CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216264Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 216264, Indigo Carmine
OPQ Integrated Quality Assessment (IQA)

Table of Contents

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 216264
Assessment 1

Drug Product Name	Bludigo (indigotindisulfonate sodium) injection
Dosage Form	Injection
Strength	0.8% (40 mg/5 mL)
Route of Administration	Intravenous injection
Rx/OTC Dispensed	Rx
Applicant	Provepharm SAS, France
US agent, if applicable	Arvind Pathak

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	09/09/2021	OPQ-CMC, Microbiology, Process/Facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Joe Leginus	Zhengfu Wang (T:Su Tran)
Drug Product	Ann Marie Russell	Danae Christodoulou
Facilities/Process	Ash Bekele	Yuansha Chen
Microbiology	Ash Bekele	Christine Craig
Biopharmaceutics	Jing Li	Om Anand
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Eldon E. Leutzinger	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	12/22/2021	N/A
	III			Adequate based on information in NDA	5/03/2022	N/A

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	137856	Indigo Carmine

2. CONSULTS: N/A

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

No issues remain from the primary reviews of Chemistry, Manufacturing and Controls (CMC) and from the manufacturing facilities. Hence, Bludigo (indigotindisulfonate sodium) injection meets all applicable standards to support the identity, strength, quality and purity that it purports.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product (Indigo Carmine) is a sterile aqueous solution of 40 mg of Indigotindisulfonate sodium in 5 mL (8 mg/mL). It is packaged in a 5 mL (b) (4) brown glass ampule (USP compliant). The color of the solution is blue (b) (4) Citric acid (b) (4) /sodium citrate (b) (4) is used (if necessary) for adjustment of pH to 3.0 – 6.5. (b) (4) . There is a (b) (4) It is intended for use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures.

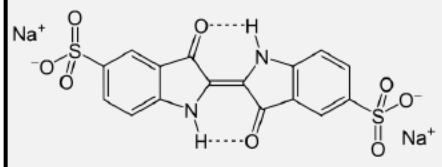
Proposed Indication(s) including Intended Patient Population	For use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures.
Duration of Treatment	Single dose
Maximum Daily Dose	(b) (4) 5mL intravenously over 1 minute
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

DESCRIPTION:

Indigo Carmin is Indigotindisulfonate Sodium, $C_{16}H_8N_6Na_2O_8S_2$ (MW 466.36), and has the following chemical structure:



It is a 5,5'-disulfonic acid disodium salt, (b) (4) , a purple-colored solid and is water soluble (10 g/L @ 25^0C). it is also known as indigotine (or FD&C Blue #2, a pH indicator), approved as a food dye in the U.S. and E.U. The acid form has IUPAC name 2-(3-hydroxy-5-sulfo-1*H*-indol-2-yl)-3-oxoindole-5-sulfonic acid.

Assessment of Chemical Type and Drug Classification Code (ATL)
It is the intense, dark blue color of **Indigo Disulfonate Sodium** (see previous section) that provides the contrast in imaging and thereby in concert with 21 CFR 314.3(A)(b)(4) **is the drug substance**. It is already marketed in the U.S., but without an approved NDA. Hence, the application type is 7 (Drug Already Marketed But Without Approved NDA).

Summary of Assessments: Indigotin Disulfonate Sodium
The drug substance review was completed on 1/14/2021 (Joe Leginus, Ph.D.) with no approvability issues identified (including DMF (b) (4)), and hence is determined to be adequate. DMF (b) (4) is determined to be adequate (12/22.2021, Joe Leginus) to support the drug product

Drug Product:

DESCRIPTION:
The drug product (Indigo Carmine) is a sterile aqueous solution of 40 mg of Indigotindisulfonate sodium in 5 mL (8 mg/mL). It is packaged in a 5 mL (b) (4) brown glass ampule (USP compliant). The color of the solution is blue to bluish purple. Citric acid (b) (4)/sodium citrate (b) (4)) is used (if necessary) for adjustment of pH to 3.0 – 6.5. (b) (4). There is a (b) (4)

Summary of Assessments: Indigo Carmine
The lion's share of issues identified for drug product fall into the area of **Quality Controls** and specifically with Specifications and Analytical Methods.

Others for **Production Chemistry** concern product batches used in clinical studies (PVP-191C01, PVP-201C02) their representativeness to the commercial scale product (generated in the 74 day letter); these along with additional ones identified at mid-cycle have all been **Resolved**. Microbiological Quality is summarized (from the Microbiology review) later in this document. Some of the others identified later ranged from a (b) (4) on changing methods from (b) (4) (an issue that impacts identification, assay and related substances for drug product), to **stability data** to **labeling** dovetailing off the issues of visible particles and discoloration (relating to how the drug product is to be inspected – see section for Labeling), **Resolved**. There are some differences in pH and assay values seen in the stability data that limit extrapolation to an expiry, leaving only 18 months of applicable stability data at 25^0C/60% RH. **Thus, these current 18 months of useful stability data is what they have that supports an expiry of 18 months**.

Within Quality Controls, most are of a typical nature for drug products (tightening acceptance criteria for impurities, and tightening those at release and shelf-life, etc.). But a subset of these **arise specifically on account of the dark blue color of Indigo Carmine** that create challenges in quality controls. These issues result from properties assessable by virtue of absorption and reflection of light of the visible spectrum (quality attributes of color, clarity) and those quality attributes assessable by visualization (visible particles), the first of these because of lack of a color standard, and clarity because of lack of a method for assessment. All issues involving **Color and Clarity are Resolved.**

That for Visible Particles is especially challenging because the dark blue color prevents

normal visual examination. In their response to the concern raised for absence of a test for visible particles that is required for parenteral injections, Provepharm proposes [redacted]. **Resolved** with an **acceptance criteria consisting of a minimum of** [redacted]**% rejection of defective ampules** [redacted]**µm, and a minimum rejection of** [redacted]**% for ampules containing particles in the range of** [redacted] **µm.**

[redacted]

[redacted]

(b) (4)

Labeling:

Most of the issues for labeling from the standpoint of drug product review are of typical nature requiring edits for clarity and accuracy (e.g., pH range, osmolality; chemical name), Description and How Supplied sections of the PI. Dovetailing off the primary issues for Indigo Carmine, ascribed to its intense dark colored solution (that are discussed earlier in this Executive Summary), it also registers in the labeling, specifically on **how the ampules should be inspected by users of the produ**ct.

There is also a Label and Labeling Review (4/28/2022) performed by DMPA 2 and consists of recommendations to DIRM to convey to Provepharm, and include the vial container label, the carton labels identifying areas of vulnerability that may lead to medication errors.

Manufacturing:

(b) (4)

Biopharmaceutics:

NDA 216264 is recommended for approval by Biopharmaceutics, based on a scientific bridge established between Provepharm's proposed product (40 mg/5 mL) and the products used in certain key publications that included information in the application.

Comprised in this information (provided in the application) are (1) the result that Provepharm's proposed product has the same composition as the American Regent and Akorn products, (2) comparable physiochemical properties of the products and (3) that any differences in inactive ingredients are not expected to impact the disposition of the drug *in vivo*.

Also it is included by Biopharmaceutics that a BCS Designation is not applicable for injections. At a concentration of 8 mg/mL, the drug substance is fully dissolved in solution.

Microbiology:

There are numerous issues for microbiology (identified by Microbiology reviewer, Ash Bekele) that ranged across a wide swath of considerations impacting microbiological quality.

In summary, these issues broadly fall into categories involving **validation** (b) (4) **quality control and testing** (b) (4) , **annual requalification** (b) (4) See review by Ash Bekele (recommending approval).

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking[1]**	**Risk Mitigation Approach**	**Final Risk Evaluation[2]**	**Lifecycle Considerations/ Comments**
	(b) (4)	(H, M, or L)	(b) (4)		
Color		M		L	N/A
Clarity		M		L	N/A
Visible Particles		H		L	N/A
Impurities (organic)		M[8]		L	N/A

Impurities (elemental)	[redacted]	H[9]	[redacted]	N/A

(1) Within Quality Controls, most of the CQA's are of a typical nature for drug products (tightening acceptance criteria for impurities, and tightening those at release and shelf-life, etc.) and for Indigo Carmine are of no particular noteworthy significance. See the Drug Product review (Anne Marie Russell) for discussion of the full panel of specifications. But a subset of these **arise specifically on account of the dark blue color of Indigo Carmine** that create challenges for quality controls and therefore keynoted in this risk assessment. These issues result from properties assessable by virtue of absorption and reflection of light of the visible spectrum (quality attributes of color, clarity) and those quality attributes assessable by visualization (visible particles). Included are the impurities, since they have as their origin multiple sources (process) and may potentially include degradative mechanisms. These CQA's create the lion's share of the issues that form the basis of risk to product quality.

(2) Overall risk assessment – L. All facilities acceptable. Microbiology recommends approval.

(3) No official color standard for the dark blue color of Indigo Carmine. Provepharm resolved this issue by developing their own color standard (a picture).

(4) [redacted]

(5) [redacted]

(6) Provepharm proposes [redacted] Based on the range for visible particles, [redacted] µm (the lower bound) is the limit of detection.

(7) Impurities arising from the drug substance synthesis, and that from the drug product process are controlled by specifications. two of the known impurities [redacted] arise from synthesis of the drug substance. There are 5

others that are from degradation, but also controlled by the specifications. what remains are degradation impurities that theoretically could arise from the [redacted (b) (4)].

(8) Per the issue of [redacted (b) (4)], the risk depends on the presence of [redacted (b) (4)] not evident from either the drug substance synthesis or drug product process. Based on this not evident initial assessment, L for low risk would be inappropriate. But, also H would be inappropriate, leaving M as the more suitable level of risk.

(9) Elemental impurities. Risk listed here, because of absence of any information (testing, other supportive information).

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies *(Specify discipline, such as Environmental)*

N/A

Application Technical Lead Name and Date:

Eldon E. Leutzinger, Ph.D.
6/01/2022

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	
NDA Number	216264
Assessment Cycle Number	1
Drug Product Name/ Strength	Indigo Carmine (Indigotindisulfonate Sodium) Injection USP 0.8% (40 mg/5ml)
Route of Administration	Intravenous injection
Applicant Name	Provepharm
Therapeutic Classification/ OND Division	Division of Imaging and Radiation Medicine
RLD/RS Number	N/A
Proposed Indication	a diagnostic dye indicated for use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures.

Assessment Recommendation: **Adequate**

Assessment Summary:

Indigo Carmine has been sold in the United States for more than a century as an unapproved drug product. The current NDA seeks approval of the drug product, primarily based on the results of Provepharm's clinical study PVP-19IC01. The Applicant also intended to reply on literature as supportive evidence. Among the publications the Applicant provided, the Clinical Review team has identified two high-quality publications that provide supportive evidence for the efficacy and safety of the proposed drug product. This Biopharmceutics Review is focused on evaluation of the data supporting the scientific bridge between the proposed drug product and the products used in the two key publications.

Based on the time when the studies in the key publications were conducted, and the market status of the Indigo Carmine products, the Applicant speculated that the drug products used in both publications are likely to be either the American Regent or Akorn products. A scientific bridge is established between the proposed drug product and the products used in the key publications, based on the following information submitted:

(1) Provepharm's indigo carmine has exactly the same composition as the American Regent and Akorn products;

(2) the physiochemical properties of the drug products are comparable;

(3) any differences in the inactive ingredients (i.e., pH adjuster) are not expected to impact the disposition of the drug in vivo.

From a Biopharmaceutics perspective, NDA 216264 for Indigo Carmine (Indigotindisulfonate Sodium) Injection USP 0.8% (40 mg/5ml), is **recommended for APPROVAL**.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
N/A				

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original NDA	**09/09/2021**
Response to Filing issues	**01/10/2022**

Highlight Key Issues from Last Cycle and Their Resolution: None. This is the first review cycle.

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: None.

B.1 BCS DESIGNATION

Assessment: BCS designation is not applicable for injectables.

Solubility: The Applicant noted that the drug substance is slightly soluble in water[1]. It is reported that the water solubility of indigo carmine is 10-50 mg/mL at 70.0°F[2]. The concentration of the proposed drug product is 8 mg/mL with the drug substance fully dissolved in solution.

Permeability: N/A

[1] Drug Substance Properties. \\CDSESUB1\evsprod\nda216264\0013\m3\32-body-data\32s-drug-sub\indigo-carmine (b) (4) \32s1-gen-info\general-properties.pdf

[2] PubChem-Indigo Carmine. https://pubchem.ncbi.nlm.nih.gov/compound/Indigo-carmine#section=Color-Form

Dissolution: N/A

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Indigo carmine has been sold in the United States for more than a century as an unapproved drug product. In this NDA submission, the efficacy and safety of the proposed indigo carmine injection is primarily based on the results of Provepharm's clinical study PVP-19IC01. The Applicant also intended to reply on literature as supportive evidence. This Biopharmceutics review is focused on evaluation of the data supporting the scientific bridge between the proposed drug product and the products used in literature.

Marketing Status

(b) (4)

(b) (4)

[redacted]

Comparative Composition and Physiochemical Properties

As requested by FDA through the filing letter[4], The Applicant submitted on 01/10/2022[5] a tabular summary containing the qualitative and quantitative composition of their indigo carmine finished product compared to indigo carmine products sold by American Regent, Akorn, and the European company, SERB. As presented in Table 1, Provepharm's indigo carmine has exactly the same composition and primary packaging as the American Regent and Akorn products. Provepharm's indigo carmine is similar in composition to the SERB product with the only difference being [redacted] (b) (4)

[3] Figure 2 on Page 11. \\CDSESUB1\evsprod\nda216264\0008\m1\us\111-information-amendment\0008-response-to-fda-filing-review-issues-identified-cmc-and.pdf

[4] NDA 216264 FDA filing review letter. \\CDSESUB1\evsprod\nda216264\0006\m1\us\111-information-amendment\0006-fda-filing-review-issues-identified-22-nov-2021.pdf

[5] NDA 216264 Response to Filing comments. \\CDSESUB1\evsprod\nda216264\0008\m1\us\111-information-amendment\0008-response-to-fda-filing-review-issues-identified-cmc-and.pdf

Table 1[6]. Comparative Composition of Indigo Carmine by Manufacturer

Manufacturer	Provepharm	American Regent	Akorn	SERB
Primary Packaging	5 mL brown glass ampules	5 mL brown glass ampules	5 mL brown glass ampules	5 mL brown glass ampules
Product Name	TRADENAME (Indigotindisulfonate sodium injection) 40 mg/5 mL (0.8%)	Indigo Carmine Injection (Indigotindisulfonate Sodium Injection, USP) 0.8% Solution	Indigo Carmine - Indigotindisulfonate Sodium Injection USP, 0.8% Solution 8 mg/mL	(b) (4) (b) (4) 40mg/5mL
Active Pharmaceutical Ingredient (API)				
Indigo carmine (Indigotindisulfonate sodium)	40 mg	(b) (4)	40 mg	40 mg
Excipients				
Citric Acid Monohydrate	pH adjuster*	pH adjuster*	pH adjuster*	None
Sodium Citrate	pH adjuster*	pH adjuster*	pH adjuster*	None
				(b) (4)
Shelf Life	(b) (4)	Unknown**	Unknown**	2 years

*If needed to reach pH 3.0 – 6.5; **Not referenced in package label – presumed to be (b) (4)

Results of physical, chemical and microbial testing comparability are presented in Table 2. Both American Regent and Akorn products are declared USP, which means that they are compliant to the current USP monograph of Indigotindisulfonate Sodium Injection, including identification tests, pH, assay by UV, Bacterial Endotoxins test (USP-41. (2018)) and requirements for Injection products according to USP general chapter <1> (USP-37 (2014)). Osmolarity and pH data of all products are similar.

Comparative data on the assay and related substances showed that the Provepharm product is similar to non-expired batches of American Regent and SERB., though the expired products, especially the Akorn batch that expired in April 2015, showed slightly more impurities than the Provepharm product.

[6] Table 1 on Page 8. \\CDSESUB1\evsprod\nda216264\0008\m1\us\111-information-amendment\0008-response-to-fda-filing-review-issues-identified-cmc-and.pdf

Table 2[7]. Comparative Physical, Chemical and Microbiological Properties of Indigo Carmine by Manufacturer

Manufacturer		Provepharm	American Regent		AKORN	SERB		
Lot Number		F9001	9113	7112	041463	2622	2550B	2456
Manufacturing Date (mm/yyyy)**		06/2019	03/2019	04/2017	04/2013	03/2019	09/2018	10/2017
Expiry Date (mm/yyyy)		06/2022	03/2021	04/2019	04/2015	03/2021	09/2020	10/2019
Analysis Date (mm/yyyy)		06/2019	02/2020	05/2019^	10/2019^	02/2020	02/2020	02/2020^
Test	Specification							
Appearance/Clarity	Clear Solution	complies	complies	complies	complies	NA	NA	NA
Appearance/Color	Blue or bluish purple solution	complies	complies	complies	complies	NA	NA	NA
USP Identification Tests B, C, D	Color change or precipitation	complies	complies	complies	complies	NA	NA	NA
Visible Particulates	Essentially free from particles. max. 0	complies	complies	complies	complies	NA	NA	NA
Subvisible particles ≥ 10 µM	Max. (b) (4)	(b) (4)	complies	complies	complies	NA	NA	NA
Subvisible particles ≥ 25 µM	Max. (b) (4)		complies	complies	complies	NA	NA	NA
Extractable volumes	Min. (b) (4) mL		complies	complies	complies	NA	NA	NA
pH	3.0 – 6.5	4.6	3.8	3.9	4.7	4.2	4.0	4.6
Osmolarity (mOsm/L)	For information only	28	30	NA	33	31	NA	NA
Sterility test	Sterile	complies	USP compliant	USP compliant	USP compliant	NA	NA	NA
Bacterial endotoxins	Max. (b) (4) EU/mg	(b) (4)	USP compliant	USP compliant	USP compliant	NA	NA	NA

*Data listed is from release testing of Provepharm's clinical lot compared with lots from other manufacturers as listed. Additional testing for the lots listed as well as the data from the non-clinical lots of Provepharm's indigo carmine are provided in Annexure 2
**Manufacturing date presumed (b) (4) from expiry date if not explicitly stated in package labeling; ^Product expired at the time of analysis; NA = not analyzed

Key Supporting Publications and the Scientific Bridge

Among all the publications the Applicant provided, the Clinical Review team has identified the following two high-quality publications that provide supportive evidence for the efficacy and safety of the proposed drug product. Therefore, this Review is focused on evaluation of the bridging between the products used in these two key publications and the proposed drug product.

Key Publications:

1. *Ibeanu, O. A., Chesson, R. R., Echols, K. T., Nieves, M., Busangu, F., & Nolan, T. E. (2009). Urinary tract injury during hysterectomy based on universal cystoscopy. Obstet Gynecol, 113(1), 6-10.*[8]
2. *Vakili, B., Chesson, R. R., Kyle, B. L., Shobeiri, S. A., Echols, K. T., Gist, R., Zheng, Y. T., & Nolan, T. E. (2005). The incidence of urinary tract injury during hysterectomy: a prospective analysis based on universal cystoscopy. Am J Obstet Gynecol, 192(5), 1599-1604.*[9]

[7] Table 2 on Page 9. \\CDSESUB1\evsprod\nda216264\0008\m1\us\111-information-amendment\0008-response-to-fda-filing-review-issues-identified-cmc-and.pdf
[8] Ibeanu 2009. \\CDSESUB1\evsprod\nda216264\0001\m5\54-lit-ref\ibeanu-2009.pdf
[9] Vakili 2005. \\CDSESUB1\evsprod\nda216264\0001\m5\54-lit-ref\vakili-2005.pdf

In both of the key publications, the manufacturer of the indigo carmine injection was not stated. Based on the time when the studies were conducted, which was 2000-2009 for the Ibeanu paper and 2000-2003 for the Vakili paper respectively, the Applicant speculated that the drug product used in both publications are likely to be either the American Regent or Akorn product. Based on the comparison of the composition and the physiochemical properties (Tables 1 and 2), Provepharm's indigo carmine has exactly the same composition as the American Regent and Akorn products, and the physiochemical properties of the drug products are comparable.

In addition, given the formulation of the drug product is composed of the API and pH adjusters, even if there are differences in the pH adjusters, they are not expected to impact the disposition kinetics of the drug in vivo.

Therefore, a scientific bridge is established between the proposed drug product and the products used in the key publications.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date: Jing Li, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Om Anand, Ph.D.

Om Anand

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Date: 5/26/2022 01:17:10PM
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Jing Li

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	The drug product is a diagnostic agent indicated for use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures.
NDA Number	216264
Assessment Cycle Number	1
Drug Product Name/ Strength	Indigo Carmine (Indigotindisulfonate Sodium) Injection USP 0.8%, (40 mg/5 mL)
Route of Administration	Intravenous injection
Applicant Name	Provepharm SAS.
Therapeutic Classification/ OND Division	OSM/Division of Imaging and Radiation Medicine
Manufacturing Site	Cenexi, 52, rue Marcel et Jacques Gaucher, Fontenay-sous-Bois, France 94120 FEI#: 3007250542
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: Recommended for Approval

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0001 (1), Original submission	09/9/2021
Seq 0002 (2), Labelling	09/29/2021,
Seq 0006 (6), Filling Review issues	12/8/2021
Seq 0007 (7), Facility withdrawal	12/21/2021
Seq 0013 (13), IR response	03/04/2022
Seq 0018 (18), IR response	04/06/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks:

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):

Supporting Documents: None

S DRUG SUBSTANCE

The drug substance (Indigotindisulfonate sodium) is tested for bioburden following USP <61> method (Limits: ≤100 CFU/g for total aerobic microorganisms and ≤50 CFU/g for total yeast and mold), endotoxins per USP <85> method (limit of ≤2.5 EU/mg) and for absence of specified microorganisms. [redacted].

Assessment: (Adequate)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Section 3.2.P.1, description-and-composition)

Description of drug product – The drug product (Indigo Carmine/ Indigotindisulfonate Sodium, 40 mg/5 mL solution for injection) is a sterile, blue [redacted] color solution for injection filled in 5 mL glass ampules.

Drug product composition –The qualitative and quantitative composition of the drug product is described in the applicant table shown below. The drug product is composed of the API [redacted].

NAME OF INGREDIENT	QUANTITY PER AMPULE (5 mL)	QUANTITY PER ML	FUNCTION	REFERENCE TO STANDARD
SUBSTANCE				
Indigo carmine (Indigotindisulfonate sodium) USP	40 mg	8 mg	Active substance	USP #
EXCIPIENTS				
[redacted]	[redacted]			USP #
Citric acid [redacted]	Solutions at [redacted] if necessary to reach pH at 3.0 – 6.5	Until pH 3.0 – 6.5	pH adjusters	USP #
Sodium citrate*				
[redacted]				USP #, Ph. Eur #

Current edition

* Citric acid and sodium citrate are used, if necessary, to reach pH specifications

Description of container closure system – The primary CCS is a 5 mL [redacted] brown glass ampule with a white One Point Cut (OPC). A description of the primary container closure system along with the manufacturer's information is provided in the following applicant table (modified from document "Container Closure System" in section 3.2.P.7).

Description of the primary containers and closures

Component	Description .	Manufacturer/Supplier	DMF No and Type
Container-glass ampule	5 mL brown glass ampule	[redacted]	[redacted] Type III

Assessment: (Adequate)
The applicant provided acceptable description of the drug product and the primary container closure system. The ampules (b) (4) .

(b) (4)

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/s/

ANIKA A LALMANSINGH
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