CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211580Orig1s000

PRODUCT QUALITY REVIEW(S)

EXECUTIVE SUMMARY

Recommendation: APPROVAL

NDA 211580
Review #1

Drug Name/Dosage Form	Indocyanine Green, USP (ICG)/ Powder for Injection
Strength	25 mg ICG per vial
Route of Administration	Intravenous Injection or Interstitial use
Rx/OTC Dispensed	Rx
Applicant	Novadaq Technologies ULC
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	1/23/2018	ALL
Labeling	3/12/2018	CMC/ALL
IR Response	5/9/2018	Drug Product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain/Donna Christner	OPQ/ONDP/New Drug Product API
Drug Product	John Amartey	OPQ/ONDP/DNDPII/BVI
Process	Yongming Lu/Pei-I Chu	OPQ/OPF/DPAII/BVI
Microbiology	Shimanovich, Avital	OPQ/OPF/DMA/BI
Facility	Yeung Chan	OPQ/OPF/DIA/BIII
Biopharmaceutics	NA	
Regulatory Business Process Manager	Lalmansingh, Anika	OPQ/OPRO/RBPMI/BI
Application Technical Lead	John Amartey/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: NONE REFERENCED

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	011525	RLD
ANDA	040811	

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

From CMC quality perspective the application is recommended for approval.
There are no pending CMC deficiencies. A microbiology PMC was agreed with the applicant. Additional microbiology studies will be submitted post-approval by 2/28/2019 to support the 6 hour in-use period.
Manufacturing facility 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 • Visualization of vessels, blood flow and tissue perfusion • Visualization of extrahepatic biliary ducts and • Visualization of lymph nodes and lymphatic (b) (4)
Duration of Treatment	NA
Maximum Daily Dose	Do not exceed 2 mg ICG/kg
Alternative Methods of Administration	Intravenous Injection or Interstitial use

The drug product SPY AGENT Green is a sterile lyophilized powder of 25 mg Indocyanine Green in a glass vial capped with a (b) (4) rubber stopper with tear-off seal. The only excipient in the drug product is sodium iodide not more than (NMT) 5%.

B. Quality Assessment Overview

SPY AGENT Green Indocyanine Green or ICG or IC2000 is lyophilized powder, reconstitution solution for intravenous injection or interstitial use. It is proposed for the following indications:

- visualization of vessels, blood flow and tissue perfusion
- visualization of extrahepatic biliary ducts
- visualization of lymphatic nodes and lymphatic vessels during lymphatic mapping for cervical and uterine tumors.

This NDA is being submitted through the 505(b)(2) pathway. The proposed product is SPY AGENT Green (Indocyanine Green USP) for Injection. It is a sterile lyophilized powder for injection (25 mg/vial) containing the drug substance indocyanine green (ICG). ICG was originally approved by the FDA in 1959 (NDA 011525, Akorn Inc.). In 2004 Novadaq filed a Request for Designation (RFD) for the SPY Intra-Operative Imaging System which consists of device components (light and camera, etc.) and IC-Green as a combination product.

When injected intravenously, ICG binds to blood proteins and it is confined to the vascular space. Because of protein binding the absorption wavelength peak of the molecule shifts from 780 nm to approximately 806 nm. The wavelength is further shifted to the near-IR region by laser excitation, and emission occurs at a longer wavelength which constitutes the signal for detection.
The drug substance API is Indocyanine Green, ICG.
Chemical Name: 2-[7-[1,3-dihydro-1,1-dimethyl-3-(4-sulfobutyl)-2*H*-benz[*e*] indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)- 1*H*-Benz [*e*]indolium iodide, hydroxide, inner salt, sodium salt.
The drug substance (b) (4) under cGMP conditions and tested according to USP monograph for Indocyanine Green. ICG is water soluble, tricarbocyanine dye. The drug substance is processed to obtain the drug product lyophilized powder.
The drug substance section of the NDA was reviewed by Dr. Sam Bain and was found adequate. The drug substance is manufactured (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 25 mg lyophilized drug substance with NMT 5% sodium iodide (NaI) excipient presented in a glass vial capped with a rubber stopper and a crimp seal. The lyophilized powder is reconstituted with 10 mL or 20 mL sterile water for injection (WFI) to obtain two strengths of 2.5 mg/mL or 1.25 mg/mL of ICG.
SPY AGENT Green is not stable as a solution (b) (4) It is stable as a lyophilized powder. The manufacturing process i (b) (4) Stability data show that the drug product powder is stable under long-term storage condition (b) (4) n the container. The drug product powder is photostable. There are unknown related impurities when the reconstituted drug product is stored for over 6 hours. 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 t (b) (4) months. A 36-month shelf-life is granted for the drug product stored at 25°C (b) (4) %RH. The reconstituted solution is for a single-patient use, and the remainder solution is to be discarded.
The process team: The drug product manufacturer is Patheon, Italy, S.p.A. A large body of manufacturing data (batch analysis) and process validation support the drug product. The microbiology team reviewed this product as a sterile product and concluded that microbial controls and testing methods USP<61> and <62> are suitable.
The drug product manufacturer is Patheon, Italy. The manufacturing facility received acceptable cGMP recommendation by the facilities reviewer team (2/16/2018 in panorama).

C. Special Product Quality Labeling Recommendations (NDA only)

The instruction for disposal of the remainder oral solution after reconstitution and dosing is critical because the solution is not stable beyond 6 h and should be prominent in the PI. However, Microbiology send to the applicant a Non-506B Reportable Postmarketing Commitment (PMC) as follows *"The current DMA policy is that a microbiological post-*

reconstitution hold time study must be performed if the drug product has an in-use period of more than 4 hours at room temperature to demonstrate that the drug product does not support growth of inadvertent microbial contamination. Because the drug product has an in-use period of 6 hours with multiple vial re-entries, DMA requires a microbiological hold time study to support the drug product labeling". The applicant committed to the PMC.
Vial Label: the applicant did not include the quantitative composition of the drug product (lyophilized powder) and was asked to revise the vial label in both kits.

DMEPA (8/7/2018) did not accept the proposed global proprietary name SPY AGENT Green because the name is *"fanciful"* and the accepted proprietary name is pending.

D. Final Risk Assessment (see Attachment)

Attachment A						
Product Attribute/CQA	**Factors that can impact the CQA**	**Probability (O)**	**Severity of Effect (S)**	**Detectability (D)**	**FMECA RPN Number**	**Comment**
Drug Substance: Indocyanine green, USP (ICG)						
Identity	Method of manufacture	3	3	2	18 (L)	Risk is acceptable. The starting materials, method of manufacture and other components are adequately controlled. Specifications: MS: Molecular weight= 774.96 Da
Purity	Method of manufacture	3	3	2	18 (L)	Risk is acceptable (b) (4) [redacted]
Related substances	Method of manufacture, storage	3	2	2	12 (L)	Risk is acceptable. Risk is mitigated through analytical testing and further purification and controls in the drug product.
Water content	Method of manufacture, storage and hygroscopicity [redacted] (b) (4)	3	3	2	18 (L)	Risk is acceptable (b) (4) [redacted]
Drug Product: TRADENAME (indocyanine green, USP) powder for Injection						

Identification by HPLC	Analytical method, control of drug substance, and process parameters	2	3	3	18 (L)	Risk is acceptable. Identification by two methods and control of identity of drug substance.
Purity	Assay by HPLC, degradation products by HPLC	2	3	3	18 (L)	Risk is acceptable. Purity is determined by the proposed validated methods.
Assay	Assay of ICG is performe (b) (4)	2	3	2	12(L)	Risk is acceptable. Purity is determined by a validated HPLC assay and controlled in the drug product.
Water Content	Increases upon storage because of the hygroscopic nature	3	2	2	12 (L)	Risk is acceptable (b) (4)
Sterility	Components, manufacturing and reconstitution process	5	5	5	125 (H)	Risk is acceptable. Simulations and interventions conducted (b) (4)
Bacterial Endotoxins	Components, manufacturing process	4	4	4	64 (H)	Risk is acceptable. Controlled by specification in the finished product (based on micro. review).
Photostability	Drug product is in (b) (4) container/closure system	3	3	2	18 (L)	Risk is acceptable.

John Amartey

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QUALITY ASSESSMENT

MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA/ANDA: N211580

Drug Product Name / Strength: SPY AGENT Green (Indocyanine green for injection), 25 mg lyophilized powder

Route of Administration: intravenous, interstitial

Applicant Name: Novadaq Technologies ULC

Manufacturing Site:
Patheon Italia S.p.A.
(b) (4)
Ferentino, Frosinone (FR)
Italy, 03013

Method of Sterilization: Sterile (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): **N/A**

Review Summary: Drug product is ster (b) (4) 20 mL/13 mm vial (b) (4)

List Submissions Being Reviewed: 01/23/2018, 03/05/2018 (CMC/Microbiology IR response), 03/12/2018 (CMC/Microbiology IR response), 03/16/2018 (Labeling IR response), 05/17/2018 (Labeling IR response), 06/26/2018 (Labeling IR response), and 07/25/2018 (CMC/Microbiology IR response), 08/03/2018 (IR response to labeling and clinical), 08/15/2018 (CMC/Microbiology IR response), and 08/22/2018 (CMC/Microbiology IR response)

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The 08/03/2018 labeling/clinical IR response adds a pediatric indication. Additionally, a post-marketing commitment for a microbiology issue is associated with this application. The package insert for this drug product will be approved to contain

language indicating a hold period of up to 6 hours at room temperature prior to use in the patient, after the drug product is reconstituted with WFI. The applicant commits to submit data from a post-reconstitution hold study to support the labeling after approval of the application.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents:

- Type V DMF [redacted] (b) (4)
- Review D [redacted] (b) (4) M11R01, dated 04/11/2018 (V-drive).

List Number of Comparability Protocols (ANDA only): N/A

In the microbiology filing review, it was noted that microbiology related validation studies were not provided in the application.

Information request:
The following IR was sent to the applicant on 02/23/2018.

We acknowledge your statements that the commercial production processe [redacted] (b) (4) *. Additionally, the study report and results to validate the integrity of the container closure system cannot be located. Provide this information.*

If any of the above information is located in a Drug Master File (DMF), then provide a current Letter of Authorization indicating the DMF number and reference to the location of all information relevant to the validation of the above process.

For more information on the type of information to provide in the application, see the Guidance for Industr [redacted] (b) (4)

Information request response:
An IR response was provided on 03/05/2018. The specific information is reviewed in the corresponding sections below.

Reviewer's Assessment: ***Adequate***

The applicant provided an adequate response to the filing information request.

S Drug Substance

The drug substance is not reviewed in this application as the final drug product is subject (b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Olive green, dark green, blue green, dark blue, or black lyophilized sterile powder.
- **Drug product composition** –

Ingredient	Function	Quantity per unit
Indocyanine green	API	25 mg
Sodium iodide (NaI) (b) (4)	(b) (4)	≤ 5.0% (b) (4)
WFI		

- **Description of container closure system** –

Primary container closure:

Container closure	Description
Vial	0 mL (b) (4) glass via (b) (4)
Stopper	3 mm (b) (4) stoppe (b) (4)
Seal	20 mm grey (b) (4)

Secondary packaging:

The following additional information was provided in the 06/26/2108 labeling IR response. The drug product is further packaged in three kits: SPY Elite Kit, PINPOINT Kit, and PINPOINT Lymphatic Mapping Kit. The components are described in the table below:

Kit component:	Labeled sterile:	Manufacturer/information provided:
10 mL water for injection	Sterile	Fresenius Kabi or Hospira NDC 63323-185-10 NDC 0409-4887-10
USP plastic vial	Sterile	Not provided
ND800 drape	Sterile	Not provided
3 mL syringes	Sterile	Not provided
10 mL syringes	Sterile	Not provided
Luer lock 10 mL syringes with controlled handle	Sterile	Not provided
18 G 1 inch needle	Sterile	Not provided
22G 3.5 inch spinal needles	Sterile	Not provided
3-way stopcock	Sterile	Not provided

The following kit picture (PINPOINT Kit) is copied below from the 05/17/2018 IR response. Pictures of the SPY Elite Kit and PINPOINT Lymphatic Mapping Kit were not provided.

Figure 1: Diagram of SPY ELITE Kit Assembly

Information request:

The following IR was sent to the applicant on 08/06/2018.

We acknowledge that the drug product will be packaged in three possible kits with other accessories for patient administration. For all accessories/items that are packaged with the drug product, address the following:

a. *Confirm that the Water for Injection, USP, is an approved sterile drug product (b) (4) Fresenius Kabi or Hospira.*
b. *For all other items that will have contact with the sterile drug product or are labeled as sterile (USP plastic vials, ND800 drapes, 3 mL syringes, 10 mL syringes, Luer lock 10 mL syringes with controlled handles, 18G 1 inch needles, 22G 3.5 inch needles, and 3 way stopcocks), indicate if these items are approved devices and purchased as sterile, and provide the 510k numbers for each component. For kit items that are not approved devices and have product contact or are labeled as sterile, provide data to validate the sterilization of these items, as appropriate.*

Information request response:

The following response was provided on 08/10/2018.

a. The applicant confirmed that the WFI is an approval sterile drug product (b) (4) Fresenius Kab (b) (4) or Hospira (b) (4) with NDC numbers 63323-185-10 and 0409-4887-17, respectively. The sterile WF (b) (4) Fresenius Kabi is manufacture (b) (4)
b. The NDC and 510k numbers for the drug product and devices contained in the kit are as follows:

Kit component:	Labeled sterile:	Manufacturer/information provided:
10 mL water for injection USP in plastic vials	Sterile drug product	Fresenius Kabi or Hospira NDC 63323-185-10 NDC 0409-4887-10
ND800 drape	Sterile	(b) (4)
3 mL syringes	Sterile	
10 mL syringes	Sterile	
Luer lock 10 mL syringes with controlled handle	Sterile	
18G 1 inch needle	Sterile	
22G 3.5 inch spinal needles	Sterile	
3-way stopcock	Sterile	

		(b) (4)

Reviewer's Assessment: ***Adequate***

It is noted that the kits will only contain 2 needles (PINTPOINT and PINPOINT Lymphatic Mapping kit); however, the package insert allows for up to 4 injections, suggesting that the needles would need to be reused. The needle reuse concern was conveyed to the medical officer and labeling reviewer via email on 08/01/2018 to assure that this practice is appropriate. However, this issue relates to surgical practice, and is not a sterility assurance issue.

The applicant packages the drug product with items in a kit, all items are purchased as sterile and NDC and 501k numbers are provided.

P.2 Pharmaceutical Development
P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

A container closure integrity test (CCIT) to ensure container closure integrity is provided in the 01/23/2018 submission in the "*Microbial Attributes*" document. CCIT was performed with 10 vials from exhibit batch 14GRF02 (b) (4)

(b) (4)

Information request:
The following IR was sent to the applicant on 07/08/2018.

We acknowledge the (b) (4) *test provided in the "Microbial Attributes" document of the 01/23/2018 submission, and the* (b) (4) *validation test provided in the "* (b) (4) *document in Section P.3.5 of the 03/05/2018 IR response submission. However, the significance of both tests to meet the requirements for*

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control that demonstrates the viability of the organisms over the duration of the test period.

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: *Avital Shimanovich, Ph.D., 09/28/2018*
Secondary Reviewer Name and Date (and Secondary Summary, as needed): *Marla Stevens-Riley, Ph.D., 09/29/2018*

Avital Shimanovich

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Marla Stevens Riley

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