CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208630Orig1s000

PRODUCT QUALITY REVIEW(S)

1.12.14 Environmental Analysis

NX Development Corporation (NXDC) is claiming a categorical exclusion from providing an environmental assessment of 5-aminolevulinic acid (5-ALA) because approval of this orphan drug will not significantly affect the quality of the human environment (21 CFR 25.31(b)). FDA's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The highest number of vials expected to be produced for direct use in the next 5 years is (b) (4). Each vial contains 1,170 mg of the 5-ALA active moiety (b) (4) kg/year). This will result in an amount of active moiety entering the aquatic environment of less than 1 ppb. 5-ALA is used currently as an agricultural fertilizer at the metric ton basis in worldwide utilization and as such the pharmaceutical addition to the footprint will be negligible. To the applicant's knowledge, no extraordinary circumstances exist.

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/s/

JONATHAN T DOW
06/15/2017

Recommendation: APPROVAL

NDA 208630
Review #1

Drug Name/Dosage Form	Gliolan(5-aminolevulinic acid hydrochloride)oral solution
Strength	1.5 g 5-ALA HCl per vial
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	NX Development Corp
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	12/6/2016	ALL
Amendment	3/3/2017	Microbiology
Amendment	3/10/2017	Drug Product, Microbiology
Amendment	4/7/2017	Process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	OPQ/ONDP/DNDPAPI/BII
Drug Product	John Amartey	OPQ/ONDP/DNDPII/BVI
Process	Yongming Lu/Pei-I Chu	OPQ/OPF/DPAII/BVI
Microbiology	Erika Pfeiler	OPQ/OPF/DMA/BI
Facility	Carl Lee/Vidya Pai	OPQ/OPF/DIA/BIII
Biopharmaceutics	None needed	
Regulatory Business Process Manager	Thao Vu	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Danae Christodoulou	OPQ/ONDP/DNDPII/BVI
Laboratory (OTR)	NA	
ORA Lead		
Environmental Analysis (EA)	John Amartey	OPQ/ONDP/DNDPII/BVI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate		Martin Haber
	Type III					Sufficient info. in application
	Type III					Sufficient info. in application

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110,655	(pre-NDA only)

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

From CMC perspective the application is recommended for approval.
There are no pending CMC deficiencies.
Manufacturing facilities received acceptable cGMP recommendation (see Panorama).

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.
Duration of Treatment	NA
Maximum Daily Dose	15.65 mg 5-ALA/kg
Alternative Methods of Administration	NA

The drug product is (b) (4) lyophilized powder of 1.5 g 5-ALA HCl in a glass vial capped with a (b) (4) rubber stopper with Al crimp. The powder (1.17 g 5-ALA) is dissolved in 50 ml tap water (23.4 mg 5-ALA/ml) and administered to the patient orally based on body weight (15.65 mg/ 5-ALA/kg or 0.666ml solution/kg).The solution is administered 3 (b) (4) h prior to anesthesia.

B. Quality Assessment Overview

Gliolan (5-aminolevulinic acid hydrochloride) or 5-ALA HCl for oral solution is proposed as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. Since malignant glioblastoma is fatal, with no known cure, 5-ALA HCl received fast track designation on 12/21/2015 and orphan track designation on 1/15/2013. The NDA is filed as a 505(b)(2) application relying on published literature and foreign studies. Gliolan has been approved in about 40 countries outside the US. The active moiety, 5-ALA HCl has been approved in the US as a topical solution for photodynamic therapy as Ameluz, NDA 208081and Levulan, NDA 20965. 5-ALA is metabolically converted to protoporphyrin IX . which accumulates in tumor cells and epithelial tissue. This results in fluorescence of malignant gliomas, which allows fluorescence–guided surgery. The chemical name of 5-ALA HCl is 5-amino-4-oxo-pentanoic acid hydrochloride.

The drug substance is referenced to DMF (b) (4) by (b) (4) (b) (4) The DMF was reviewed by Dr. Martin Haber and found adequate. Details of the manufacturing process, scale and characterization of impurities are

included in the DMF. One of the degradation products, (b) (4) (b) (4) therefore a structural alert for mutagenicity. The proposed specification in the drug substance is (b) (4) %. During the pre-NDA meeting of 7/16/2015, the applicant was asked to conduct a mutagenicity analysis and (b) (4) acceptance limits. No evidence of mutagenicity was found from S. typhimurium reverse mutation assay (Ames test), *in vitro* micronucleus assays in lymphocytes and *in vivo* mouse bone marrow micronucleus tests and the limit of (b) (4) was not changed. This analysis was acceptable by the Pharmacology Toxicology reviewer Dr. Ron Honchel and therefore the limit of (b) (4) % is acceptable. Stability data support a retest date of (b) (4) months when stored at (b) (4). A large body of data (batch analysis results) and process validation support the drug substance manufactured at (b) (4)

The drug product section of the NDA was reviewed by Dr. John Amartey and found adequate. As described above, the drug product is 1.5 g lyophilized drug substance without excipients presented in a glass vial capped with a rubber stopper with Al crimp seal. The lyophilized powder is reconstituted with 50 ml tap water (equivalent t 1.17 g 5-ALA) or 30 mg/ml 5-ALA HCl (equivalent to 24.3 mg/ml 5-ALA) and dosed at 15.65 mg/kg body weight or 0.666ml/kg. The formulation is (b) (4)

(b) (4)

(b) (4) Stability data and leachables/extractables study support (b) (4) (b) (4) in the container. Two degradants are controlled in the drug product, (b) (4) to NMT (b) (4) % and (b) (4) at NMT (b) (4) %. The latter was found not to be mutagenic. These are controlled consistent with ICH Q3B(R) but the drug is intended to be dosed only during surgery. The applicant was asked to provide relative retention times for all impurities identified during analytical method validation and submitted the information. Analytical validation included comparisons of two HPLC methods and all methods are found suitable for their intended use. Stability data for the lyophilized powder are available up to 60 months, and microbial limits up to 36 months. A 36-month expiry is granted for the drug product. The reconstituted oral solution is stable up to 24 h at 25°C/60%RH. The reconstituted oral solution is for a single dose, and the remainder solution is to be discarded.

The process team (Dr. Yongming Lu) asked the applicant to (b) (4) (b) (4) based on historical data and the applicant agreed. The production scale batch is (b) (4) L for about (b) (4) vials. The drug product manufacturer is IDT Biologika GmbH, Germany. A large body of manufacturing data (batch analysis) and process validation support the drug product. The microbiology team (Dr. Erika Pfeiler)

reviewed this product as a non-sterile product and concluded that microbial controls and testing methods USP<61> and <62> are suitable.
The two manufacturing facilities received acceptable cGMP recommendation by the facilities reviewer Mr. Carl Lee. No product-specific, pre-approval inspection was performed for the drug substance manufacturer, (b) (4), but the 2014 pre-approval and cGMP inspection covered the non-sterile API profile. The IDT drug product manufacturing facility was also evaluated based on review of inspections conducted in 2016, 2014 and 2012. One labeling and secondary packaging site, (b) (4) was also evaluated by review of inspections conducted in 2015 and 2013 and found acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

The established name is 5-aminolevulinic acid hydrochloride and is in the salt form. The previously approved products Ameluz and Levulan use the salt form. Instructions for reconstitution are based on the salt form globally. The established name is recommended to remain as the salt form.
The instruction for disposal of the remainder oral solution after reconstitution and dosing is critical because the solution is not stable beyond 24h and should be prominent in the PI.
DMEPA did not accept the proposed global proprietary name Gliolan because of the "gli" prefix and the accepted proprietary name is now "Gleolan".

D. Final Risk Assessment (see Attachment)

Danae Christodoulou

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background: -

NDA/ANDA/BLA: 208630

Drug Product Name / Strength: Gliolan (5-amino-4-oxo-pentanoic acid hydrochloride)/1.5 g/vial

Route of Administration: Oral

Applicant Name: NX Development Corp

Manufacturing Site: IDT Biologika GmbH

Method of Sterilization: Not applicable, product is nonsterile

Review Summary: Recommended for approval

List Submissions being reviewed: 06 December 2016, 03 March 2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: N/A

Remarks Section: N/A

S Drug Substance

Not applicable. Product is nonsterile, intended for oral administration.

P.1 Description of the Composition of the Drug Product

- Description of drug product –
  - Product is a lyophilized powder intended for reconstitution to 30 mg/mL with drinking water prior to administration. Product is intended for single use.
- Drug product composition –

Component	Purpose	Quantity/Vial
5-ALA HCl	Drug Substance	1.5 g
		(b) (4)

- Description of container closure system –
  - The container closure system consists of a clear, colorless 50 mL vial, (b) (4) (b) (4) stopper, and aluminum crimp seal.

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbiological quality of the product.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Reviewer's Assessment: N/A, product is nonsterile. CCIT is not assessed.

Antimicrobial Effectiveness Testing

Reviewer's Assessment: N/A, product is intended for single use. Inclusion of a preservative and subsequent AET is not required.

P.3 Manufacture

P.3.1 Manufacturers

Drug product

IDT Biologika GmbH
Am Pharmapark
Dessau-Rosslau, 06861, Germany

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(b) (4)

Reviewer's Assessment: The manufacturing process described in the submission is adequate to ensure the microbiological quality of a nonsterile drug product.

Aseptic Fill Manufacturing Process/Terminal Sterilization Process

Reviewer's Assessment: N/A, product is nonsterile.

Buildings and Facilities

Reviewer's Assessment: N/A, these items are not typically assessed in the review for the manufacture of a nonsterile product.

Sterilization/Depyrogenation of containers, closures, equipment and components

Reviewer's Assessment: N/A, product is nonsterile.

Environmental Monitoring

Reviewer's Assessment: N/A, these items are not typically assessed in the review for the manufacture of a nonsterile product.

P. 3.5 Process Validation and/or Evaluation

Reviewer's Assessment: N/A, process validation is not typically assessed in the microbiology review for the manufacture of a nonsterile product.

Bulk Drug Solution Components that are Sterilized Separately

Reviewer's Assessment: N/A

Component/Equipment Sterilization

Reviewer's Assessment: N/A

Component Depyrogenation

Reviewer's Assessment: N/A

Media Fill Procedures and Specification

Reviewer's Assessment: N/A

Actions Concerning Product When Media Fills Fail

Reviewer's Assessment: N/A

P.5 Control of Drug Product

P. 5.1 Specification

Product should contain NMT (b) (4) CFU/g TAMC, NMT (b) (4) CFU/g TYMC, and *Escherichia coli* should be absent. Testing is performed using methods described in USP <61> and USP <62>, respectively.

Reviewer's Assessment: The specification, which is in agreement with USP <1111>'s specification for non-aqueous preparations for oral use, is adequate.

Note to Reviewer: Since this product is non-aqueous, it is low-risk for proliferation of *Burkholderia cepacia* complex organisms. A release specification for the absence of these organisms is not necessary.

P.5.2 Analytical Procedures

Microbial enumeration is performed using methods described in USP <61> membrane filtration method.

The absence of specified microorganisms is tested using methods described in USP <62>, utilizing MacConkey Broth and MacConkey Agar.

Reviewer's Assessment: Methods described are adequate.

P.5.3 Validation of Analytical Procedures

(b) (4)

Reviewer's Assessment: Adequate method suitability testing was performed.

Absence of Specified Microorganisms

(b) (4)

Acceptance criteria for this testing were met.

10 March 2017 Response: The applicant provided routine testing methods. This information was incorporated into section P.5.2.

Reviewer's Assessment: Adequate method suitability testing was performed.

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment: See P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Stability studies were conducted under long-term, intermediate, and accelerated conditions. (b) (4) The applicant states that since this testing is more stringent than microbial limits testing, that it acts as a surrogate for meeting the current microbiological stability specification (which is the same as the release specification). The proposed shelf-life specification is storage at 25°C for 36 months.

Reviewer's Assessment: The applicant's proposal (b) (4) stability data is adequate. Since the product is non-aqueous, (b) (4) the likelihood for microbial proliferation is low, and can be sufficiently monitored by ongoing stability studies after commercialization.

Adequate

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to placing one batch into the stability program annually under long-term storage conditions. Product will have the same microbiological specification as for release, and will be tested at 0, 12, 24, and 36 months.

Reviewer's Assessment: The post-approval stability protocol and commitment are adequate.

P.8.3 Stability Data

(b) (4)

Reviewer's Assessment: See P.8.1. Data are adequate.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: N/A

A.2.1 Materials of Biological Origin

Reviewer's Assessment: N/A

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: N/A

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: N/A

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: N/A

R Regional Information

Executed Batch Records

Records from batch 160176 were provided.

Reviewer's Assessment: The information provided is adequate.

Comparability Protocols: N/A

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

2.A. Package Insert

Product is reconstituted for administration using drinking water. Following reconstitution, product may be held in a (b) (4) vial for up to 24 hours at room temperature (25°C). Product is single-use.

Reviewer's Assessment: Since this product is nonsterile, and is intended for oral administration, no further information is necessary to support a 24 hour post-reconstitution hold time. Microbial proliferation to a level that would result in an exposure risk is unlikely in this time period.

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

Reviewer's Assessment: Product is recommended for approval on the basis of quality microbiology.

List of Deficiencies:

The following deficiencies are considered: ☐ **Major** ☐ **Minor**
N/A

Primary Microbiology Reviewer Name and Date: Erika Pfeiler, Ph.D.

Secondary Reviewer Name and Date: John Arigo, Ph.D.

Erika Pfeiler

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John Arigo

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Attachment A						
Product Attribute/CQA	**Factors that can impact the CQA**	**Probability (O)**	**Severity of Effect (S)**	**Detectability (D)**	**FMECA RPN Number**	**Comment/Risk after review**
Drug Substance: 5-aminolevulinic acid HCl (5-ALA HCl)						
Identity	Method of [redacted]	2	3	2	12 (L)	Risk is acceptable. (b) (4) [redacted] adequately controlled. (b) (4) testing methods used.
Assay, Purity	Method of Manufacture Suitability of analytical methods	3	3	2	18 (L)	Acceptable. Risk is mitigated through controls in the drug substance and product. Structural alerts were assessed for mutagenicity and are negative.
Drug Product: 5-ALA HCl for oral solution						
Assay, purity	Formulation, analytical methods, control of drug substance, and process parameters	2	3	3	18 (L)	Risk is acceptable. No excipients in formulation. (b) (4) (b) (4) analytical methods are suitable.
(b) (4)	(b) (4)	5	3	2	30 (M)	Acceptable. Risk is mitigated by drug substance and product specification for (b) (4)
Microbial limits	Components, manufacturing process	2	3	2	12 (L)	Risk is acceptable. Controlled by specification in the finished product (USP<61> and <62>).
Accuracy of dose (oral solution)	(b) (4)	5	3	2	30(M)	Acceptable. Risk is mitigated by (b) (4) (b) (4) (Clinically relevant attribute).
Manufacturing Facilities (See Facilities review)	IDT Biologika GmbH				78(M)	Acceptable. OPF recommends a post-approval inspection to evaluate the manufacturing process of Gliolan, particularly the (b) (4) process.

Danae Christodoulou

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