

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207987Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 207987 Resubmission 17 (Ablysinol) Dehydrated Alcohol Injection, USP

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Dehydrated Alcohol Injection, USP
Strength	(b) (4)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Belcher Pharmaceuticals LLC
Submissions (s) Reviewed	NDA 207987 Resubmission 17, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	ONDP/DNDPI/NDPBI
Drug Product/Environmental Assessment (EA)	Mariappan Chelliah	ONDP/DNDPI/NDPBI
Process	Nathan Davis	OPQ/OPF/DPAI/PABI
Facility	Viviana Matta	OPF/DIA/IABI
Biopharmaceutics	Jing Li	ONDP/DB/BBI
Microbiology	Yeissa Chabrier Rosello	OPQ/OPF/DMA/MABII
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead (ATL)	Mohan Sapru	ONDP/DNDPI/NDPBI

RELATED/SUPPORTING DOCUMENTS

Document	Application Number	Description
Type II DMF	# (b) (4)	The DMF has been reviewed in the context of the current submission and found adequate.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Using science and patient-focused risk assessment approach, this NDA has been reviewed from quality perspective in view of totality of evidence available i.e., CMC information provided in the application, including the type II DMF, product quality controls, long history of human use of the proposed low risk product, and intended use of the drug product. From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 207987 Resubmission 17 (Dehydrated Alcohol Injection, USP) is recommended for approval.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background and Quality Summary:

- On 12 February, 2015, the applicant submitted the original New Drug Application (NDA 207987) for Dehydrated Alcohol Injection, USP to seek U.S. marketing approval in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.
- The proposed indication is to improve (b) (4) exercise capacity in patients with symptomatic, (b) (4) hypertrophic obstructive cardiomyopathy (HOCM) (b) (4). Specifically, Dehydrated Alcohol is used in performing percutaneous transluminal septal myocardial ablation (PTSMA). Specifically, it is a potent tissue toxin that produces a small, controlled infarction when injected percutaneously into a target septal vessel.
- This product received orphan designation for a broader indication of treatment of HOCM on 11 September, 2013.
- For this NDA, the applicant is relying on data from the published literature and an additional database of patient-level outcomes for 100 patients with HOCM treated by PTSMA. Alcohol and Dextrose Injection (NDA 004589; approved 17 January 1946) is the listed drug.
- Upon completion of review of the originally submitted NDA 207987, the Agency sent the Complete Response Letter (CRL) to the applicant on 9 December, 2015.
- Based on review of the current NDA 207987 Resubmission 17, each of the CMC deficiencies listed in the CR letter; including the drug substance manufacturing facility-related deficiencies have been satisfactorily addressed.

A. Drug Substance Quality Summary

The CMC information concerning the drug substance, including its manufacturing (b) (4) is cross-referenced to DMF No. (b) (4). The DMF was reviewed in the context of this application and found adequate. Per the current submission, starting material, (b) (4)

Based on information provided in this NDA resubmission, proposed specification for the drug substance involves monitoring the critical quality attributes (CQAs) on release. The acceptance limits for assay and volatile impurities is NLT (b) (4)% (by gas chromatography), NMT (b) (4) ppm for (b) (4) NMT (b) (4) ppm for (b) (4) and

NMT (b) (4) ppm for (b) (4) respectively. Given the use of USP monograph testing methods, analytical method validation is not required. The specification of bacterial endotoxin in the drug substance is based on a (b) (4) maximum total dose of (b) (4). Based on stability data, (b) (4) has assigned a retest period of (b) (4) months for the drug substance.

B. Drug Product Quality Summary

The drug product, a sterile liquid for injection containing NLT 99% by weight of ethyl alcohol, does not contain any excipients other than the (b) (4).

The drug product is (b) (4) Ablysinol® is supplied as a (b) (4) clear glass ampoule containing 1 mL Dehydrated Alcohol Injection, USP and as a (b) (4) clear glass ampoule containing 5 mL Dehydrated Alcohol Injection, USP. The applicant has indicated that currently two other pharmaceutical companies, Akorn, Inc. and American Regent, Inc., are marketing unapproved dehydrated alcohol in the US under the non-registered grandfathered drugs category. The current application by Belcher Pharmaceuticals, LLC is the first application to seek FDA approval for the Dehydrated Alcohol Injection, USP. The pharmaceutical development has been guided mainly by adherence to USP monograph for Dehydrated Alcohol Injection. The drug product specification proposed by the applicant in the original NDA submission was based on (b) (4).

Per Agency's recommendation, the applicant developed gas chromatography (GC) method for assay, and determination of impurity levels in the product. The proposed criterion of (b) (4) % by weight for assay is tighter than recommended USP limit. The GC method, used for quantitating the organic impurities, and for the assay, has been validated for specificity, linearity, precision, accuracy, and solution stability. The applicant provided risk assessment for the elemental impurities. No (b) (4) elemental impurities were added during manufacturing of the API. The drug product does not contain any added excipient and the manufacturing process is not expected to leach elemental impurities. The applicant tested three batches of drug substance and found that the (b) (4) impurities were present at (b) (4) of their respective ICH Q3D (b) (4) limits. Therefore, the lack of testing for elemental impurities is acceptable. The acceptance limit of (b) (4) EU/mg for the bacterial endotoxins test has been set on on a (b) (4) maximum total dose of (b) (4).

Although this high dosage is no longer recommended, the endotoxins specification has been adjusted accordingly. In summary, the revised specification for the drug product is adequate to assure product quality.

Fill Volume: Per 21CFR201.51 (g) and USP <1151>, the maximum volume of liquid, including fill-variation, cannot exceed 1.1 mL for the 1 mL ampoule and 5.3 mL for the 5-mL ampoule. The applicant contends that mean fill volume is controlled in a suitable range in order to guarantee the nominal extractable volume of solution per ampoule per USP <697>. However, the proposed fill-ranges of (b) (4) mL for the 1 mL ampoules and (b) (4) mL for the 5 mL ampoules do not strictly meet USP <1151> requirement. (b) (4)

(b) (4)

Per recommended use, Dehydrated Alcohol from the ampoule is transferred to a percutaneous transluminal catheter where dispensing volume is carefully measured during the alcohol septal ablation procedure. Per Dr. Fortunato Senatore, the clinical reviewer, the desired volume of the drug is drawn using a syringe and then injected into the catheter port. The drug is subsequently delivered to the ablation site using the percutaneous transluminal septal myocardial ablation (PTSMA) procedure. (b) (4)

Per Dr. Senatore, (b) (4)

the proposed fill-volume is deemed acceptable.

Compatibility: The compatibility data for the use of the drug product with percutaneous transluminal catheters are adequate. Specifically, the drug product is to be dosed using commonly available commercial catheters. Accordingly, the choice of two of the most commonly used catheters for the compatibility study is acceptable. All the impurities that leach above (b) (4) ppm are considered non-mutagenic. These impurities are well below the ICH Q3B qualification threshold of NMT (b) (4) %. However, as a precaution, the Pharm/Tox reviewer recommended that the exposure of alcohol in the catheter be limited as much as possible, preferably < (b) (4)

Manufacturing: The drug product is manufactured by Sintetica SA, Switzerland. Briefly, the manufacturing process involves: (b) (4)

Microbiological Aspects: Dehydrated Alcohol, USP contains no bacteriostat or antimicrobial agent or any buffer. However, ethanol by itself is an antimicrobial agent and the applicant has demonstrated drug product sterility based on stability studies. The manufacturing process involves a (b) (4)

The information and results provided for the depyrogenation process for the glass ampoules are adequate. The validation studies for the (b) (4)

As per the Agency recommendation, the drug product endotoxins specification has been revised from < (b) (4) EU/mg to < (b) (4) EU/mg. This revised drug product endotoxins specification is based on a (b) (4) maximum total dose of (b) (4) mL. The applicant has indicated that the sterility and the endotoxin limits comply with the USP <71> Sterility Test and USP <85> Bacterial Endotoxin Test. The leak test data provided in support of the (b) (4) container closure configurations are acceptable. (b) (4)

Biopharmaceutics Aspects: The biopharmaceutics evaluation of the original NDA submission focused on the evaluation of the information/data supporting the bridging between the proposed drug product and the products used in the key clinical studies from the published literature. Briefly, the method of delivery and the local action of injected Dehydrated Alcohol imply that little if any drug reaches the systemic circulation. No bioavailability/bioequivalence data have been provided. Based on evaluation of biopharmaceutics aspects and risk-based considerations, it is reasonable to conclude that bridging of the to-be-marketed formulation to the formulations employed in the scientific studies (where compositional information is provided) is acceptable. It is noted that the resubmitted NDA does not include new biopharmaceutics-related information/data, and the resubmission remains adequate and acceptable from a biopharmaceutics perspective.

Container Closure System: The primary packaging for Dehydrated Alcohol Injection is (b) (4) (USP) (b) (4) clear colorless glass ampoules with score-break manufactured by either (b) (4). Given that the drug product is (b) (4) liquid, the risk of potential formation of (b) (4) in the ampoule is low. The secondary container is a cardboard-box, each containing 10 ampoules. Packaging components comply with compendial requirements and are standard materials used for parenteral dosage form containers. The stability data show that the container is adequate to provide protection to the drug product through the product's shelf-life.

Expiration Date & Storage Conditions: The stability data support a shelf-life of 18 months when stored at controlled room temperature (20°C – 25°C; 68°F – 77°F) in the proposed commercial container closure system. In addition, the stability data adequately support sterility assurance of the drug product for the duration of shelf-life.

C. Assessment of Manufacturing Facilities: (b) (4) is the designated manufacturing facility for the drug substance, which is shipped in bulk to the U.S. market. It has been inspected several times by FDA, including in 1999, 2001, 2004, 2009, 2012 and 2016. Recent inspections have been satisfactory and the firm has been found to be an acceptable supplier of the APIs. A review of the application and all the inspectional documents of the facilities responsible for manufacturing Dehydrated Alcohol Injection, USP per NDA-207987-ORIG-1-RESUB-17 has determined that there are no outstanding issues with the firms involved in the manufacturing of the product. Hence, the office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA.

III. Summary of Drug Product and Intended Use

Proprietary Name of the Drug Product	Ablysinol
Non Proprietary Name of the Drug Product	Dehydrated Alcohol Injection, USP
Active ingredient	Dehydrated Alcohol
Route of Administration	Injection
Strength(s)	1 or 5 ml of solution for injection containing not less than 99% (by weight) of Dehydrated Alcohol, USP.

Proposed Indication(s)	(b) (4) to improve (b) (4) exercise capacity in patients with symptomatic, (b) (4) hypertrophic obstructive cardiomyopathy (HOCM) (b) (4)
Maximum Daily Dose/ Duration of Treatment	Per labeling, the maximum dose that should be used in a single procedure is 5 mL. In most situations, 1 to 2 mL is sufficient.
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation: The proposed drug product is an injectable solution, and the applicant has not request an official BCS designation,
2. Biowaivers/Biostudies:
 - Biowaiver Requests: None.
 - PK studies: None
3. IVIVC: N/A.

E. Product Quality Labeling Recommendations: All labeling recommendations were accepted by the applicant, and are reflected in the most recent version of the product labeling. The labels comply with all regulatory requirements from a CMC perspective.

F. Environmental Assessment: The calculated discharge of ethanol at the point of entry into aquatic environment, indicated by the applicant, is less than (b) (4) ppb/day, which is less than 1 ppb limit. (21 CFR 25.31(b)). Hence, the applicant's request for categorical exclusion from environmental assessment is acceptable.

G. Life Cycle Knowledge Information

Final Risk Assessment is depicted on the next page.

Final Risk Assessment

NDA 207987 Resubmission 17 (Ablysinol) Dehydrated Alcohol Injection, USP

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	H (High)	Release specification for the drug product includes sterility (USP <71>) and bacterial endotoxin testing. Container closure studies indicate that the container closure system remains integral and therefore can maintain the sterility of the product.	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	M (Moderate)	The proposed endotoxin limit of NMT < (b) (4) EU/mg is more conservative than the recommended USP limits and is based on a (b) (4) maximum total dose of (b) (4).	Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)	Stability of the API and the drug product, and suitability of commercial container closure system have been well demonstrated. Manufacturing process is reasonably well-controlled.	Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))	Mean fill volume is controlled in a suitable range in order to guarantee the nominal extractable volume of solution per ampoule per USP <697>. As for this drug product, the contents are transferred to a percutaneous transluminal catheter where dispensing volume is carefully measured during the alcohol septal ablation procedure.	Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	Given that the drug product consists of NLT 99% by weight of ethyl alcohol with no excipients, and dehydrated alcohol from the ampoule is transferred to a percutaneous transluminal catheter where dispensing volume is carefully measured, product osmolality is not a relevant quality risk factor	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	Acidity is monitored on release	Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	M (Moderate)	Particulate matter (b) (4) is monitored on release per USP <788>.	Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	The compatibility data for the use of the drug product with percutaneous transluminal catheters provided are adequate.	Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)	The drug substance appearance is routinely monitored on release.	Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

Using science and patient-focused risk assessment approach, this NDA has been reviewed from quality perspective in view of totality of evidence available i.e., CMC information provided in the application, including the type II DMF, product quality controls, long history of human use of the proposed low risk product, and intended use of the drug product. From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 207987 Resubmission 17 (Dehydrated Alcohol Injection, USP) is recommended for approval.

Mohan Sapru, M.S., Ph.D.

Application Technical Lead (ATL)

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LABELING**I. Package Insert****1. *Highlights of Prescribing Information***

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	ABLYSINOL
Dosage form, route of administration	Percutaneous injection
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	ABLYSINOL® (b) (4) [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	None

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection
Strengths: in metric system	1 mL, 5 mL
Active moiety expression of strength with equivalence statement (if applicable)	NLT 99% by weight.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	ABLYSINOL®; dehydrated alcohol
Dosage form and route of administration	Injection
Active moiety expression of strength with equivalence statement (if applicable)	NLT 99% by weight
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A (no excipients)
Statement of being sterile (if applicable)	Sterile
Pharmacological/ therapeutic class	Tissue toxin
Chemical name, structural formula, molecular weight	ethyl alcohol (b) (4); C ₂ H ₆ O; 46.07
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	flammable liquid miscible with water

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	1 mL and 5 mL
Available units (e.g., bottles of 100 tablets)	Carton of 10
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 62250-105-10 NDC 62250-105-15
Special handling (e.g., protect from light)	Do not refrigerate. (b) (4) [REDACTED]
Storage conditions	Store at room temperature, between 20°C and 25°C (68°F and 77°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Belcher Pharmaceuticals, LLC, Largo, FL 33777 USA

Reviewer's Assessment of Package Insert: Adequate

The Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:**1. Container and Carton Labels**

As a representative example, the container label corresponding to the 1 mL ampule (eCTD seq. 0021) is shown below.

(b) (4)

2. Carton Label

As a representative example, the carton label corresponding to the 1 mL ampule (eCTD seq. 0021) is shown below.

(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)))	Ablysinol; dehydrated alcohol	Ablysinol; dehydrated alcohol
Dosage strength	NLT 99% by weight	NLT 99% by weight
Net contents	1 mL, 5 mL	1 mL, 5 mL
“Rx only” displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	NDC 62250-105-01 (1 mL) NDC 62250-105-02 (5 mL)	NDC 62250-105-10 (1 mL) NDC 62250-105-15 (5 mL)
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Store between 20°C to 25°C (68°F to 77°F)	Store between 20°C to 25°C (68°F to 77°F)
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Belcher Pharmaceuticals, LLC	Belcher Pharmaceuticals, LLC, Largo, FL 33777
And others, if space is available	--	--

Reviewer’s Assessment of Labels: *Adequate*

The labels comply with all regulatory requirements from a CMC perspective

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

Primary Reviewer: Mariappan Chelliah (see below for date)

Secondary Reviewer: Wendy Wilson-Lee (see below for date)



Mariappan
Chelliah

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Wilson- Lee

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BIOPHARMACEUTICS CHAPTER**BACKGROUND:**

NDA: Class 2 Resubmission of NDA 207987 (eCTD seq. 0016)
Submission Date: December 22, 2017
Name/Strength: ABLYSINOL™ (Dehydrated Alcohol Injection, USP) in 1mL and 5mL ampule
Route of Administration: Injection (into septal arterial branches)
Applicant Name: Belcher Pharmaceuticals, LLC

REVIEW SUMMARY:

The original NDA 207987 for Dehydrated Alcohol Injection, USP was submitted to FDA on February 12, 2015. The Original NDA received a Complete Response action on December 9, 2015, mainly due to the ‘withhold’ recommendation issued by the Office of Process and Facilities for the drug substance manufacturing facility.

The Biopharmaceutics review for the Original NDA submission was focused on the evaluation of the information/data supporting the bridging between the proposed drug product and the products used in the key clinical studies from the published literature. The Division of Biopharmaceutics found the provided supporting information adequate and acceptable and recommended approval of the NDA (refer to Biopharmaceutic review¹).

The current Class 2 Resubmission of NDA 207987 dated Dec 22, 2017, includes the Applicant’s responses to the deficiencies identified in the Complete Response Letter dated December 9, 2015. It is noted that the NDA’s resubmission does not include new Biopharmaceutics related information/data to be reviewed and the Resubmission remains **ADEQUATE** and acceptable from a Biopharmaceutics perspective.

RECOMMENDATION:

From a Biopharmaceutics perspective, the Resubmission of NDA 207987 for Dehydrated Alcohol Injection, USP is recommended for **APPROVAL**.

SIGNATURES:

Primary Biopharmaceutics Reviewer: *Jing Li, Ph.D., 4/19/2018*

Secondary Reviewer Name and Date: *Angelica Dorantes, Ph.D., 4/19/2018*

¹Maziar Kakhi and Elsbeth Chikhale, “Assessment of Biopharmaceutics Information” in NDA 207987 OPQ Integrated Quality Assessment dated 10/30/2015.



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MICROBIOLOGY**Product Background:****NDA:** 207987**Drug Product Name / Strength:** Ablysino/ (b) (4)**Route of Administration:** Percutaneous injection**Applicant Name:** Belcher Pharmaceuticals, LLC**Manufacturing Site:** Sintetica SA, Via Penate 5, Menderisio, Ticino, Switzerland CH-6850**Method of Sterilization:** (b) (4)**Review Recommendation:** Adequate**Theme (ANDA only):** N/A**Justification (ANDA only):** N/A**Review Summary:** Recommended for Approval on the basis of sterility assurance**List Submissions Being Reviewed:** 4/10/2018, 2/20/2018 & 12/22/2017**Highlight Key Outstanding Issues from Last Cycle:** N/A

Remarks: This is an eCTD submission. This amendment provides responses to the Agency's complete response letter, dated 12/9/2015. The microbiology deficiencies/comments included in the IQA review dated 10/30/2015 (207987.doc) were not sent to the firm in the complete response letter. The microbiology deficiency sent to the firm did not have microbiology concurrence/approval. The firm also provided gratuitous information in support of a new ampoule size (b) (4). This information is reviewed below. Some of the tables used in this review were adapted from the submission.

Concise Description Outstanding Issues Remaining: None**Supporting Documents:** 207987.doc (dated 9/3/2015) & NDA 207987 OPQ Integrated Quality Assessment.pdf (dated 10/30/2015)

The subject amendment (submitted 12/22/2017) provides a response to the microbiology deficiency sent in the Agency's complete response letter dated 12/9/2015. The deficiency sent to the firm differs from the original deficiencies and B comments finalized in the IQA review (dated 10/30/2015), which had concurrence of the secondary reviewer and ATL. The deficiency sent to the firm is italicized below.

Microbiological Aspects: You have not adequately specified the number and types of runs that will be performed (b) (4) as part of the revalidation/ requalification program for (b) (4) With regard to the endotoxin testing, you have not provided adequate validation information regarding the chromogenic kinetic method.

Response: The firm indicated that the requalification studies for the (b) (4)

The parameters to be used are the same as for production,

(b) (4)

The validation information and results for the endotoxin testing were provided. The studies included inhibition/enhancement test with the corresponding linear regression data curve and the drug product validation studies using the MVD. The inhibition/enhancement test was performed using drug product (batch # 130667) dilutions of (b) (4) (see results below); no inhibition/enhancement was observed with dilutions between (b) (4) The acceptance criterion for the test is an endotoxin recovery between (b) (4)%. The validation was conducted with 3 drug product batches (17131, 17132 & 17133), using the MVD (b) (4) The results are shown below.

Inhibition/enhancement test results:

(b) (4)

Validation results:

(b) (4)

17133

The acceptance criterion was met for all three batches at the MVD. The dilution to be used during routine testing will be (b) (4)

Adequate

Gratuitous information submitted in the 12/22/2017 re-submission:

The firm included gratuitous information for the addition of a new ampoule size, (b) (4) The relevant information and results in support of the (b) (4) ampoule presentation are reviewed below.

P.1 Description of the Composition of the Drug Product

- Description of container closure system –

Configuration	Component	Description	Manufacturer
(b) (4)	Ampoule	(b) (4) (USP) (b) (4) clear glass ampoule with score-break	(b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(P.3.5 Process validation and/or evaluation)

(b) (4)

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls***Overall Manufacturing Operation***

(P.3.3 Description of manufacturing process and process controls)

(b) (4)

(b) (4)

Adequate

Reviewer's Assessment: The information provided for the proposed manufacturing of the product configuration is deemed adequate. (b) (4)

P. 3.5 Process Validation and/or Evaluation

(b) (4)

P.5 Control of Drug Product

P.5.3 Validation of Analytical Procedures

Endotoxins

The endotoxin specification (b) (4) EU/mg) remains unchanged, but the proposed maximum dose has been changed to 5 ml (b) (4) mg/ml) per single procedure. The calculation for the endotoxin dose at the proposed endotoxins specification and maximum dose is shown below.

(b) (4)

The endotoxin dose at the proposed endotoxins specification and maximum dose as calculated by this reviewer is within the USP <85> recommendation of 5EU/kg/hr.

P.8 Stability

P.8.3 Stability Data

The stability data for 3 batches for each configuration (b) (4) batches 17130, 17131 & 17132; (b) (4) batches 17133, 17134 & 17135) were provided for the 0-month time point. The results for all batches were (b) (4) EU/mg and sterile; the acceptance criteria were met.

Primary Microbiology Reviewer Name and Date: Yeissa Chabrier-Roselló, Ph.D. (4/12/2018)

Secondary Reviewer Name and Date: Dupeh Palmer, Ph.D. (4/12/2018)



Yeissa
Chabrier Rosello

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NDA 207987(Ablysinol; Dehydrated Alcohol Injection) Review # 1

Recommendation: Complete Response

Drug Name/Dosage Form	Dehydrated Alcohol Injection, USP
Strength	(b) (4)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	BELCHER PHARMACEUTICALS LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New/NDA	02/12/2015	ALL
Quality/Response to Information Request	05/18/2015	Drug Substance, Drug Product, Microbiology
Quality/Response to Information Request	07/08/2015	Drug Substance
Quality/Response to Information Request	08/07/2015	Drug Substance, Drug Product, Process, Microbiology

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker, Ph.D.	ONDP/DNDAPI/NDBI
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Process	JiYoung Park, Ph.D.	OPF/Division III
Microbiology	Yeissa Chabrier-Roselló, Ph.D.	OPF/DMA
Facility	Donald C. Obenhuber, Ph.D.,	OPF/DIA
Biopharmaceutics	Maziar Kakhi, Ph.D.	ONDP/DB
Regulatory Business Process Manager	Don Henry	OPRO/IO
Application Technical Lead (ATL)	Mohan Sapru, Ph.D.	ONDP/DNDPI
Laboratory (OTR)	NA	
ORA Lead	NA	
Environmental Assessment (EA)	NA	

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
	Type II					
	Type III (if applicable)					
	Type IV (if applicable)					
	Other					

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Approved application	NDA 4589	Referenced application for 505(b)(2) submission

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, NDA 207987 cannot be recommended for approval due to a myriad of unresolved CMC deficiencies, including the 'withhold' recommendation issued by the Office of Process and Facility for the drug substance manufacturing facility, and applicant's inability to enlist any viable alternative facility for commercial manufacturing of the pharmaceutical grade drug substance.

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

Not applicable.

II Summary of Quality Assessments

This 505(b)(2) NDA by Belcher Pharmaceuticals, LLC proposes to use dehydrated alcohol injection ($\geq$ (b) (4) % by volume of ethanol) for performing percutaneous transluminal septal myocardial ablation (PTSMA) to treat obstruction associated with hypertrophic cardiomyopathy (HCM), a genetic disease causing thickening of the heart septum that can obstruct proper blood flow. Dehydrated alcohol acts as a potent tissue toxin that produces a small, controlled infarction when injected percutaneously into a target septal vessel. Currently, two other pharmaceutical companies, Akorn, Inc. and American Regent, Inc., are marketing unapproved dehydrated alcohol in the US under the non-registered grandfathered drugs category. This application by Belcher Pharmaceuticals, LLC is the first application to seek FDA approval for the dehydrated alcohol for injection. This proposed product received orphan designation (13-4025) for a broader indication of treatment of HCM on September 11, 2013.

A. Drug Substance [Dehydrated Alcohol] Quality Summary

Dehydrated alcohol/ethyl alcohol absolute/ ethyl alcohol ((b) (4) USP) has an applicable USP quality standard in the form of a USP-NF monograph. Structurally, the drug substance has been characterized by infrared (IR) absorption spectroscopy.

Key Raw Material: The key raw material designated by the applicant is (b) (4)

(b) (4)

Manufacturing Process and Process Controls: Based on NDA submission, the applicant has stated that commercial ethyl alcohol (b) (4) USP, is manufactured by the (b) (4) (b) (4) Regarding process controls of the (b) (4)

(b) (4)

However, details of in-process controls or in-process testing data have not been adequately described to evaluate the adequacy of the proposed in-process controls.

Control Strategy: The critical quality attributes (CQAs) of drug substance such as identity, purity, levels of impurities, and bacterial endotoxins are controlled by specification. To address the issue of drug substance attributes that could potentially impact drug product quality, the applicant revised the drug substance specification. Per drug product manufacturer's specification for drug substance, the residual levels of (b) (4) are controlled at NMT (b) (4) ppm. Given that dehydrated alcohol has an applicable USP quality standard in the form of a USP-NF monograph, the drug substance manufacturer adopted the compendial analytical methods.

Container Closure System and Retest Period: The drug substance is appropriately stored in (b) (4)

The drug substance, which is classified as flammable is to be stored in accordance with OSHA and NFPA regulations in a cool (b) (4) dry place away from heat, sparks, and direct sunlight. The applicant has proposed a (b) (4) month retest period for dehydrated alcohol stored in a dry place at (b) (4)

B. Drug Product [Dehydrated Alcohol Injection, USP] Quality Summary

The drug product is a sterile liquid for injection containing not-less-than (NLT) (b) (4) % by volume dehydrated alcohol. It is packaged in (b) (4) USP clear glass ampules. Each ampule contains 1 mL (b) (4) mg/mL) of dehydrated ethyl alcohol. (b) (4)
There are no excipients in the drug product.

Product Administration: The drug product is used for percutaneous transluminal septal myocardial ablation, and administered via a percutaneous transluminal catheter into a septal branch of the heart, to thin a hypertrophied septum for relieving left

ventricular outflow tract pressure gradient and other debilitating symptoms associated with hypertrophic obstructive cardiomyopathy.

Manufacturing Process: The drug product is manufactured by Sintetica SA, Switzerland. The drug product manufacturing process has been adequately described. Briefly, the manufacturing process involves: (b) (4)

The critical quality attributes (CQAs) potentially affected by the manufacturing process include the (b) (4)

Control Strategy: The product control strategy consists of : a) control of material attributes, b) control of the critical process parameters, c) in-process controls, and d) release testing. However, the specification initially proposed by the applicant was based on the (b) (4)

(b) (4), the proposed release specification is not adequate to control the quality of the drug product. Therefore, the Agency recommended revising the drug product specification by including quantitative tests using appropriate analytical methods. The applicant agreed with the proposal, however, this requires developing new analytical methods. The sponsor has indicated that the validated analytical methods and the final specification will be made available in October 2015. Hence, the current product release specification is not adequate.

Microbiological Aspects: Dehydrated alcohol contains no bacteriostat or antimicrobial agent or any buffer. However, ethanol by itself is an antimicrobial agent and the sponsor has demonstrated drug product sterility based on stability studies. The manufacturing process involves a (b) (4)

(b) (4) to be used for commercial production. The critical parameters for (b) (4) are adequately monitored. As per the Agency recommendation, the drug product endotoxins specification has been revised from (b) (4) EU/mg to (b) (4) EU/mg. This revised drug product endotoxins specification is based on a (b) (4) (b) (4) maximum total dose of (b) (4) mL. The applicant has indicated that the sterility and the endotoxin limits comply with the USP <71> Sterility Test and USP <85> Bacterial Endotoxin Test.

Biopharmaceutics Aspects: The method of delivery and its local action of injected dehydrated alcohol imply that little if any drug reaches the systemic circulation. No

bioavailability/bioequivalence data has been provided. Based on evaluation of biopharmaceutics aspects and risk-based considerations, it is reasonable to conclude that bridging of the to-be-marketed formulation to the formulations employed in the scientific studies (where compositional information is provided) is acceptable.

Product Container Closure: The primary packaging is (b) (4) (USP) (b) (4) clear colorless glass ampoules with score-break. Packaging components comply with compendial requirements and are standard materials used for parenteral dosage form containers.

Product Stability and Expiration Date: Based on 12-month long-term and 6-month accelerated stability data, the applicant has proposed shelf-life of (b) (4) months for dehydrated alcohol injection. However, the current stability specification includes several qualitative tests. Absent adequate quantitative testing of several product CQAs, it is difficult to accurately interpret stability data, including evaluation of any trends in the levels of possible degradants, such as (b) (4). Based on FDA's recommendation, the sponsor has revised the drug product specification extensively. The revised specification lists analytical tests to detect the degradants quantitatively and is suitable for assessing the trend of the degradants during the product shelf-life. The applicant will need to generate product stability using the revised product specification. Hence, the applicant's proposed expiry period is unacceptable at this stage.

Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	ABLYSINOL
Non Proprietary Name of the Drug Product	Dehydrated Alcohol Injection
Non Proprietary Name of the Drug Substance	Ethyl alcohol (b) (4) USP
Proposed Indication(s) including Intended Patient Population	To improve (b) (4) exercise capacity in patients with symptomatic, (b) (4), hypertrophic obstructive cardiomyopathy (b) (4)
Duration of Treatment	To be decided by the clinical review team
Maximum Daily Dose	To be decided by the clinical review team
Alternative Methods of Administration	Not applicable

Biopharmaceutics Considerations

1. BCS Designation: N/A. The proposed drug product is an injectable solution and administrated via catheter to the site of action.
 - Drug Substance: N/A
 - Drug Product: N/A
2. Biowaivers/Biostudies
 - Biowaiver Requests: None.
 - PK studies: None.

- IVIVC: None.

- **Novel Approaches:** Not Applicable.
- **Any Special Product Quality Labeling Recommendations:** Not Applicable.
- **Life Cycle Knowledge Information:** Not Applicable.

III Basis for Not Recommending Approval

1. Drug Substance Manufacturing Facility: The Office of Process and Facility has issued a 'withhold' recommendation for the following drug substance manufacturing facility:

(b) (4) (b) (4)

There is no previous inspection history for this facility. During inspection of the facility, the Agency's inspector noted that the facility is (b) (4) for the applicant. In addition, several other facility-related deficiencies have been identified. In response to the Agency's 483 letter, the President and General Manager of (b) (4) (b) (4) has stated that (b) (4)

This issue was discussed in detail with the applicant via T-con. During the T-con, the applicant acknowledged problems with the (b) (4) Inc. facility and indicated that the applicant would explore the option of listing some other facility for drug substance manufacturing. However, the Agency has not received any formal submission from the applicant listing any other facility for manufacturing of the drug substance.

2. Drug Substance Manufacturing Process: Given (b) (4) Inc. will not be manufacturing drug substance for the applicant, the validity of CMC information concerning drug substance i.e., manufacturing process, in-process controls and release specification is unclear.

3. Drug Product Specification: The applicant has not provided CMC information concerning the validated analytical methods to be included in the revised drug product specification.

4. Compatibility Studies: The applicant has not provided compatibility data concerning the drug product and the percutaneous transluminal catheter.

5. Drug Product Stability: The applicant will need to generate product stability data using the revised product specification, which includes monitoring product critical quality attributes using appropriate quantitative analytical methods.

6. Microbiological Aspects: The applicant has not adequately specified the number and types of runs that will be performed (b) (4) as part of the revalidation/requalification program for (b) (4). With regard to the endotoxin testing, the applicant has not provided adequate validation information regarding the chromogenic kinetic method.

7. Labeling: FDA has approved the trade name 'ABLYSINOL' for this drug product. The applicant has not revised the carton and container labels using the approved trade name.

OVERALL ASSESSMENT AND SIGNATURES

Overall Assessment: From CMC perspective, NDA 207987 cannot be recommended for approval due to a myriad of above-specified unresolved CMC deficiencies, including the 'withhold' recommendation issued by the Office of Process and Facility for the drug substance manufacturing facility, and applicant's inability to enlist any viable alternative facility for commercial manufacturing of the pharmaceutical grade drug substance.

Application Technical Lead (ATL) Signature:

Mohan Sapru, Ph.D.

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ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

Introduction

NDA 207987 (Dehydrated Alcohol Injection, USP, (b) (4)) is a 505(b)(2) application that provides for an injectable solution containing ethanol in not less than (b) (4)% by volume¹ per (b) (4) glass ampoule. The proposed drug product is indicated for use in improving (b) (4) exercise capacity in patients with symptomatic, (b) (4), hypertrophic obstructive cardiomyopathy (HOCM) (b) (4) by means of percutaneous transluminal septal myocardial ablation (PTSMA). The dosage form is injected at the site of action (target septal vessel) using a guiding catheter via the left main coronary artery. PTSMA reduces the septum's size by infusing a necrosis-producing ethanol solution into the septal coronary artery, causing a localized infarction.

The Applicant states that the listed drug, upon which NDA 207987 is based, is Alcohol and Dextrose Injections USP (NDA 004589, B. Braun Medical Inc.). The listed drug was approved in 1946. NDA 004589 provides for two strengths (by volume) of alcohol, namely 5% and 10% ethyl alcohol² and is indicated for increasing caloric intake³. It is noted that neither the composition of the listed drug nor its indication correspond to the proposed drug product. On June 2, 2014, B. Braun Medical Inc. informed the FDA that it is withdrawing NDA 004589 since this drug product is no longer manufactured or marketed⁴.

NDA 207987 does not contain any bioavailability/bioequivalence data. The Applicant states in Section 2.7.2.2.1⁵ that no PK studies of alcohol used for PTSMA procedures were found in the published literature. The method of delivery and its local action imply that little if any drug reaches the systemic circulation. The Biopharmaceutics review will therefore only focus on the assessment of the bridging of the to-be-marketed (TBM) drug product to the drug product formulations referenced in the retrospective cohort literature studies to support safety and efficacy claims.

18. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The Applicant has not submitted any *in-vitro* dissolution test and acceptance criteria pertaining to the quality control and bioavailability of Dehydrated Alcohol Injection, USP, (b) (4). The proposed drug product is designed to be administered as a

(b) (4)

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>

³ \\cdsesub1\evsprod\nda004589\0007\m1\us\11-forms\356h.pdf

⁴ \\cdsesub1\evsprod\nda004589\0007\m1\us\12-cover-letter\cv1.pdf

⁵ \\cdsesub1\evsprod\nda207987\0000\m2\27-clin-sum\summary-clin-pharm.pdf

solution via a percutaneously inserted catheter and is injected directly at the site of action. Therefore, *in-vitro* dissolution testing and acceptance criteria are not relevant.

Reviewer's Assessment:

The lack of an *in-vitro* dissolution test and acceptance criteria is acceptable.

19. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The formulations referenced in the retrospective cohort studies (literature supporting safety and efficacy claims), where compositional information is provided, are adequately bridged to the TBM formulation. There is insufficient information to establish a bridge between the literature-cited drug products in which information regarding the composition of the formulations is not provided and the TBM formulation.

Table 1 below shows the composition of the drug substance and drug product.

Table 1: Drug substance and drug product composition

Material	Function	Quantity (mg/mL)	Reference to Standard
Dehydrated Alcohol (ethanol)	Drug substance	(b) (4)	USP
		(b) (4)	USP
TOTAL		(b) (4)	

NDA 207987 relies entirely on retrospective cohort clinical studies sourced from the open scientific literature. The Applicant has performed no clinical investigations of its own to verify its safety and efficacy claims. An information request was sent to the Applicant on April 17, 2015 with the following comments regarding the bridging of the formulations referenced in the cited literature studies to the TBM formulation presented in Table 1 above:

FDA Comment: *Your submission relies on numerous studies from the published literature to support safety and efficacy. Provide a table with columns describing:*

- Cited study critical to demonstrating the safety and efficacy of your proposed drug product,*
- Precise composition of administered drug product in the cited study,*
- Administered dose (and duration of delivery, where relevant) in the cited study,*

d. Bridging justification: Where the administered drug product in your cited study differs from your proposed drug product, provide a justification why you can extrapolate its results to the expected clinical response from the administration of your proposed drug product.

Applicant's Response (summarized):

On May 18, 2015 the Applicant provided a response⁶. All literature references used to support safety and efficacy claims were tabulated (pages 42-46). From the 45 cited studies only 18 contained limited compositional information, e.g. alcohol 96%, "absolute ethanol" and alcohol $\geq 98\%$. There is no certainty that any of the drug products used in the cohort studies exactly correspond to the Applicant's proposed drug product as shown in Table 1. Furthermore, the dose volume, rate, and duration used were not stated in all the studies.

Reviewer's Comment: For the literature sources in which compositional information is provided a scientific bridge to the proposed drug product (and TBM formulation) is conceivable based on input from Dr. Fortunato Senatore (medical officer, DCRP) stated in July 6, 2015 in an FDA-internal email:

- Administration of product (alcohol 96% in the studies by Veselka, "absolute ethanol" in the study by Nagueh, and alcohol $> 98\%$ as described by Baggish) as described in the literature appears to be therapeutically equivalent to the Applicant's proposed product of 99^{(b)(4)}%. This is based on the Veselka studies showing a hemodynamic improvement and subjective improvement of symptoms using 96%.
- I agree with your opinion that systemic exposure would be essentially the same if alcohol 96%, "absolute ethanol", alcohol $> 98\%$ and the proposed dehydrated alcohol (99^{(b)(4)}%) were administered because of local delivery and action at the site of delivery.
- I do not consider 99^{(b)(4)}% alcohol as opposed to 98% to pose a safety risk to the patient.

Based on the above points, a risk-based consideration leads to the conclusion that bridging of the TBM formulation to the formulations employed in the scientific studies where compositional information is provided is adequate.

There is insufficient information to establish a bridge between the literature-cited drug products in which information regarding the composition of the formulations is not provided and the TBM product.

⁶ [\\cdsesub1\evsprod\nda207987\0006\m1\us\multiple-module.pdf](#)

Reviewer's Assessment:

The formulations referenced in the retrospective cohort studies (sourced from the open scientific literature), in which compositional information is provided, are adequately bridged to the TBM formulation. Therefore, these clinical studies can be used to support the safety and efficacy of the TBM formulation. The formulations referenced in the literature where the composition is not stated do not provide enough information to establish a bridge between them and the TBM drug product. The inclusion of these latter clinical studies to support the safety and efficacy of the TBM formulation is left to the discretion of the reviewing Medical Officer.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS****Reviewer's Conclusion, Recommendation and Signature:**

The Division of Biopharmaceutics has reviewed the formulation bridging information in NDA 207987 and finds it to be acceptable. From a Biopharmaceutics perspective, NDA 207987 for Dehydrated Alcohol Injection, USP, (b) (4) is recommended for APPROVAL.

September 1, 2015

Maziar Kakhi, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
ONDP/OPQ

Team Lead Concurrence and Signature:

I concur with Dr. Kakhi's assessment and recommendation of approval for NDA 207987.

September 1, 2015

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
ONDP/OPQ

ASSESSMENT OF MICROBIOLOGY

20. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

*The Microbiology reviewer's assessment is detailed below and the deficiencies found are listed at the end of the document under the "list of deficiencies to be communicated"-Microbiology.

Applicant's Response:

Reviewer's Assessment:**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA****P DRUG PRODUCT****P.1 Description of the Composition of the Drug Product**

- Description of drug product –

The drug product is an injectable solution containing Ethanol in not less than (b) (4) % by volume

- Drug product composition –

Ingredient	Content per mL
Dehydrated Alcohol (ethanol)	(b) (4)

- Description of container closure system –

Configuration	Component	Description	Manufacturer
(b) (4)	Ampoule	(b) (4) (USP) (b) (4) clear colorless glass ampoule with score-break	(b) (4)

P.2 Pharmaceutical Development**P.2.5 Microbiological Attributes**

- Container-Closure and Package integrity -
(3.2.P.3.5.5.1 process-validation.pdf, pages 34-41 of 47)

The container/closure system used for validation was: Same as the drug product

Study/Report # and date: Not Provided

15 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

(b) (4)

(b) (4)

Acceptable

P.7 Container Closure System - See P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

(3.2.P.8.1 stability-summary.pdf, page 9 of 9)

Proposed Expiry: (b) (4) months

P.8.2 Post-Approval Stability Protocol and Stability Commitment

(3.2.P.8.2 postapproval-stability.pdf)

The product stability specification includes the following microbiological tests:

Test	Test Method	Specification
Bacterial Endotoxins	USP <85>	< (b) (4) EU/mg
Sterility	USP <71>	Sterile

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25±2°C

Test	Time (Months)							
	0	3	6	9	12	15	18	24
Bacterial Endotoxins	X							X
Sterility	X							X

Post Approval Stability Commitment

The applicant states that the proposed expiry date could be extended as real-time data is generated on three post-approval production batches supporting the expiry beyond (b) (4) months. The applicant commits to inform the Agency via Annual Reports.

Note to reviewer: According to the March 2014 Guidance “CMC Post Approval Manufacturing Changes To Be Documents in Annual Reports”, the extension of product expiration based on stability is now acceptable to be included in annual reports (Appendix section 7.1).

Acceptable

P.8.3 Stability Data

Stability storage conditions: 25°C ±2

Test	Time (Months)
	0
Bacterial Endotoxins	< (b) (4) EU/mg
Sterility	Sterile

Acceptable

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed lot #: 13227

The batch records confirm that validated (b) (4) process and component (b) (4) processes were used for the manufacture of the exhibit batch.

Acceptable

R.2 Comparability Protocol – No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT (draft-labeling-text.pdf)

(b) (4)

Store (b) (4) at 20 to 25°C (68 to 77°F) (b) (4)
Do not refrigerate (b) (4)

Route of administration: (b) (4) injection; Container: Single dose

Acceptable

2.3.P.7 Container/Closure System

21. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment:

See response in question #35 above

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

22. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment:

See response in question #35 above

23. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

See response in question #35 above

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The product quality microbiology reviewer does not recommend approval on the basis of sterility assurance. Specific comments and deficiencies are provided at the end of the document under section II, "List of deficiencies to be communicated".

Yeissa Chabrier-Roselló, Ph.D.- 10/21/2015

Secondary Review Comments and Concurrence: I concur.

Dupez Palmer, Ph.D. 10/21/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

24. Is the applicant's claim for categorical exclusion acceptable?

25. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

The applicant has requested categorical exclusion from environmental assessment for the following reason: The maximum expected use of the drug product is (b) (4) kg/year. Assuming 100% of the drug product is excreted unchanged, this corresponds to a discharge of (b) (4) ppb/day into aquatic environment. This amount is far lower than the the NMT 1 ppb limit required for environmental assessment exemption under 21 CFR § 25.31(b).

Reviewer's Assessment: Adequate

The applicant's claim for categorical exclusion from environmental assessment appears reasonable and it may be granted.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The drug product may be categorically exempted from environmental assessment. Therefore, environmental assessment is not required for the approval of the drug product.

Mariappan Chelliah, 27-Oct-2015

Secondary Review Comments and Concurrence:**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1****Labeling & Package Insert****1. Package Insert****(a) "Highlights" Section (21CFR 201.57(a))**

ABLYSINOL® (dehydrated alcohol injection, USP) (b) (4)
Initial U.S. Approval: _____

INDICATIONS AND USAGE

ABLYSINOL is (b) (4) indicated to improve (b) (4) exercise capacity in (b) (4) with symptomatic, (b) (4) hypertrophic obstructive cardiomyopathy (b) (4)

DOSAGE AND ADMINISTRATION

(b) (4)

DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		Adequate
Dosage form, route of administration		Adequate
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		Adequate

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	injection	Adequate
Strengths: in metric system	1 mL	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	N/A	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

ABLYSINOL® (Dehydrated Alcohol Injection, (b) (4)) is a sterile, preservative free solution of $\geq$ (b) (4) % by volume ethyl alcohol and no excipients. (b) (4)
It has a molecular formula of C₂H₆O and a molecular weight of 46.07.

(b) (4)

Dehydrated Alcohol Injection, USP is a potent tissue toxin (b) (4)
Ethanol is a clear, colorless, volatile, and flammable liquid miscible with water. It has the following structural formula:



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	ABLYSINOL	Adequate
Dosage form and route of administration	To be administered by (b) (4) injection	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	$\geq$ (b) (4) % by volume ethyl alcohol	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	No excipients	Adequate
Statement of being sterile (if applicable)	Sterile	Adequate
Pharmacological/ therapeutic class	Tissue toxin	Adequate
Chemical name, structural formula, molecular weight	Ethyl alcohol, molecular formula of C ₂ H ₆ O and a molecular weight of 46.07	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Volatile flammable liquid	Adequate

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

ABLYSINOL® (Dehydrated Alcohol Injection, USP)
Carton of 10- 1 mL Single-Dose Ampules NDC 62250-105-10

(b) (4)
Do not refrigerate. (b) (4)

Store at room temperature, between 20°C and 25°C (68°F and 77°F).

Highly flammable, store away from any heat source.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	1 mL	Adequate
Available units (e.g., bottles of 100 tablets)	Carton of 10 -1 mL ampules	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC # is listed	Adequate
Special handling (e.g., protect from light, do not freeze)	(b) (4) Do not refrigerate. (b) (4)	Adequate
Storage conditions	20 - 25°C	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Sintetica SA Via Penate 5 6850 Mendrisio, Switzerland	Adequate

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Sponsor has not updated the label with the proprietary name ABLYSINOL, which has been granted by FDA.	Not Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	NLT (b) (4) %.	Adequate
Route of administration (21.CFR 201.100(b)(3))	(b) (4)	Adequate
Net contents* (21 CFR 201.51(a))	1 mL	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Contains no excipients	Adequate
Lot number per 21 CFR 201.18	Lot # is printed	Adequate
Expiration date per 21 CFR 201.17	Exp dates is printed	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Rx only is printed	Adequate
Storage (not required)	20-25°C	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC# 62250- (b) (4)	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Bar code is printed	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Belcher Pharmaceuticals, LLC	Adequate
Others	N/A	N/A

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

****Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.**

Conclusion: Not Adequate

FDA has granted the trade name ABLYSINOL for this drug product. The sponsor has not revised the container label with the trade name.

Deficiency: Provide revised container label with the trade name printed on it.

2) Carton Labeling



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Sponsor has not updated the label with the proprietary name ABLYSINOL, which has been granted by FDA.	Not Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	NLT (b) (4) %.	Adequate
Net contents (21 CFR 201.51(a))	1 mL	Adequate
Lot number per 21 CFR 201.18	Lot # is printed	Adequate
Expiration date per 21 CFR 201.17	Exp date is printed	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Contains no excipients	Adequate
Sterility Information (if applicable)	Sterile	Adequate
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Rx only is printed	Adequate
Storage Conditions	20-25°C	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC# 62250- (b) (4) (justifies carton of 10 ampules)	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Bar code is printed	Adequate
Name of manufacturer/distributor	Belcher Pharmaceuticals, LLC Largo, FL 33777	Adequate
“See package insert for dosage information” (21 CFR 201.55)	(b) (4)	Adequate
“Keep out of reach of children” (optional for Rx, required for OTC)	Not listed	Adequate
Route of Administration (not	(b) (4)	Adequate

required for oral, 21 CFR
201.100(d)(1) and (d)(2))

Conclusion: Not adequate

FDA has granted the trade name ABLYSINOL for this drug product. The sponsor has not revised the carton label with the trade name.

Deficiency: Provide revised carton label with the trade name printed on it.

OVERALL ASSESSMENT AND SIGNATURES: LABELING**Reviewer's Assessment and Signature:**

The container and carton labels are not adequate at this time. The sponsor must provide revised labels that contain the trade name.

Mariappan Chelliah 27-Oct-2015

Secondary Review Comments and Concurrence: I concur.

Wendy Wilson-Lee 03-SEP-2015

II. List of Deficiencies Already Communicated/To Be Communicated

Drug Substance: Following are the Drug Substance Deficiencies to be communicated to the applicant.

1. Referring to section 2.3.S.4.1 (drug Substance specification by (b) (4) two acceptance criteria are noted for (b) (4) % and NMT (b) (4) ppm), harmonize the specification as per IR dated 23 June 2015.
2. In drug substance controls, test method numbers and method descriptions are provided; however, some of the test method names (e.g. GC) are not noted in S.4.2., in TM112. Specify the test methods in the drug substance specification.
3. Based on the information provided for drug Substance stability, a retest period of (b) (4) month can be granted for ethyl alcohol. Extra polation of retest period is not acceptable due to the lack of data at accelerated or intermediate conditions (ICH Q1E).

Drug Product

1. Provide compatibility data between the drug product and the percutaneous transluminal catheter. *(this deficiency has already been communicated to the sponsor)*
2. Provide validated analytical methods to reflect the recent revision to the proposed drug product specification. *(this deficiency has already been communicated to the sponsor)*
3. Since the drug product specification has been revised extensively, we recommend that you update the batch analysis data that complies with the revised drug product specification.
4. The specification used for the stability evaluation of the drug product includes many tests that are only qualitative. We acknowledge that Belcher has recently revised the drug product specification and is currently developing analytical methods that are quantitative. Provide stability data for the drug product as per the revised drug product specification.
5. We recommend that you evaluate the photostability of the drug product using the revised specification.

Microbiology Deficiencies

1. Please state the number and types of runs that will be performed (b) (4) as part of the revalidation/requalification program for (b) (4)
2. With regard to the endotoxin testing, please provide validation information corresponding to the chromogenic kinetic method to include the acceptance criteria, maximum valid dilution and the proposed drug product dilution for release and stability testing.

Microbiology Review Comments

1. The validation information for the container/closure integrity test (CCIT) by leak test and microbial ingress is acknowledged. However, please note that the information/data for only one CCIT suffices, therefore, the microbial immersion validation data was not reviewed and only the leak test method was evaluated. If the microbial ingress validation is the preferred method, please clearly indicate so. The absence of further comments regarding the microbial ingress test is not a recommendation for further performance of the test.
2. It is noted that the Biological Indicator (BI) from (b) (4) lot # S-455 used in the (b) (4) validation of the (b) (4) has an associated Certificate of Analysis and (b) (4) meets the US FDA/RIT protocol or meets the performance parameters published in the current United States Pharmacopeia. Please note that existing FDA CDRH

guidance on (b) (4) for BIs as derived from the draft *Guidance for Industry Biological Indicator Premarket Notification [510(k)] Submissions* (2001) is specifically directed towards BIs used to monitor sterilization processes in healthcare facilities and specifically not directed towards “BIs intended for use in a manufacturing setting.” CDER does not generally recognize the acceptance criterion that the minimum (b) (4) % positive BIs subjected to a (b) (4) (b) (4). Therefore, please consider the use of more suitable BIs and/or (b) (4) for future sterilization validation studies.

Label/Labeling

1. Provide revised container label with the trade name printed on it.
2. Provide revised carton label with the trade name printed on it.

III. Attachments

- A. Lifecycle Knowledge Management: Not Applicable.

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

/s/

BRIAN L PROCTOR
06/27/2018