradant. (b) (4), is consulted with a pharm/tox reviewer. Test for (b) (4) should be included in the specification; that is requested from New Haven Pharmaceuticals, Inc. (NHP). The non-compendial analytical methods were adequately validated. Batch analysis provided for three registration batches of commercial scale (b) (4) (b) (4)) demonstrate that all tested parameters comply with the proposed specifications including the currently proposed dissolution specification. Container/closure system is 90 count (commercial) and 30 count (professional sample) HDPE bottles with (b) (4) closures. (b) (4). The 12-month stability data for (b) (4) registration batches stored at long term and intermediate conditions (b) (4) are provided. Based on this data, HNP proposed an expiry of (b) (4). Results of stability testing are acceptable for long-term and intermediate conditions (b) (4) (b) (4) (b) (4). Based on the provided stability data for (b) (4) registration batches, the 15 months expiration dating period could be granted to drug product packaged in 90 count HDPE bottles (commercial product). This preliminary determination on shelf life is conditional pending the recommendation of the biopharmaceutics reviewer. (b) (4) (b) (4) (b) (4)

The active ingredient, aspirin (chemical name acetylsalicylic acid), is a small molecule with Molecular weight 180.16. Aspirin is white or almost white crystalline powder slightly soluble in water (b) (4) Aspirin does not exhibit any polymorphic form or isomers. The applicant is referencing (b) (4).' Type II DMF (b) (4) for information on the drug substance (b) (4). The original DMF (b) (4) was reviewed by this reviewer, and it was found to be currently Inadequate: IR was sent to DMF holder. The DMF (b) (4) for Aspirin associated with DMF (b) (4) was also reviewed by this reviewer, and was found to be Adequate (b) (4). NHP (the applicant) informed the Agency that after (b) (4) the original facility (b) (4) at the (b) (4) will be closed for drug substance manufacturing, and the (b) (4) facility (b) (4) will perform the manufacturing and testing. On Agency's request, NHP clarified that the (b) (4) facility (b) (4) will not be involved in the production of drug substance batches for the proposed NDA; the API produced at the (b) (4) facility will be used to produce the drug product capsules for this NDA. The (b) (4) Aspirin is obtained by synthesis. The partial information on drug substance is provided in the submitted NDA. The (b) (4) upcoming quality control specifications based on USP monograph for Aspirin with an additional test for particle size are submitted in the NDA as well as batch analysis data for 3 lots used in the manufacture of drug product at the (b) (4) site. The test and acceptance criteria for major degradant, (b) (4), is controlled by this specification. Additional information on acceptance criteria for several tests in the specifications should be provided; this request is included in the IR.

Executive Summary Preliminary Risk Assessment for Drug Product Aspirin ER Capsules					
From Initial Quality Assessment (IQA)			Review Assessment		
Product Property/ Impact of Change CQAs	Factors Affecting CQAs	*Risk Ranking	Risk Mitigation Approach in Control Strategy	Risk Evaluation	Lifecycle Consideration/ Comments
Assay, Stability	Degradation (b) (4)	Low	Control of major degradant (b) (4) in the DP specification; storage of drug product at 25ºC/ (b) (4)	Acceptable	(b) (4)
Physical stability (solid state)	(b) (4)	Low		Acceptable	
Content Uniformity	(b) (4)	Low		Acceptable	
Microbial limits	(b) (4)	Low	(b) (4)	Acceptable	
Alcohol dose dumping	Dose dumping due to enhanced solubility of rate controlling excipients and drug in alcohol	High	Abou % of the drug is dumped within 1 hour in 40% alcohol. Biopharm reviewer recommends that the clinical a pharmacology reviewer evaluate the clinical relevance of the in vitro results.	Acceptable	To be determined based on the results of clinical pharmacology evaluation.
Dissolution	(b) (4)	Med	(b) (4)	Acceptable	(b) (4) Additional considerations to be determined based on biopharm evaluation of the dissolution method and acceptance criteria.

*Risk ranking is FM o product attribute/CQA. Low ≤25RPN, Med=25 – 60 RPN, High ≥60RPN

B. Description of How the Drug Product is Intended to be Used

NDA 200671 Aspirin Extended Release Capsules is being developed by New Haven Pharmaceuticals, Inc. for the secondary prevention of acute cardiovascular events.

Proposed Aspirin Administration (from currently proposed PI)

- (b) (4): One DURLAZA (b) (4) Capsule 162.5 mg per day. (b) (4) recommended (b) (4) the capsule is taken with a full glass of water, (b) (4), at the same time each day. (b) (4)

Do not take DURLAZA 2 hours before or 1 hour after consuming alcohol.

C. Basis for Approvability or Not-Approval Recommendation

NDA 200671 cannot be approved as submitted from the CMC standpoint. The outstanding issues that need to be resolved include deficiencies in the DMF (b) (4), and the drug substance and drug product deficiencies in the submitted NDA summarized in the IR Letter. An overall acceptable recommendation from the OPF facilities reviewer for drug substance and drug product facilities is required as well.

III. Administrative

A. Reviewer's Signature

Lyudmila N. Soldatova

B. Endorsement Block

Chemist: Lyudmila Soldatova, Ph.D./09-Feb-2015
Chemistry Branch Chief: Olen Stephens, Ph.D.
CMC Lead: Kasturi Srinivasachar, Ph.D.

C. CC Block

Quality Project Manager: Yvonne Knight
Clinical Project Manager: Alison Blaus

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

(b) (4)

[redacted]

EVALUATION: The carton and container labels should be revised according to the comments below. The labeling (PI) is very inconsistent regarding the dosage form name and established name through the Package insert; the CMC-related sections in the "Highlights" section and in the "Full Prescribing Information" of the PI needs editing that will be performed in the labeling text and discussed through the series of labeling meetings at DCRP clinical division and communication with the applicant. The Product Data Element (PDE) in the provided Structured Product Labeling (SPL) is acceptable except for the title of PDE (see comment below).

COMMENTS

1. Revise a name of the drug on the carton and container labels to DURLAZA™ (aspirin) Extended Release Capsules
2. Explain the meaning of the equivalency statement "[redacted] (b) (4) on the carton and container labels.
3. 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.

B. Environmental Assessment Or Claim Of Categorical Exclusion

NHP claims a categorical exclusion from the requirement to prepare an Environmental Assessment in accordance with 21 CFR 25.31(b,c) based on the fact supported by calculations that the concentration of the drug substance at the point of entry into the aquatic environment is expected to be below the 1ppb level.

EIC-Aquatic (ppb) = A x B x C x D where:
A = [redacted] (b) (4) produced for direct use (as active moiety)
B = [redacted] (b) (4) entering POTWs*
C = year/365 days
D = [redacted] (b) (4) (conversion factor)
* [redacted] (b) (4) entering publicly owned treatment works (POTWs),
As a result of calculations, EIC-Aquatic = [redacted] (b) (4)

EVALUATION: Acceptable. The applicant indicated a qualification for a categorical exclusion for an environmental assessment for aspirin based on 21 CFR Part 25.31(b) as the concentration of the active moiety will be significantly less than 1 ppb. To NHP's knowledge, no extraordinary circumstances exist. Therefore, an environmental assessment is not required.

III. List Of Deficiencies To Be Communicated

1. The DMF [redacted] (b) (4) that you are referencing for [redacted] (b) (4) is currently deficient. A Deficiency Letter dated December 01, 2014 was sent to DMF holder. In order to have an approval of the submitted NDA, the DMF [redacted] (b) (4) should receive an adequate status.
2. Specify the drug substance acceptance criteria for [redacted] (b) (4) for [redacted] (b) (4) substances and for Substances [redacted] (b) (4).
3. Confirm the commercial grade of the [redacted] (b) (4) [redacted] (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 [redacted] (b) (4) at release and stability in the drug product specification, or justify its absence.
5. Include a limit for [redacted] (b) (4) in the drug product specification.
6. Provide justification for not including a [redacted] (b) (4) in the container/closure system since it is known that aspirin is susceptible to [redacted] (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.

Lyudmila Soldatova -S

Digitally signed by Lyudmila Soldatova -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300147892, cn=Lyudmila Soldatova -S
Date: 2015.02.09 11:46:57 -05'00'

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.02.09 12:44:57 -05'00'

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet
II. Application Detail
III. Filing Checklist
IV. Manufacturing Summary
V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Vibhakar Shah, Ph.D.

2. NDA Number: 200671
   Submission Date: 09/05/2014
   21st C. Review Goal Date: 05/05/2015
   PDUFA Goal Date: 07/05/2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Durlaza (proposed)
Established or Non-Proprietary Name (USAN) and strength:	Aspirin (USAN)
Dosage Form:	Capsules, Extended Release

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD [505(b)(2) application]
Applicant Name:	New Haven Pharmaceuticals, Inc.
Responsible Organization (OND Division):	Division of Cardio-Renal Drug Products

Reference ID: 3675767

II. Application Detail

1. INDICATION: Secondary prevention of acute cardiovascular events
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 162.5 mg
4. Rx/OTC DISPENSED: ☒ Rx ☐ OTC
5. ELECTRONIC SUBMISSION (yes/no)? ☒ Yes ☐ No
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

Reference ID: 3675767

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?	X		

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		X	

Reference ID: 3675767

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?			– 1st application for the sponsor
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	X		
	Have all EERs been updated with final PAI recommendation?		X	
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

Reference ID: 3675767

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights:

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	All CMC information pertaining to the drug substance, Acetylsalicylic acid has been cross-referenced to DMF (b) (4)

Drug Substance Manufacturing Process flow chart/diagram (see eCTD Section 3.2.S.2.2)

Detailed information on the manufacturing process, flow chart, and process controls for the drug substance is provided in (b) (4) Type II DMF (b) (4) for (b) (4)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

(b) (4)

Reference ID: 3675767

(b) (4)

Drug Product Manufaturing Process Flow:

(b) (4)

Reference ID: 3675767

Drug substance and Drug Product Manufacturing Facilities Chart

Establishment	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Facts Assignment ID	Inspection Start-end Dates	OAI Alert Status	Most Recent Milestone	Most Recent EER Compliance Status	Comment
(b) (4)							-	-	-	Submitted to DO	PN	
							-	-	-	Submitted to DO	PN	
							-	-	Yes*	Submitted to DO	PN	A PAI may be warranted**

DS: Drug substance; **DP:** Drug product; **AC**: Acceptable; **NA**: Not Applicable; **TBD**: To be determined; **PN**; Pending

***Remark:**
In PANORAMA (b) (4) has been flagged with a "Potential Official Action Indicated " Action status. The last inspection which ended on (b) (4) was a for cause inspection, and it was classified NAI. (b) (4) (b) (4) As a result , it is not clear on what basis this alert is assigned/triggered. This OAI aert could be due to a glitch in the system.

** Manufacturing of this extended release drug product involves (b) (4) (b) (4) process of the API (b) (4) with particle size ramge between (b) (4) (b) (4). The (b) (4) process was originally developed in (b) (4), and has been transferred to (b) (4). As a result a PAI may be necessary to ensure that (b) (4) has been successful in transferring this technology at their site for the commercial manufacture of the drug product.

Reference ID: 3675767

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no)	**YES**
At this time, is a KTM warranted for any PAI? (yes – site / no):	**NO**
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no):	**NO**
Comments for 74 Day Letter	**None**
1.	
2.	
3.	

REVIEW AND APPROVAL

Reference ID: 3675767

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

/s/

VIBHAKAR J SHAH
12/18/2014

MAHESH R RAMANADHAM
12/18/2014

IQA and Filing Review Cover Sheet

1. **NEW DRUG APPLICATION NUMBER:** 200671

2. **DATES AND GOALS:**

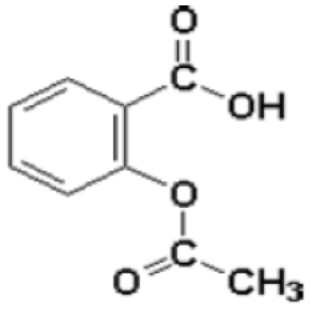
Letter Date:	05-Sep-2014
Filing: Filing 74 Day Issues: PDUFA Goal Date:	04 -Nov-2014 19-Nov-2014 05-Jul-2015

3. **PRODUCT PROPERTIES:**

Trade or Proprietary Name:	Durlaza (proposed)
Established or Non-Proprietary Name (USAN):	Aspirin (USAN)
Dosage Form:	Capsules, Extended Release
Route of Administration	Oral
Strength/Potency	162.5 mg
Rx/OTC Dispensed:	Rx

4. **INDICATION:** Secondary prevention of acute cardiovascular events

5. **DRUG SUBSTANCE STRUCTURAL FORMULA:**



Molecular formula: $C_9H_8O_4$

Molecular weight: 180.16 g/mol

6. **NAME OF APPLICANT (as indicated on Form 356h):**

New Haven Pharmaceuticals, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	S
Submission Classification (Chemical Classification Code):	Type 3
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DCRP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	Categorical exclusion
CDRH		X	
Other	X		Microbiology

9. QUALITY REVIEW TEAM:

Discipline	Reviewer
CMC	Lyudmila Soldatova, Ph.D (DS), Shastri Bhamidipati, Ph.D. (DP)
Biopharmaceutics	Sandra Suarez Sharp, Ph.D.
Biopharmaceutics TL (Secondary)	Angelica Dorantes, Ph.D.
Microbiology	No reviewer will be assigned
Facilities	Vibhakar Shah, Ph.D.

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues: None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes
CMC Comments for 74-Day Letter: 1) Submit Master Batch Records; 2) provide DMF references for packaging components

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? **Yes**
Biopharmaceutics Filing Issues:
No

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? **Yes**
Biopharmaceutics Comments for 74-Day Letter:
Provide the following information/data: 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 (b) (4) (b) (4). 4. Data on the effect of (b) (4) particle size distribution on dissolution. 5. Data on the effect of (b) (4) 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 ± 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

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes

Microbiology Filing Issues: None.

```
From: CDER OPS IO MICRO
Sent: Friday, September 12, 2014 8:54 AM
To: Srinivasachar, Kasturi; Stephens, Olen; CDER OPS IO MICRO;
Dorantes, Angelica
Cc: Blaus, Alison; Knight, Yvonne
Subject: RE: NDA 200671 - New 505b2 NDA - Need Reviewers

This submission is acceptable from a product quality microbiology
standpoint and will be recommended for approval.  Therefore, no product
quality microbiology reviewer assignment will be made for this
submission. A review memo describing the assessment of the microbial
controls for the drug product will be entered into DARRTS.
Thanks, Vera
```

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

CMC Summary of Critical Issues and Complexities

Initial Assessment of Risk based on DS Properties and DP Formulation/Process

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	FACTORS AFFECTING CQA	O	S	D	FMECA RPN	Comments
Assay, Stability	Degradation (b) (4)	3	2	Release 1 Stability 3	6 18	(b) (4)
Physical stability (solid state)	(b) (4)	3	2	4	24	Polymorphic forms not known
Content Uniformity		2	2	4	16	(b) (4)
Microbial limits	(b) (4)	1	2	3	6	(b) (4)
Alcohol dose dumping	Dose dumping due to enhanced solubility of rate controlling excipients and drug in alcohol	4	4	4	64	Dose dumping seems to occur in the presence of 20% and 40 % alcohol in 01N HCl
Dissolution	(b) (4)	4	3	4	48	(b) (4)

RPN < 25 is conside **low**
RPN 25-60 is considered **moderate** risk; RPN > 60 is considered as **high** risk.
O is occurrence; S is severity; D is detectability

Drug Substance:

- Particle size distribution critical to ensure effective [redacted] (b) (4) using standard particle [redacted] (b) (4) techniques and desired extended release characteristics.
- DMF [redacted] (b) (4) reviewed only for safety in IND 116348.

Drug product:

- Only compendial specifications are proposed for the [redacted] (b) (4) [redacted] (b) (4). Are these sufficient to ensure the desired dissolution profile across multiple batches from the same or different suppliers of these critical excipients?
- Ranges are proposed for critical parameters in the [redacted] (b) (4) and [redacted] (b) (4) processes along with targets. Has it been established that operating anywhere within these ranges yields product with similar dissolution profiles?
- The container/closure system does not seem to include a [redacted] (b) (4) although it is well-known that aspirin is susceptible to [redacted] (b) (4).
- An expiration dating period of [redacted] (b) (4) is requested based on [redacted] (b) (4) [redacted] (b) (4) (b) (4) [redacted] (b) (4) [redacted] (b) (4)
- Master Batch Records have not been provided

Labeling:

- Labeling is very inconsistent and haphazard – the dosage form is referred to as "controlled release" in some places and "extended release" in others; the names "aspirin", " acetyl salicylic acid" and ASA are used interchangeably; the shelf-life is mentioned in the How Supplied section; the draft carton labels have an unknown equivalency statement [redacted] (b) (4) for the strength etc.

Quality Assessment

This is a 505(b)(2) application in e-CTD format for extended release aspirin capsules, 162.5 mg, developed for the secondary prevention of acute cardiovascular events. There is no approved NDA for aspirin. The Applicant believes that this formulation allows aspirin to diffuse progressively along the length of the gastrointestinal tract resulting in prolonged absorption over 24 hours and consequently a prolonged duration of action. Clinical studies, primarily PK, PD, safety and tolerability comparisons between this and the reference product, in connection with this application were carried out under IND 116348. Several multi-disciplinary meetings have been held with the Applicant to discuss general CMC and dissolution expectations for an NDA. Preliminary responses sent in advance of a meeting scheduled for Sep. 10, 2013 clearly indicated that a minimum of 12 months of long term stability data on 3 primary batches should be available at the time of NDA submission and that a [redacted] (b) (4), could result in a "refuse to file" action. An in-vitro alcohol dose dumping study was also required for this extended release product. The meeting was cancelled by the Agency since it was determined that the responses were clear and did not merit further discussion.

Drug Substance: [redacted] (b) (4) which is used in the manufacture of the drug product [redacted] (b) (4)

Drug Product: Only one strength of the drug product, 162.5 mg is proposed. The dosage form is a size 2 [redacted] (b) (4) gelatin capsule containing a white [redacted] (b) (4) -white crystalline powder [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4)
All excipients used in the [redacted] (b) (4) formulation as well as in the [redacted] (b) (4) are compendial grade. The formulation and manufacturing process for the product was first developed by [redacted] (b) (4) and subsequently transferred to [redacted] (b) (4) which will be the commercial production site for the US market.
Particle size of the drug substance is a critical attribute to achieve the target dissolution profile of the product and to efficiently [redacted] (b) (4) the aspirin particles using standard [redacted] (b) (4) techniques such as the [redacted] (b) (4) process. After evaluating various particle size ranges it was determined that a PSD predominantly in the [redacted] (b) (4) range was optimal.
The [redacted] (b) (4) formulation contains the commonly used excipients, [redacted] (b) (4) [redacted] (b) (4) to impart the desired extended release characteristics. [redacted] (b) (4) [redacted] (b) (4)

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

Biopharmaceutics Assessment

Submission:
The Applicant is seeking approval of Aspirin (ASA) Controlled Release Capsules (NHP-554C, [redacted] (b) (4) capsules), 162.5 mg as a 505 (b)(2) submission for the secondary prevention of acute cardiovascular events. The proposed dose is 162.5 mg once a day.

NHP-554C (also known as Flamasacard®, Caspac®, Asacard®, Asacard XL®, Asacard LP®, and Therasacard®) is a controlled release aspirin product developed by Flamel Technologies (Flamel) of Pessac, France and a Marketing Authorization Application was approved in the EU by EMA in 1998. The product was acquired by New Haven Pharmaceuticals in 2009 and the manufacturing process was transferred to [redacted] (b) (4) [redacted] (b) (4) facility in [redacted] (b) (4). Aspirin capsules (162.5 mg), have been approved in Europe as "over-the counter" drug product.

Product's Description:
[redacted] (b) (4) is a controlled release aspirin product made up of microparticles, [redacted] (b) (4) According to the Applicant, the [redacted] (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. ASA drug substance in a particle-size range of [redacted] (b) (4) was selected because of its compatibility with the [redacted] (b) (4) process and the intended release profile.

[redacted] (b) (4) [redacted] (b) (4). BE Study PKFT 9542 was conducted to stablish a bridge between formulation [redacted] (b) (4) This study will be reviewed by ONDQA-Biopharmaceutics.

Following acquisition of the drug product by NHP the product was transferred to [redacted] (b) (4)

(b) (4)

Review: The biopharmaceutics review will be focus on the evaluation and acceptability of the data provided to support; 1) the dissolution method and acceptance criteria, 2) In vitro alcohol dose-dumping; 4) BE Study PKFT 9542 study; 3) Controlled release designation claim; and 5) Appropriate bridging of formulations used across the developmental phases.

Review Issues Identified:

a. (b) (4)

b. In vitro alcohol-interaction study showed that the product content is dumped within 2hrs in the presence of 20% and 40% alcohol. The Clinical and Clinical Pharmacology review teams should decide if this issue can be addressed through appropriate labeling or an in vivo alcohol-dose dumping study is needed.

CMC FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Incomplete information in original 356 h. Amendment received
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			DS information in DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			DS information in DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?			DS information in DMF (b) (4)
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		DS information in DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		No master batch record
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Incomplete—DMF references for packaging components not provided

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	Mar. 11, 2013	
	IV			Aug. 11, 2013	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

_____Biopharmaceutics Filing Review Checklist

The following parameters are usually necessary to initiate a full Biopharmaceutics review (i.e., the NDA is complete enough to review but may have deficiencies). On **initial** overview of the NDA application for filing:

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
33.	Does the application contain dissolution data?	X		The proposed dissolution method appears to be: 0.05 M Potassium Phosphate Buffer (pH 7.4) with Trypsin and Sodium Azide \\cdsesub1\evsprod\NDA200671\0000\m3\32-body-data\32p-drug-prod\nhp-554c\32p2-pharm-dev The Applicant will be requested to provide details on the method.
34.	Is the dissolution test part of the DP specifications?	X		The following dissolution acceptance criterion is being proposed: Time (h) | % Dissolution Specifications (Proposed Commercial Specification) | Lower Limit | Upper Limit 1 (b) (4) 3 (b) (4) 9 (b) (4) 22 \\cdsesub1\evsprod\NDA200671\0000\m2\27-clin-sum The approvability of the proposed acceptance criteria will be a review issue.
35.	Does the application contain the dissolution method development report?		X	The Applicant in being requested to provide the dissolution method report along with data showing its discriminating ability.
36.	Is there a validation package for the analytical method and dissolution methodology?		X	
37.	Does the application include a biowaiver request?		X	
38.	Are there adequate data supporting the waiver?			
39.	Does the application include an IVIVC model?		X	

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is information on mixing the product with foods or liquids included?		X	
42.	Is there any in *vivo* BA or BE information in the submission?			There are several PK/PD studies included in the submission. Included are some relevant biopharm studies: • ASA-001: Single fed/fasted PK/PD study comparing the proposed product to IR aspirin formulation. This study will be reviewed by OCP. • BE study PKFT 9542: Bio-Equivalence Study of Two Formulations of Asacard 162.5 mg Containing 162.5 mg of Aspirin After a Single Oral Administration in 24 Healthy Volunteers. This study will be reviewed by ONDQA-biopharmaceutics. \\cdsesub1\evsprod\NDA200671\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\pkft-9542
43.	Are there any manufacturing changes implemented to the biobatch/clinical trial formulation?	X		There is a BA/BE study bridging [redacted] (b) (4). There is PK data on the commercial formulation manufactured at the final proposed commercial site [redacted] (b) (4)
44.	Are there data supporting the controlled release designation claim?		X	The Applicant is being requested to provide this information.

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
45.	Are there data on in vitro alcohol-dose dumping?		X	The in vitro data showed that the product content is dumped within 2 hrs in the presence of 20% and 40% alcohol in 0.1 N HCL. \\cdsesub1\evsprod\NDA200671\0000\m3\32-body-data\32p-drug-prod\nhp-554c\32p2-pharm-dev
FILING CONCLUSION				
46.	**ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
47.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
48.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
49.	Are there any potential review issues identified?	X		Refer to page 10 of this document for the Biopharmaceutics potential review issues.

This document will be sequentially signed by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Kasturi Srinivasachar, Ph.D
CMC-Lead or
Division I, Branch 1
Office of New Drug Quality Assessment

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Sandra Suarez, Ph.D.
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