CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206333Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: **April 24, 2015**

From: **Hitesh Shroff**
Senior CMC Reviewer
Office of New Drug Products
Branch V/DNDP II

Hitesh N. Shroff -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=2000348333, cn=Hitesh N. Shroff -S
Date: 2015.04.24 17:17:00 -04'00'

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

Moojhong Rhee -S

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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: 2015.04.24 18:31:20 -04'00'

To: **CMC Review #1 of NDA 206333**

Subject: **Final Recommendation**

The CMC review #1 has noted the following two pending issues:

1. Final "Acceptable" recommendation from the Office of Compliance was not issued.
2. Label/labeling issues were not resolved.

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

On Feb 13, 2015, the Office of Compliance issued the overall "Complete" manufacturing inspection recommendation for the facilities involved in the NDA (**Attachment 1**).

On April 24, 2015 the label and labeling were submitted and they are revised satisfactorily from the CMC perspective (**Attachment 2**).

Recommendation:

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

ATTACHMENTS:

Attachment 1:

Attachment 2:

1. ***Package Insert***

(a) "Highlights" Section

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

KYBELLA (deoxycholic acid) injection, for subcutaneous use
Initial U.S. Approval: 2015

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 10 mg/ml sterile solution, supplied in 2 ml vials. Each vial is for single patient use. (3)
- Dilution or admixture with other compounds is not recommended. (3)

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

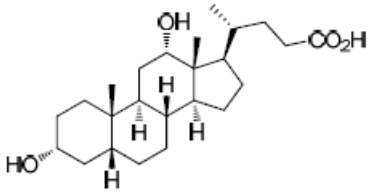
3 DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL. KYBELLA injection is a clear, colorless, sterile solution supplied in 2 mL vials intended for single patient use. Each milliliter of the solution contains 10 mg of deoxycholic acid.

#11. Description

11 DESCRIPTION

KYBELLA (deoxycholic acid) injection, 10 mg/mL is a clear colorless, sterile solution for subcutaneous use. It contains a cytolytic agent, deoxycholic acid, as the active ingredient. The chemical name of deoxycholic acid is 3α,12α-dihydroxy-5β-cholan-24-oic acid, and its molecular formula is $C_{24}H_{40}O_4$, and its molecular weight is 392.57 g/mol. The chemical structure of deoxycholic acid is:



Each 2 mL vial of KYBELLA (deoxycholic acid) injection contains 20 mg synthetic deoxycholic acid as the active ingredient and the following inactive ingredients: benzyl alcohol (18 mg), dibasic sodium phosphate (2.84 mg), sodium chloride (8.76 mg), sodium hydroxide (2.86 mg) in water for injection, USP. Hydrochloric acid and additional sodium hydroxide are added as necessary to adjust the formulation to pH 8.3. Each vial is for single patient use.

#16 How Supplied/storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

KYBELLA (deoxycholic acid) injection, 10 mg/mL is a clear, colorless, sterile solution supplied in 2 mL, single patient use vials in the following dispensing pack:

4 vials, NDC 61168-101-04

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

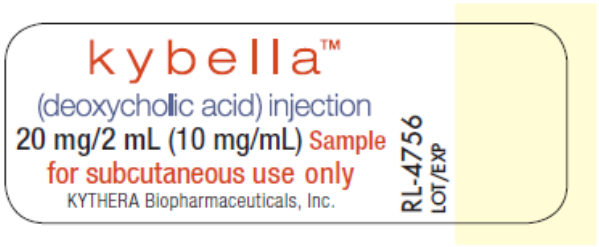
KYBELLA has a unique hologram on the vial label. If you do not see a hologram, do not use the product and call 1-844-KYTHERA (1-844-598-4372).

Each vial is for a single patient use. Do not dilute. Discard unused portion.

2. ***Labels***

Immediate container label

Physician's sample immediate container label



Container label

Physician Sample Container Label

NDA 206333

Kybella (deoxycholic acid) injection
10 mg per ml

Kythera Biopharmaceuticals, Inc.

Hitesh Shroff, Ph.D.
Review Chemist

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

CMC Review of NDA 206333
For the Division of Dermatology and Dental Products
(HFD-540)

Table of Contents

Chemistry Review Data Sheet

1. NDA 206333

2. REVIEW:#1

3. REVIEW DATE: 17-Dec-2014

4. REVIEWER: Hitesh Shroff, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12-May-2014
Quality/Stability amendment	06-Jun-2014
Stability amendment	25-Jul-2014
Quality amendment	27-Oct-2014
Quality amendment	29-Oct-2014

7. NAME & ADDRESS OF APPLICANT

Name:	Kythera Biopharmaceuticals, Inc.
Address:	27200 West Agoura Road, Suite 200 Calabasas, CA 92301
Representative:	Diane Stroehmann Vice President Regulatory Affairs
Telephone:	818-587-4521
Email:	dstroehmann@kytherabiopharma.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Kybella
b) Non-Proprietary Name (USAN): Deoxycholic acid
b) Code Name/# (ONDQA only): None
c) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Cytolytic agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg deoxycholic acid per 1 ml solution

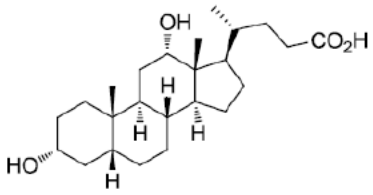
13. ROUTE OF ADMINISTRATION: Injection

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: Deoxycholic acid
Chemical Names: (3α,5β,12α,20R)-3,12-dihydroxycholan-24-oic acid

(4R)-4-[(3R,5R,8R,9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17- yl]pentanoic acid

3α,12α-dihydroxy-5β-cholan-24-oic acid
3α,12α-dihydroxycholanic acid

CAS Numbers: 83-44-3
Molecular Formula: $C_{24}H_{40}O_4$
Molecular Weight: 392.57 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3, 4	Adequate	20-Mar-2014	
	III			3, 4	Adequate	28-Jul-2014	
	III			4	Adequate		
	III			4	Adequate		

[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: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		Christina Capacci-Daniel
Pharm/Tox	Adequate	16-Dec-2014	Jill Merrill
Biopharm	N/A		
LNC	N/A		
Methods Validation	Adequate	23-Sep-2014	Jeffrey T. Woodruff
DMEPA	N/A		
EA	Claim for categorical exclusion is submitted per 21 CFR 314.50(d)(1)(iii)	13-May-2014	Hitesh Shroff
Microbiology	Adequate	01-Dec-2014	Erika Pfeiler

The Chemistry Review for NDA 206333

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has submitted sufficient information to assure the identity, strength, purity and quality of the drug product..

However, a final "Acceptable" recommendation from Office of Compliance for the manufacturing facilities has ***not*** been made.

Also, label/labeling issues have ***not*** been resolved satisfactorily from the CMC perspective.

Therefore, from the ONDQA perspective, this NDA is ***not*** ready for approval at this time in its present form per 21CFR314.125(b)(6),and (13).

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

No recommendations at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

Kybella injection is a 10 mg/ml solution of the drug substance, deoxycholic acid. It is described as a cytolytic agent. It is a white to off-white (b) (4) It is manufactured by (b) (4)

The synthesis of deoxycholic acid involves (b) (4) Kythera has provided detailed CMC information for the starting material.

(b) (4)

(b) (4)

The drug substance specification includes appearance, identification, assay, impurities, water content, residual solvents, heavy metals, specific rotation and microbial contamination. The drug substance specification is deemed adequate to assure the identity, strength, purity, and quality of the drug substance.

The drug substance is placed in (b) (4)

(2) Drug Product

Kybella is a clear colorless, sterile solution for subcutaneous administration. It is supplied in 2 ml USP Type 1 glass vial, sealed with (b) (4) rubber stopper and sealed with (b) (4) flip-top lid. Each carton contains 4 individual 2 ml vials. Each vial contains 20 mg of deoxycholic acid in 2 ml of solution. The inactive ingredients of the drug product are benzyl alcohol, dibasic sodium phosphate, hydrochloric acid, sodium chloride, sodium hydroxide and water for injection, USP. The pH of the formulation is adjusted to pH 8.3. Each vial is a single patient use vial and should not be diluted.

The manufacture of Kybella is performed i (b) (4) The proposed release specification of the finished product include appearance, identification, assay of the active ingredient and preservative, pH, impurities, particulate matter, sterility and bacterial endotoxins limits. The proposed specification of Kybella is deemed adequate to assure the identity, strength, purity, and quality of the drug product.

Three primary stability batches (b) (4) were manufactured at (b) (4) The long-term and accelerated of 3 primary stability batches and 5 supportive batches stability data provided is adequate and support the proposed 30-month expiration dating period for the drug product, when stored at 25°C in 2 ml USP Type I glass vials, sealed with (b) (4) rubber stoppers and capped with flip-top (b) (4) seals.

(3) Risk Assessment

The sterility of the drug product (b) (4) (b) (4) (b) (4) The drug product is manufactured at (b) (4) The applicant has submitted long-term and accelerated stability data for 3 primary stability and 5 supportive batches to demonstrate that during the storage the sterility of the drug product is not compromised. Thus, based on the stability data and the efforts made by the manufacturer to control the sterility and bioburden of the drug product it is concluded that there is low risk to the quality of the drug product with respect to the sterility and bioburden.

During the drug product development the antimicrobial effectiveness of benzyl alcohol concentrations (b) (4) were studied per USP <51>. The final concentration of 0.9% was selected based on its common usage for preserved parenteral products; (b) (4) Based on the information provided is concluded that there is low risk to the quality of the drug product because there is sufficient concentration of preservative, benzyl alcohol, in the drug product.

The particulate matter is monitored per USP <788>. As demonstrated during the the long-term and accelerated stability studies of the drug product that there is virtually no increase in particulate matter during the storage. The particulate matter was well below the acceptance limits in all batches tested. Thus there seems to be low risk related to particulate matter in the drug product.

The following table is a summary risk assessment of deoxycholic acid injections at the time of initial quality assessment and after the review. The applicant has adequately addressed the possible high risk product attributes to mitigate the drug product quality risk.

Risk assessment of deoxycholic acid injections

Product attribute/CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	Modified RPN
Sterility	3 (2)	4 (SC) (3)	5 (3)	60	(18)
Endotoxin pyrogen	2 (2)	4 (3)	4 (3)	32	(18)
Assay (preservative) During stability	3 (2)	4 (SC) (3)	3 (3)	36	(18)
Particulate matter	3 (2)	3 (3)	3 (2)	27	(12)

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

Kybella is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. Kybella is supplied as a sterile, clear solution in a 2 ml single use vial for subcutaneous administration. Each vial contains 20 mg of deoxycholic acid in 2 ml solution. There is (b) (4) ml overfill to ensure withdrawal of the labeled content (2 ml). Kybella should not be diluted prior to use.

C. Basis for Approvability and Not-Approval Recommendation

21 CFR 314.125(b)(13)

- No "Acceptable" recommendation from the Office of Compliance has been made for the cGMP compliance of the facilities involved.

21 CFR 314.125(b)(6)

- Labels and labeling issues have not been fully resolved

(see the **List of Deficiencies** on p. 103)

III. Administrative

A. Reviewer's Signature

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2014.12.19 12:33:48 -05'00'

Hitesh Shroff, Ph.D./ 17-Dec-2014

B. Endorsement Block

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: 2014.12.19 12:59:39 -05'00'

Moo Jhong Rhee, Ph.D., Branch Chief, Branch IV, Division II

C. CC Block

Shulin ding, Ph.D.

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IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **NDA 206333**

2. DATES AND GOALS:

Letter Date: **May 12, 2014**	Submission Received Date : **May 13, 2014**
PDUFA Goal Date: **May 13, 2015**	

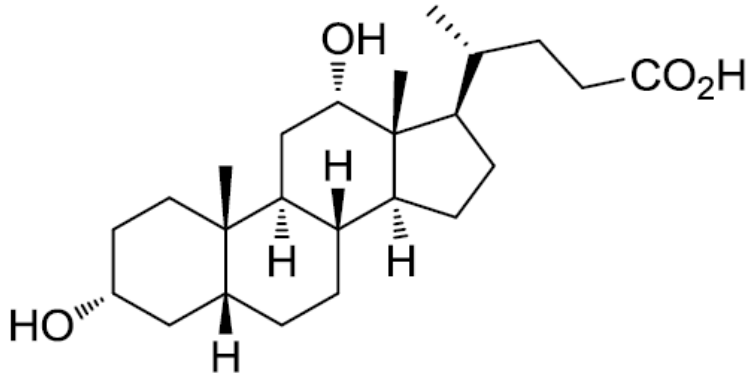
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Kybella
Established or Non-Proprietary Name (USAN):	Deoxycholic acid Note: Although the title of NF monograph on this compound is desoxycholic acid, it has been verified with USAN Council that the correct United States Adopted Name is deoxycholic aicd.
Dosage Form:	Injection
Route of Administration	subcutaneous
Strength/Potency	1%
Rx/OTC Dispensed:	Rx

4. INDICATION:

Improvement in the appearance of moderate to severe convexity of fullness associated with submental fat (SMF) in adults

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



Molecular formula: $C_{24}H_{40}O_4$
Molecularweight: 392.57 g/mol

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

Keythera Biopharmaceuticals

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 3
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Dermatology and Dental Products
Other Information	

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		Submitted on June 12, 2014
Pharmacology/Toxicology	x		Leachables
Methods Validation	x		New molecular entity
Environmental Assessment		x	Categorical exclusion claimed.
CDRH		x	
Other	x		Quality Microbiology. The assignment has been made to Erika Pfeiler.

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes x No
CMC Filing Issues:
1. None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes x No
CMC Comments for 74-Day Letter:
1. None

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes No
Not applicable.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes No x
Biopharmaceutics Comments for 74-Day Letter: Not applicable.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes x No
Microbiology Filing Issues:
None. Microbiology Filing Review was filed in DARRTS on June 25, 2014. The filing review includes comments to be forwarded to the applicant in the 74-day letter for microbiological review issues. The assigned Quality Micro reviewer is Erika Pfeiler.

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	No x
Suggested expertise for team: Not applicable.		

Summary of Critical Issues and Complexities

1. Comparability Protocol

   Comparability protocols are submitted to cover seven anticipated post-approval CMC changes. The protocols need to be critically reviewed, and concurrence should be sought from Post-approval group for each protocol.

2. Extractables/Leachables

   Extensive studies were conducted for extractables/leachables from the container/closure system (b) (4) rubber stopper and glass vial) using various analytical techniques including HPLC/DAD/MS, GC/MS, headspace GC/MS and inductively-coupled plasma/optical emission spectroscopy. HPLC/DAD detected four unknown peaks in the drug product as early as the initial time point. The other three analytical methods did not detect significant leachables in the drug product. Among these four unknown peaks, only the peak at RT= (b) (4) minutes was considered by the applicant to be significant. The applicant conducted a toxicology risk assessment, and concluded that the safety risk of this peak was acceptable. Pharm/Tox reviewer should be contacted to assess the toxicology risk assessment.

3. Sterilization Validation and Microbiological Test Methods

   The sterilization validation reports and relevant information (b) (4) are provided in Section 3.2.P.3.5. They are to be reviewed by Quality Microbiology reviewer.

   The methods for sterility and endotoxins tests are USP methods. Their method verification reports can not be located in Module 3. Quality Microbiology reviewer has indicated that this is not a filing issue, and IR will be sent to request the missing method verification reports.

Initial Quality Assessment

This is a 505(b)(1) NDA. The proposed drug substance, deoxycholic acid, is a new molecular entity (b) (4). All drug substance CMC information is provided in the NDA. The applicant proposes two drug substance suppliers: (b) (4) (b) (4) Both suppliers use the same manufacturing process. The proposed production scale is (b) (4)

The synthesis begins with (b) (4)

Chemical Synthesis of Desoxycholic Acid

(b) (4)

The applicant provides 18-24 months of long term stability data from three full scale, primary stability lots made by (b) (4) and 9 months of long term stability data from four full scale, supporting stability lots made by (b) (4) to support a retest date of (b) (4) months when stored (b) (4) The drug substance has been shown to be very stable under long term and accelerated conditions.

The proposed drug product, Kybella (deoxycholic acid) injection, 1% (w/v) is a sterile, isotonic, clear, colorless solution intended for subcutaneous administration. The product is preserved by benzyl alcohol, buffered by phosphate, and pH-adjusted to pH 8.3. All excipients are compendial. The formulation contains no novel excipients and no excipients are derived from animal origin.

The product is packed in a 2 mL fill, Type I, glass vial with a rubber stopper and an (b) (4) overseal with flip-top lid. The to-be-marketed formulation (table below) is the same formulation used in Phase 3 clinical trials and registration stability batches.

Formulation Composition for the Proposed To-Be-Marketed Formulation

Component	Quality Standard(s)	Percent of formula (w/v)	Amount per 2.0 mL	Function
Deoxycholic acid (DCA)	In-house	1.00%	20.00 mg	Drug substance
Sodium hydroxide	NF/PhEur	0.14%	2.86 mg	(b) (4)
Dibasic sodium phosphate	USP/PhEur	0.14%	2.84 mg	Buffer
Sodium chloride	USP/PhEur	0.44%	8.76 mg	(b) (4)
Benzyl alcohol	NF/PhEur	0.90%	18.00 mg	Preservative
Sodium hydroxide	NF/PhEur	q.s.	q.s.	pH adjustment
Hydrochloric acid	NF/PhEur	q.s.	q.s.	pH adjustment
Water for injection	USP/PhEur	to 100%	to 2.0 mL	(b) (4)

q.s. = Quantity sufficient

The commercial manufacture of the drug product is proposed to take place at (b) (4) at the scale of (b) (4). The manufacturing process consists of the following steps:

(b) (4)

The critical process steps ar (b) (4)

Drug product stability data provided in the initial submission to support the proposed **expiration dating period of 30 months** are 18 months of long term (25ºC//60%RH), and 6 months of accelerated temperature (40ºC/75%RH) data from three registration stability batches. The registration stability batches are commercial scale, made at the designated commercial site (b) (4) using the commercial process and packaged in the to-be-marketed container/closure systems. Both upright and inverted orientations are studied. The proposed storage condition is 20º-25°C with excursions permitted to 15º-30ºC (USP controlled room temperature).

Additional stability data (long term, and accelerated) up to 24 months from multiple supporting stability batches are also provided. Special stability studies conducted to support storage/handling of the product include **transportation simulation, photostability, refrigeration** (b) (4) **freeze/thaw,** and an **in-use stability study in plastic disposal syringe** (b) (4) These special studies were conducted using registration stability batches.

Initial Risk Assessment

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	Comment
Sterility	• Formulation • Container/closure • Process parameters • Scale/equipments • Site	4-1=3	4 (sc)	5	60	Bioburden level for the terminal sterilization is reduced (b) (4) .
Endotoxin pyrogen	• Formulation • Container/closure • Process parameters • Scale/equipments • Site	2	4	4	32	
Assay (API), stability	• Formulation • Container/closure • Raw materials • Process parameters • Scale/equipments	1 (highly stable drug)	2	1	2	No single impurity is greater than (b) (4) %. Total impurities is less than (b) (4) %.
Assay (preservative)	• Formulation • Raw materials • Container closure • Process parameters • Scale/equipments	Release (1) Stability (3)	4 (SC)	3	Release (12) Stability (36)	FMECA Ranking system over-estimates the stability risk of this CQA, which should be ranked low for the following reasons: meeting USP<51> (b) (4) and labeled as single use only.
Fill volume/deliverable volume	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	2 (non-high risk drug)	2	8	The acceptance criterion for fill volume is (b) (4)
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments	2	3 (SVP)	2	12	Change in osmolality is small when pH overshoot during pH adjustment.
pH (target pH 8.3)	• Formulation • Container/closure • Raw materials • Process parameters • Scale/equipments	3	4	1	12	The formulation is buffered by phosphate. Risk in pH change is low.
Particulate matter	• Formulation • Raw materials • Container closure • Process parameters • Scale/equipments • Site	3	3	3	27	Delamination was investigated in stressed samples, and found no signs of delamination.
Leachables	• Formulation • Raw materials • Container closure • Process parameters • Scale/equipments • Site	2	4	3	24	Comprehensive studies were conducted using various analytical techniques. Tox risk assessment was conducted, and deemed acceptable.
Appearance	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	3	3	1	9	

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		
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.**			. n/a

	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		Categorical exclusion claimed based on EIC below 1 ppb.

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

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		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?			n/a. This is a solution product.
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			n/a

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

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

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?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	2/11/14	
	V			2/11/14	
	III			2/5/14	
	III			3/26/14	

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

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

See appended electronic signature page}
Shulin Ding
CMC-Lead
Division II
Office of New Drug Quality Assessment

{See appended electronic signature page}
Moo-Jhong Rhee
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/

SHULIN DING
06/27/2014

MOO JHONG RHEE
06/30/2014
Chief, Branch IV

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

I. Review Cover Sheet

1. OMPQ Reviewer: Christina Capacci-Daniel

2. NDA/BLA Number: 206333
   Submission Date: May 13, 2014
   21st C. Review Goal Date: March 13, 2015
   PDUFA Goal Date: May 13, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	*To be determined (ATX-101)*
Established or Non-Proprietary Name (USAN) and strength:	Deooxycholic acid
Dosage Form:	Subcutaneous Injection, 10mg/mL

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Kythera Biopharmaceuticals, Inc.
Responsible Organization (OND Division):	DDDP

II. Application Detail

1. INDICATION: Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

2. ROUTE OF ADMINISTRATION: Subcutaneous

3. STRENGTH/POTENCY: 10mg/mL, 2mL units

4. Rx/OTC DISPENSED: ☒Rx ☐OTC

5. ELECTRONIC SUBMISSION (yes/no)? Yes

6. PRIORITY CONSIDERATIONS:

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

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)?	☑		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	☑		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	☑		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	☑		Several heavy metal testing sites; two stability testing facilities
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	☑		
			☑	Participation not requested.
		☑		This is Kythera Biopharmaceuticals Inc's first NDA. Additionally, ATX-101 is their only IND.

*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.

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

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	☑		New Molecular Entity
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?	☑		All EERs have been initially processed by OC.
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.	☑		Application is fileable.

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)?		☑	(b) (4) [redacted]

(b) (4) [redacted]

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		☑	• 1% (w/v) DS in the solution DP • Formulation contains 0.9% (w/v) benzyl alcohol as preservative • (b) (4); formulation is buffered • (b) (4) • Fill weight check & 100% visual inspection

(b) (4)

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.

- No Facility-Related Risks identified at this time.

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

- The drug product manufacturing facility was just inspected for SVS in (b) (4) and found to be VAI. An initial PAI WH recommendation based on process validation deficiencies was downgraded to acceptable following the firm's response.

Additional information not covered above

Manufacturing Facilities Chart (as of 6/20/2014):

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status	Comment/ Rationale
		(b) (4)	USA	DS manufacturing, testing and batch release	CSN	(b) (4) VAI, CSN covered but was mostly a PAI	SUB. TO DO (PS&GMP)	PN	PAI for NME DS manufacturer; last inspection focused on a specific product
			USA	DS manufacturing, testing and batch release, stability testing	CSN	(b) (4) VAI, CSN covered	SUB. TO DO (PS & GMP)	PN	PAI for NME DS manufacturer
			USA	DS microbiological & endotoxin testing (alt. site)	CTL	(b) (4) NAI, CTL covered	OC RECOMMENDATION	AC	AC based on Inspectional history; NME PAI waived since non-PS testing performed
			USA	DP stability storage & testing	CTL	(b) (4) NAI, CTL covered	SUB. to DO (PS & GMP)	PN	PAI for NME testing and DP storage
			USA	Heavy metal testing (alt. site)	CTL	(b) (4) VAI, CTL covered	SUB. to DO (GMP)	PN	CGMP needed; NME PAI waived since non-PS testing performed
			USA	Specific metal testing (alt. site)	CTL	(b) (4) NAI, CTL covered	SUB. to DO (GMP)	PN	CGMP needed; NME PAI waived since non-PS testing performed

(b) (4)	USA	Specific metal testing (alt. site)	CTL	(b) (4) NAI, CTL covered	OC RECOMMENDATION	AC	AC based on Inspectional history; NME PAI waived since non-PS metal testing performed
(b) (4)			CTL	(b) (4) VAI, CTL/CSN covered but mostly a PAI	SUB. to DO (PS & GMP)	PN	PAI for NME DS stability testing; last inspection focused on a specific product
			SVS	(b) (4) VAI, SVS covered	SUB.TO DO (10-Day)	PN	Facility recently inspected; NME PAI waived since nothing atypical about this DP

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. • No KTMs are warranted at this time.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/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
06/23/2014

MAHESH R RAMANADHAM
06/23/2014