

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205750Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 24, 2015

From: Gene W. Holbert, Ph.D.

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
ONDP

To: CMC Review #1 of NDA 205750

Subject: Final Recommendation

Gene W.
Holbert -A

Digitally signed by Gene W.
Holbert -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130
0122836, cn=Gene W. Holbert -A
Date: 2015.02.25 16:14:47 -05'00'

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Moojhong Rhee -S,
0.9.2342.19200300.100.1.1=1300041261
Date: 2015.02.25 16:20:53 -05'00'

The CMC review #1 noted the following three pending issues:

1. Final “Acceptable” recommendation from the Office of Compliance had not issued.
2. Label/labeling issues had not been resolved.
3. DMF issues were unresolved.

Because of these deficiencies, this NDA was not recommended for approval from the ONDQA perspective in CMC Review #1.

On August 15, 2014, the DMF holder submitted a satisfactory response to the issues raised in the DMF review. DMF (b) (4) was found adequate in DMF Review #1 dated August 26, 2014.

Also on August 15, 2014, the applicant submitted an amendment updating the following sections:

- 3.2.P.5.4 - Updated batch analysis data for the lots of cholic acid capsules packaged at Patheon (b) (4)

These batches were not different from those packaged at Patheon-France.

- 3.2.P.8.1 – Addition of discussion to discuss new stability studies that were initiated that cholic acid capsules packaged at Patheon (b) (4)
- 3.2.P.8.3 - Addition of stability tables for cholic acid capsules packaged at Patheon (b) (4)

The schedule of testing and tests performed at each interval follow the stability design described in the application.

Results are included in Section 3.2.P.8.3. Results through the 1 month storage at long term (25°C/60% RH) and accelerated (40°C/75% RH) conditions. All samples met the acceptance criteria with no trends in the data observed. This stability study is on-going.

- 3.2.P.8.3 –Transport shipping study report

The (b) (4) amendment and transport shipping study were reviewed by Christina Capacci-Daniel of the Office of Compliance and found adequate (see **Attachment III**).

- 3.2.R.1 – Updated executed packaging records and associated certificates of analysis for the lots of cholic acid capsules packaged at Patheon (b) (4)
- Corresponding updates to 2.3.P.5 and 2.3.P.8

On October 17, 2014, the Office of Compliance issued an overall “Acceptable” recommendation for the facilities involved in the NDA (see Attachment I).

The label and labeling revised as of February 19, 2015, are deemed satisfactory from ONDP perspective (see **Attachment II**).

Recommendation:

This NDA is **now** recommended for approval from the ONDP perspective.

Attachment I:

EES report

Final Manufacturing Facility Compliance Evaluation for NDA 205750
 Completed 10/17/2014

Application	NDA 205750/000	NDA 205750/000	NDA 205750/000	NDA 205750/000
Sponsor	ASKLEPION PHARMS LLC	ASKLEPION PHARMS LLC	ASKLEPION PHARMS LLC	ASKLEPION PHARMS LLC
FEI	(b) (4)	3004408553	(b) (4)	(b) (4)
Establishment Profile	(b) (4)	PATHEON FRANCE SAS CHG	(b) (4)	(b) (4)
Stage	DRUG SUBSTANCE	FINISHED DOSAGE	DRUG SUBSTANCE	FINISHED DOSAGE
Process	MANUFACTURER, OTHER TESTER	LABELER, MANUFACTURER, OTHER TESTER, RELEASE TESTER	OTHER TESTER	PACKAGER
Last Milestone Compliance Status	OC RECOMMENDATION AC	OC RECOMMENDATION AC	OC RECOMMENDATION AC	OC RECOMMENDATION AC
Milestone Date	10/17/2014	8/1/2014	12/16/2013	9/22/2014
OAI Alert Status	"NONE"	"NONE"	"NONE"	"NONE"
EER Re-eval Date	5/16/2017	3/29/2016	6/12/2016	8/26/2017
Overall Recommendation	ACCEPTABLE			
Overall Re-eval Date	3/28/2016			

Attachment II: Final Labels/labeling

The following PI update is based on the Amendment February 19, 2015.

A. PI

a. Highlights section

CHOLBAM (cholic acid) capsules, for oral use
Initial U.S. Approval: 2015

-----INDICATIONS AND USAGE-----

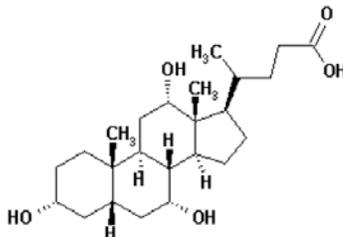
(b) (4)

Limitation of use:

(b) (4)

b. Description

Cholic acid is a bile acid produced by the liver where it is synthesized from cholesterol. The chemical formula is $C_{24}H_{40}O_5$, the molecular weight is 408.57 and the chemical structure is:



Cholic acid is a white to off-white powder. It is practically insoluble in water and in 0.1 M HCl at 20°C and is sparingly soluble in 0.1 M NaOH at 20°C. It is soluble in glacial acetic acid, alcohols and acetone. A saturated solution in water at 20°C has a pH of 4.4.

CHOLBAM (cholic acid) capsules contain 50 mg or 250 mg of cholic acid as the active ingredient in size 2 Swedish orange or size 0 white opaque gelatin capsules, respectively. Inactive ingredients in CHOLBAM include silicified microcrystalline cellulose, magnesium stearate and hard gelatin capsules. The size 2 shells contain gelatin, red iron oxide and titanium dioxide and the size 0 shells contain gelatin and titanium dioxide. CHOLBAM is administered orally.

c. How supplied

50 mg Capsules

CHOLBAM capsules are available as two-piece gelatin capsules with a Swedish orange cap imprinted with “50mg” and Swedish orange body with imprinted with “ASK001”. The capsules contain a white or off-white powder and are supplied in bottles of:

- 90 capsules (NDC 43472-001-02)

250 mg Capsules

CHOLBAM capsules are available as two-piece gelatin capsules with a white cap imprinted with “250mg” and white body with imprinted with “ASK002”. The capsules contain a white or off-white powder and are supplied in bottles of:

- 90 capsules (NDC 43472-002-02)

Storage and Handling

Store at 20–25°C (69–77°F), excursions permitted between 15–30°C (59–86°F). [see USP Controlled Room Temperature].

B. Labels



(b) (4)

b. Cartons

On December 23, 2014, the applicant also proposed to eliminate the use of cartons. Asklepion makes the following statement:

“In keeping with what is already a widespread industry practice, drug product will be shipped without secondary packaging and the package insert (PI) will be affixed to the primary package (bottle/container) via detachable glue.”

Elimination of the carton is acceptable since it provides no light protection for the drug product.

Attachment III: Evaluation of Shipping Studies

From: [Capacci-Daniel, Christina](#)
To: [Holbert, Gene W](#)
Subject: RE: NA 205750 (Cholic Acid)
Date: Thursday, December 11, 2014 4:20:28 PM

Hi Gene,

I read the packing operation transfer amendment along with the shipping studies and finding them to be adequate. I entered the following comment in the OC Recommendation for this facility in EES but didn't write up a memo about this study.

EER Re-Evaluation Date Comment:

26-AUG-2013 +4YRS FOR PACKAGING ONLY; ADDITIONAL SHIPPING STUDIES ACCEPTABLE

Comments:

REVIEWED ADDITIONAL DRUG PRODUCT SHIPPING STUDIES PROVIDED IN THE AMENDMENT; STUDIES FOUND TO BE ACCEPTABLE.

Let me know if there is anything else you need.

Best,
Christina

From: Holbert, Gene W
Sent: Thursday, December 11, 2014 3:03 PM
To: Capacci-Daniel, Christina
Subject: NA 205750 (Cholic Acid)

Christina,

Have you looked at the information Asklepion provided in SD 0031 (08/15/2014) (b) (4) (b) (4) Please take a look and see if it conforms with your requests.

Thanks, Gene

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Gene Holbert, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)
E-mail Address: gene.holbert@fda.hhs.gov
Phone: (301)-796-1440

FROM: FDA

Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 205750

Name of Product: CHOLBAM™ (cholic acid) capsules, 50 mg and 250 mg

Applicant: Asklepion Pharmaceuticals, LLC

Applicant's Contact Person: Gary R. Pasternack, MD, PhD

Address: 729 E. Pratt St., Baltimore, MD 21202

Telephone: (410) 545-0494 Fax: (410) 545-0584

Date Methods Validation Consult Request Form Received by DPA: 18-Dec-2013

Date Methods Validation Package Received by DPA: 18-Dec-2013

Date Samples Received by DPA: 14-Jan-2014

Date Analytical Completed by DPA: 22-Sep -2014

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: Analyst's comments and summary of results are attached.

The following method was evaluated. DPA could not meet the method's system suitability requirement for column efficiency when performing the method as specified. Column efficiency was calculated using the applicant's chromatograms as shown in the attached summary. The applicant's data did not appear to meet the system suitability requirement. DPA suggests that the applicant provide data to support the system suitability specified and clarify how the calculation is made. Is the column efficiency requirement per column length or per meter?

- 3.2.P.5.2 Identification, Assay, and Related Substances of Cholic Acid Capsules by HPLC



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, MO 63110
Tel. (314) 539-2155

Date: September 22, 2014
To: Gene W. Holbert, Ph.D., CMC Reviewer
Through: John Kauffman, Ph.D., Deputy Director, Division of Pharmaceutical Analysis.
From: Laura Pogue, Ph.D., Chemist, Division of Pharmaceutical Analysis

Subject: Method Validation for NDA 205750: Cholbam Capsules, 50 mg & 250 mg, Asklepiion Pharmaceuticals, LLC

The following method was evaluated and is acceptable for quality control and regulatory purposes:

- 3.2 S.4.2.8 Assay and Related Impurities for Drug Substance (Cholic Acid)

The following method was evaluated and is acceptable for quality control and regulatory purposes with modification:

- 3.2.P.5.2 Identification, Assay, and Related Substances of Cholic Acid Capsules by HPLC

The DPA has the following comments about these methods.

1. Assay and Related Impurities for Drug Substance (Cholic Acid)
 - a. The drug substance method did not pass system suitability using the applicant's original method (b) (4). With an adjustment (b) (4) the method passed system suitability.
2. Identification, Assay, and Related Substances of Cholic Acid Capsules by HPLC
 - a. The drug product method did not pass system suitability with the applicant's original method. Using the (b) (4). Adjustments (b) (4) corrected this problem, but the method (b) (4). See Table 3.
3. General comments
 - a. The cholic acid peaks exhibit (b) (4), which is not captured in the system suitability requirements. (b) (4).

Link to analyst's work sheets and chromatograms:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8807e2560>

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

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

/s/

MICHAEL L TREHY
09/23/2014

JOHN F KAUFFMAN
09/25/2014

NDA 205750

**Cholbam (Cholic Acid) Capsules
50 mg and 250 mg**

Asklepion Pharmaceuticals, LLC

Gene W. Holbert, PhD

**Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment**

**Chemistry Review for the
Division of Gastroenterology and Inborn Errors Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer’s Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Cholic Acid, (b) (4)]	10
S.1 General Information [Cholic Acid, (b) (4)]	10
S.2 Manufacture [Cholic Acid, (b) (4)].....	10
S.3 Characterization [Cholic Acid, (b) (4)].....	11
S.4 Control of Drug Substance [Cholic Acid, (b) (4)]	11
S.5 Reference Standards or Materials [Cholic Acid, (b) (4)].....	20
S.6 Container Closure System [Cholic Acid, (b) (4)].....	20
S.7 Stability [Cholic Acid, (b) (4)]	20
P DRUG PRODUCT [Cholbam Capsules].....	20
P.1 Description and Composition of the Drug Product [Cholbam Capsules]	20
P.2 Pharmaceutical Development [Cholbam Capsules].....	21
P.3 Manufacture [Cholbam Capsules]	32
P.4 Control of Excipients [Cholbam Capsules]	37

Chemistry Assessment Section

P.5 Control of Drug Product [Cholbam Capsules].....	39
P.6 Reference Standards or Materials [Cholbam Capsules].....	55
P.7 Container Closure System [Cholbam Capsules].....	56
P.8 Stability [Cholbam Capsules]	57
A APPENDICES	68
R REGIONAL INFORMATION	68
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	69
A. Labeling & Package Insert.....	69
B. Environmental Assessment Or Claim Of Categorical Exclusion	77
III. List of Deficiencies to be Communicated.....	77

Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA: 205750
2. REVIEW #: 1
3. REVIEW DATE: 16-JUL-2014
4. REVIEWER: Gene W. Holbert, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents
None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original
Amendment
Amendment
Amendment
Amendment

Document Date
21-NOV-2013
20-DEC-2013
30-MAY-2014
05-JUN-2014
11-JUL-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Asklepion Pharmaceuticals, LLC
Address: 729 E. Pratt Street
Suite 360
Baltimore, MD 21202
Representative: Gary R. Pasternack, MD, PhD
Telephone: 410-545-0494
FAX: 410-545-0584
E-mail: gary.pasternack@asklepionpharm.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cholbam
- b) Non-Proprietary Name (USAN): Cholic acid
- c) Code Name/#: P321
- d) Chem. Type/Submission Priority:
 - Chem. Type: 1
 - Submission Priority: P

Chemistry Assessment Section

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: [REDACTED]

(b) (4)

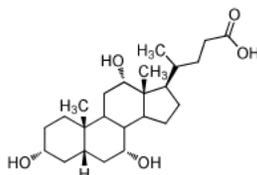
11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 50 mg and 250 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product, SPOTS Form Completed Not a SPOTS product

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

Chemical Name: (3 α ,5 β ,7 α ,12 α)-3 α ,7 α ,12 α -trihydroxy-5 β -cholan-24-oic acid
Cholan-24-oic Acid

INN: Cholic acid

Molecular Formula: C₂₄H₄₀O₅

Molecular Weight: 408.57

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	I	[REDACTED]	(b) (4)	1	Adequate	Pending	LOA: 07-JUN-2013
	III	[REDACTED]		4	N/A		LOA: 29-MAY-2013
	IV	[REDACTED]		4	N/A		LOA: 06-JUN-2013
	IV	[REDACTED]		3	Adequate	07-AUG-2013 C Cruz	LOA: 06-JUN-2013

Chemistry Assessment Section

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
IND	45,470	Cholic acid

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Dissolution method is acceptable	07/24/2014	Kareen Riviere
LNC	N/A		
Methods Validation	Pending		
DMEPA	N/A		
EA	Categorical exclusion [21 CFR 25.31 (c)]	07/01/2014	Raanan Bloom
Microbiology	Acceptable	12/03/2013	Bryan S. Riley

The Chemistry Review for NDA 205750

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has *not* provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

All facilities involved are *not* in compliance with cGMP and labels *do not* have adequate information as required.

Therefore, from a CMC perspective, this NDA is *not* ready for “Approval” in its present form per 21 CFR 314.125 (b)(1),(6), and (13).

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

None at this time.

II. Summary of Chemistry Assessments

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

Cholbam (cholic acid) capsules, 50 mg and 250 mg, are hard gelatin capsules for oral administration. The active pharmaceutical ingredient is cholic acid (INN). Each size “2” Swedish Orange capsule contains 50 mg of cholic acid while each size “0” Opaque White capsule contains 250 mg of the active ingredient. Inactive ingredients include Silicified Microcrystalline Cellulose, NF and Magnesium Stearate, NF, Gelatin, NF and pharmaceutical ink. In addition to gelatin, the Swedish Orange capsule shells contain Red Iron Oxide, NF and Titanium Dioxide, NF; the Opaque White capsule shells contain Titanium Dioxide, NF.

Cholic acid is produced in the liver from cholesterol. The liver converts cholesterol into the conjugated salts of glycocholic and taurocholic acid. These conjugated salts are secreted into the bile and released into the intestine where they emulsify fats and aid in digestion.

Chemistry Assessment Section

Cholic acid drug substance is [REDACTED] (b) (4)

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

Treatment with cholic acid is intended as replacement therapy in cases of [REDACTED] (b) (4). Cholic acid is one of the primary bile acids in humans on which essential physiological functions depend. Replacement of cholic acid is intended to restore the main cholic acid functions of lipid transport in the form of mixed micelles, activation of co-lipase and fat digestion and absorption, the absorption of fat-soluble vitamins, and induction of bile flow.

Cholic acid capsules are indicated for treatment of [REDACTED] (b) (4), which are responsive to treatment with cholic acid, in infants from [REDACTED] (u) (4) of age through adulthood.

Cholbam (cholic acid) capsules are administered orally. The recommended dosage is 10-15 mg/kg once daily in both pediatric and adult patients. For those patients who are unable to swallow capsules, the capsule contents may be mixed with one or two [REDACTED] (b) (4) of infant formula, breast milk or soft food such as mashed potatoes or apple sauce and administered immediately.

C. Basis for Approvability or Not-Approval Recommendation

Approval of this application is *not* recommended at this time for the following reasons:

21 CFR 314.125 (b)(1)

- DMF is not adequate to support this application due to unresolved issues, which were conveyed to the DMF holder on 05-May-2014.

21 CFR 314.125 (b)(6)

- Label/labeling issues are not resolved

21 CFR 314.125 (b)(13)

- The Office of Compliance has issued "Pending" recommendation

Chemistry Assessment Section

III. Administrative**A. Reviewer's Signature**

Signed electronically in DARRTS

B. Endorsement Block

Gene W. Holbert/16-JUL-2014
Moo-Jhong Rhee/04-AUG-2014

C. CC Block

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

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

/s/

GENE W HOLBERT
08/04/2014

MOO JHONG RHEE
08/04/2014
Chief, Branch IV

ONDQA Initial Quality Assessment (IQA) and Filing Review

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205750**

2. DATES AND GOALS:

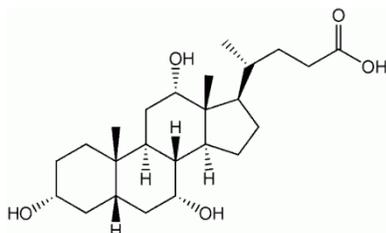
Letter Date:	Submission Received Date : 11/21/2013
PDUFA Goal Date: 5/21/2014	Filing Date: 1/21/2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	CHOLBAM
Established or Non-Proprietary Name (USAN):	cholic acid (INN) (no USAN name)
Dosage Form:	IR capsule
Route of Administration	oral
Strength/Potency	50 and 250 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: treatment of (b) (4)

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



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

7. SUBMISSION PROPERTIES:

Review Priority:	priority
Submission Classification (Chemical Classification Code):	Type 1 (NME)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Orphan Drug Designation	Yes (July 2013)
Responsible Organization (Clinical Division):	Division of Gastrointestinal and Inborn Error Products (HFD-180)

ONDQA Initial Quality Assessment (IQA) and Filing Review

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Establishment Evaluation Request (EER)	x		Sent 12/20/2013
Methods Validation	x		Sent 12/18/2013
Environmental Assessment	x		Request for categorical exclusion (a consult from OPS was requested on 12/23/2013)
CDRH		x	
Other		x	

Overall Filing Conclusions and Recommendations

CMC:

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

Yes No

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?

Yes No

CMC Comments for 74-Day Letter: none

Biopharmaceutics:

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

Yes No

Biopharmaceutics Comments for 74-Day Letter:

To aid the review of this NDA submission, the following comment need to be conveyed to the Applicant in the 74-day letter:

1. Provide solubility data for the drug substance covering the physiological pH range;
2. Provide data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products (aberrant formulations) that are intentionally manufactured with meaningful variations for the most relevant manufacturing variables (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent;
3. Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.
4. To support the Level 2 drug product manufacturing site change, provide *in vitro* comparative dissolution data and f2 similarity values (n=12) for the drug product manufactured at the old and new site in three media: and phosphate buffers pH and 6.8.

Microbiology:

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

Yes No

Microbiology Filing Issues:

See Microbiology Filing Review for details and for any potential Microbiology review issues.

ONDQA Initial Quality Assessment (IQA) and Filing Review

Summary of Initial Quality Assessment

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

Is a team review recommended?		Yes
Reviewers assigned:	CMC: Gene Holbert, PhD Biopharmaceutics: Kareen Reviere, PhD Micro: Stephen Langille, PhD / Bryan S. Riley, PhD	

Summary of Critical Issues and Complexities
<p>The cholic acid used in this product is prepared by (b) (4).</p> <ul style="list-style-type: none">It is important to determine whether the manufacturing process and controls ensure that the final drug substance (b) (4).In section 3.3 of the submission, in a document entitled “(b) (4)”, (b) (4), the manufacturer of cholic acid, confirms that currently the (b) (4). However, the company further argues that based on scientific literature, (b) (4). Based on the above document, it is not clear whether the applicant is seeking approval for using (b) (4) or using the document to emphasize that (b) (4) during the manufacturing process. This issue needs to be clarified during the course of the full review.There is no USAN name for cholic acid. The applicant has been requested to apply for a USAN as soon as possible. (The applicant was first notified in 2005 [see meeting minutes] that a USAN name would be required)

ONDQA Initial Quality Assessment (IQA) and Filing Review

Product Summary

CHOLBAM™ (cholic acid) capsules are intended for the treatment of adult and pediatric patients (b) (4). The product has been developed under IND 45,470 and will be commercialized as a hard gelatin capsule containing 50mg or 250mg of cholic acid. Administration is on a patient weight basis, with 10-15 mg/kg being recommended daily.

The product is composed of cholic acid, silicified microcrystalline cellulose NF*, and magnesium stearate. Expiration dating is based on 48 months of 25°C and 30°C stability data for product manufactured at Patheon, (b) (4). To support moving the manufacturing site for the commercial product to another facility (Patheon/France) 90 days of stability data for product manufactured at the new facility are provided.

Cholic acid is classified as an NME under the Chemical Classification Code, MAPP 7500.3, and consequently, this application is classified as a Type 1. (It should be noted that cholic acid is a natural component of the human body.) The cholic acid used in this product is (b) (4). DMF (b) (4) (owned by (b) (4)) is referenced for all information regarding this process.

ONDQA Initial Quality Assessment (IQA) and Filing Review

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?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i> .				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
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.	√		

ONDQA Initial Quality Assessment (IQA) and Filing Review

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	√		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	√		

ONDQA Initial Quality Assessment (IQA) and Filing Review

	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: <ul style="list-style-type: none"> • 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) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	√		Claim of categorical exclusion

ONDQA Initial Quality Assessment (IQA) and Filing Review

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		√	information is referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	information is referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		√	information is referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?		√	information is referenced to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		√	information is referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

ONDQA Initial Quality Assessment (IQA) and Filing Review

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?	√		
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?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

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

ONDQA Initial Quality Assessment (IQA) and Filing Review

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	<input type="checkbox"/>	<input type="checkbox"/>	A microbiology reviewer has been assigned

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√	<input type="checkbox"/>	Drug substance information has been referenced to DMF (b) (4) Hard gelatin capsules referenced to DMFs (b) (4) and (b) (4)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√	<input type="checkbox"/>	
33.	(b) (4)	√	<input type="checkbox"/>	

ONDQA Initial Quality Assessment (IQA) and Filing Review

Biopharmaceutics Filing Review

NDA Number	205-750
Submission Date	11/21/2013
Product name, generic name of the active	Cholic Acid Capsules
Dosage form and strength	IR Capsules/ 50 mg and 250 mg
Applicant	Askelpion Pharmaceuticals, LLC
Clinical Division	DGIEP
Indication	Treatment of (b) (4)
Type of Submission	505(b)(1); NME
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	x		
35.	Is the dissolution test part of the DP specifications?	x		See the Initial Assessment section for the proposed dissolution method and acceptance criterion.
36.	Does the application contain the dissolution method development report?	x		
37.	Is there a validation package for the analytical method and dissolution methodology?	x		
38.	Does the application include a biowaiver request?		x	The 50 mg and 250 mg strengths were used in the Phase 3 safety and efficacy study.
39.	Is there information provided to support the biowaiver request?		x	Not Applicable.
40.	Does the application include a IVIVC model?		x	Not Applicable.
41.	Is information such as BCS classification mentioned, and supportive data provided?		x	
42.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.

ONDQA Initial Quality Assessment (IQA) and Filing Review

43.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		Study CAC-003-01 is a relative BA, BE and PK study comparing the pharmacy and commercial formulation. This study will be reviewed by ONDQA Biopharm.
44.	Is there a complete bio-analytical method development and validation report?	x		

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
45.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?			
46.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			
47.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		IR comments will be sent to the Applicant in the 74 day letter. The comments are outlined in the Initial Assessment.

ONDQA Initial Quality Assessment (IQA) and Filing Review

INITIAL BIOPHARMACEUTICS ASSESSMENT

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method, the proposed dissolution acceptance criterion, dissolution data supporting the Level 3 drug product manufacturing site change, and the relative bioavailability study comparing the pharmacy and commercial formulation.

The Applicant conducted one Phase 1 study (Study CAC-003-01) and two Phase 3 studies (Study CAC-001-01 and Study CAC-91-10-10). The pharmacy formulation was used in the first Phase 3 study (Study CAC-91-10-10). The 50 mg and 250 mg strengths of the to-be-marketed product were used in the second Phase 3 safety and efficacy study (Study CAC-001-01). The 250 mg pharmacy capsule formulation and the 250 mg strength to-be marketed capsule formulation were used in the Phase 1 study (b) (4) the sponsor used both formulations in Phase 3 studies.

Dissolution:

The proposed dissolution method for both strengths are:

50 mg Capsules

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	500 mL	37 °C	50 mM potassium phosphate buffer, pH 6.8

250 mg Capsules

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	900 mL	37 °C	50 mM potassium phosphate buffer, pH 6.8

The proposed acceptance criterion for both strengths are:

Acceptance Criterion
$Q = \frac{(b)}{(4)}\% \text{ at } \frac{(b)}{(4)} \text{ minutes}$

Biostudies:

The title of the Phase I study (Study CAC-003-01) is Comparative Bioavailability of Three Formulations of Cholic Acid in Healthy Male Subjects Using a Multiple Dose Repeated Measures Approach. The objectives of the study were to evaluate the relative bioavailability/bioequivalence and pharmacokinetics of multiple oral doses of a new cGMP produced cholic acid capsule formulation in comparison to a previously used pharmacy capsule formulation and an oral solution or suspension (250 mg) in 18 healthy male volunteers. In addition, the safety of cholic acid, following multiple dose administration of cholic acid was also assessed.

ONDQA Initial Quality Assessment (IQA) and Filing Review

The cholic acid and total cholic acid plasma concentration data expressed as the geometric means derived from dose administration during the three Treatment cycles are presented in Figure 1 and Figure 2, respectively.

Figure 1. Geometric Mean Concentrations of Cholic Acid in Healthy Subjects Following Oral Administration of 250 mg of 3 Different Dosage Forms

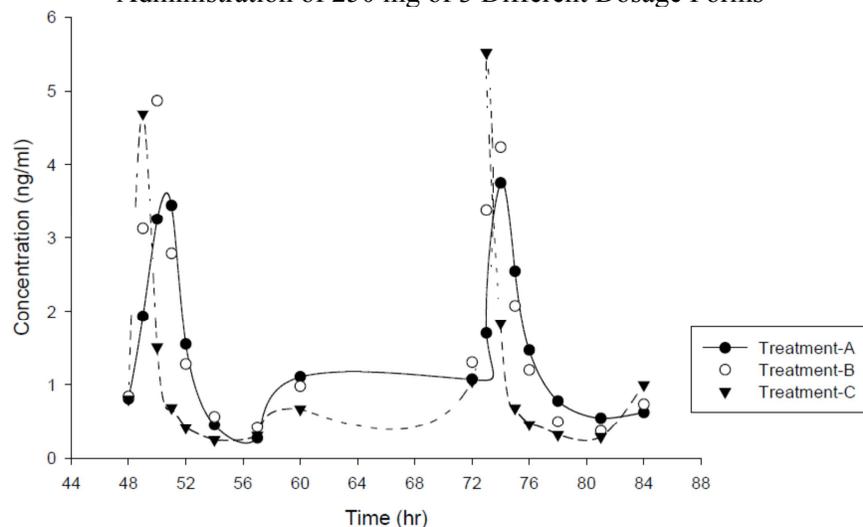
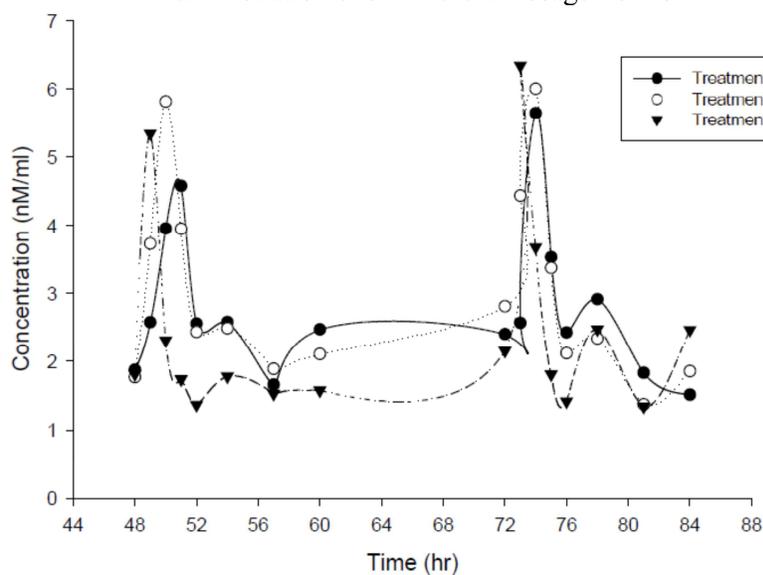


Figure 2. Geometric Mean Concentrations of Total Cholic Acid in Healthy Subjects Following Oral Administration of 3 Different Dosage Forms



Comparison of log transformed PK parameters of cholic acid and Total cholic acid across the three treatments are displayed in Table 1 and Table 2, respectively.

ONDQA Initial Quality Assessment (IQA) and Filing Review

Table 1. Bioequivalence Determination of Cholic Acid PK Parameters AUC and C_{max} for Three Cholic Acid Formulations - Model: $\text{Log}(\text{var}) = \text{treatment sequence day}(\text{Cycle})$ Uncorrected Parameters

Parameter	Pair (Test:Ref)	Reference	Test	Difference Test- Reference	Ratio Test/ Reference	(90% Conf Interval)
AUC _{tau}	B:A					(b) (4)
	A:C					
	B:C					
C _{max}	B:A					
	A:C					
	B:C					

Data source: [Appendix 16.2.2.6A](#)
 Where A = cholic acid 250 mg Capsule (Pharmacy)
 Where B = cholic acid 250 mg Capsule (cGMP)
 Where C = cholic acid 250 mg Oral Solution

Table 2. Bioequivalence Determination of Total Cholic Acid PK Parameter for Three Cholic Acid Formulations - Model: $\text{Log}(\text{var}) = \text{treatment sequence day}(\text{Cycle})$ - Uncorrected Parameters

Parameter	Pair (Test:Ref)	Reference	Test	Difference Test-Reference	Ratio Test/Reference	(90% Conf Interval)
AUC _(Tau)	B:A					(b) (4)
	A:C					
	B:C					
C _{max}	B:A					
	A:C					
	B:C					

Data source: [Appendix 16.2.2.6B](#)
 Where A = cholic acid 250 mg Capsule (Pharmacy)
 Where B = cholic acid 250 mg Capsule (cGMP)
 Where C = cholic acid 250 mg Oral Solution

The Biopharmaceutics review will focus on the evaluation and acceptability of:

- 1) the proposed dissolution methodology,
- 2) the proposed dissolution acceptance criterion,
- 3) dissolution data supporting the Level 3 drug product manufacturing site change, and
- 4) Study CAC-003-01, which is a relative BA, BE and PK study comparing the pharmacy and commercial formulation.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 205-750 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

To aid the review of this NDA submission, the following comments need to be conveyed to the Applicant in the 74-day letter:

1. Provide solubility data for the drug substance covering the physiological pH range;

ONDQA Initial Quality Assessment (IQA) and Filing Review

2. Provide data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products (aberrant formulations) that are intentionally manufactured with meaningful variations for the most relevant manufacturing variables (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent;
3. Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.
4. To support the Level 2 drug product manufacturing site change, provide *in vitro* comparative dissolution data and f2 similarity values (n=12) for the drug product manufactured at the old and new site in three media: (b) (4) and phosphate buffers pH (b) (4) and 6.8.

See appended electronic signature page.

Marie Kowblansky, PhD

CMC-Lead

Division II

Office of New Drug Quality Assessment

See appended electronic signature page.

Kareen Riviere, Ph.D.

Biopharmaceutics Reviewer

Office of New Drug Quality Assessment

See appended electronic signature page.

Tapash Ghosh, Ph.D.

Biopharmaceutics Team Leader

Office of New Drug Quality Assessment

See appended electronic signature page.

Moo-Jhong Rhee, PhD

Branch Chief

Division II

Office of New Drug Quality Assessment

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

/s/

MARIE KOWBLANSKY
01/15/2014

TAPASH K GHOSH
01/15/2014

MOO JHONG RHEE
01/15/2014
Chief, Branch IV

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: Christina Capacci-Daniel
- 2. NDA/BLA Number: NDA 205750
Submission Date: November 21, 2013
21st C. Review Goal Date: May 21, 2014
PDUFA Goal Date: July 21, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Cholbam
Established or Non-Proprietary Name (USAN) and strength:	Cholic Acid
Dosage Form:	Capsule, 50mg and 250mg

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Asklepion Pharmaceuticals LLC
Responsible Organization (OND Division):	DGIEP

II. Application Detail

1. INDICATION: Treatment of (b) (4)
2. ROUTE OF ADMINISTRATION: oral
3. STRENGTH/POTENCY: 50mg and 250mg
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

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

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

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 all site information complete (e.g., contact information, responsibilities, address)?	<input checked="" type="checkbox"/>		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	<input checked="" type="checkbox"/>		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>		356h
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	<input checked="" type="checkbox"/>		DS particle size testing at (b) (4)
15.	Additional notes (non-filing issue)	<input checked="" type="checkbox"/>		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		<input checked="" type="checkbox"/>	
	3. Is this first application by the applicant?	<input checked="" type="checkbox"/>		(b) (4)

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

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		<input checked="" type="checkbox"/>	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	<input checked="" type="checkbox"/>		NME, 2 facilities with No FDA History
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	<input checked="" type="checkbox"/>		
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.	<input checked="" type="checkbox"/>		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input checked="" type="checkbox"/>
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)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none"> DMF (b) (4) DS (b) (4) (b) (4)
(b) (4)				

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none"> • (b) (4) % DS • 50mg & 250mg capsules are (b) (4); capsule sizes 2 and 0 respectively for each dose • (b) (4)

(b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

- All DP clinical manufacturing and development was performed at Patheon ^{(b) (4)} but is being transferred to the new Patheon France facility which does not have an FDA history.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

- No issues with facility inspectional histories at this time.

Additional information not covered above

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Manufacturing Facilities Chart

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status	Comment
PATHEON FRANCE SAS	3004468553	WEU	FRA	Drug product manufacturing, testing, packaging, labeling and release	CHG	No FDA history	ASSIGNED INSPECTION TO IB (PS&GMP)	PN	First FDA evaluation of facility

(b) (4)

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) YES
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart.
<ul style="list-style-type: none">A briefing may be scheduled for the DS site (b) (4)) to discuss (b) (4) vendor qualifications, DS manufacturing, release assays and the stability studies.
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
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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

/s/

CHRISTINA A CAPACCI-DANIEL
01/08/2014

MAHESH R RAMANADHAM
01/09/2014

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Gene W. Holbert, Ph.D., CMC Reviewer
Marie Kowblansky, Ph.D., CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: gene.holbert@fda.hhs.gov
Phone: (301)-796-1368
Fax.: (301)-796-9850

Through: Moo-Jhong Rhee, Ph.D.
Phone: (301)-796-1440
and Youbang Liu
ONDQA Methods Validation Project Manager
Phone: 301-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 205750

Name of Product: CHOLBAM™ (cholic acid) capsules, 50 mg and 250 mg

Applicant: Asklepion Pharmaceuticals, LLC
Applicant's Contact Person: Gary R. Pasternack, MD, PhD
Address: 729 E. Pratt St., Baltimore, MD 21202
Telephone: (410) 545-0494 Fax: (410) 545-0584

Date NDA Received by CDER: **11/21/2013**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **N/A**

Special Handling Required: No

DATE of Request: **12/17/2013**

DEA Class: N/A

Requested Completion Date: **3/1/2013**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **7/21/14**

Paper x Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 205750
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.2
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.S.4.3 and 3.2.P.5.3 (validation)
Applicant's Test Results on NDS and Dosage Forms				Batch analyses 3.2.S.4.4 and 3.2.P.5.4
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
	Assay and Related Impurities (HPLC)	3.2.S.4.2.8	0 (NME)	For validation report see (b) (4) DMF (U) (4) (cholic acid)
	Identification, Assay and Related Substances of Cholic Acid Capsules by HPLC	3.2.P.5.2	0 (NME)	For validation reports, see section 3.2.P.5.3

Additional Comments: **See also section 3.2.R.2 Method Validation Package.**

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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

/s/

GENE W HOLBERT
12/17/2013

MOO JHONG RHEE
12/17/2013
Chief, Branch IV

YOUBANG LIU
12/18/2013