CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208912Orig1s000

OTHER REVIEW(S)

Division of Transplant and Ophthalmology Products
Associate Director for Labeling Recommendations
of the Prescribing Information

Product Title	Dexycu (dexamethasone intraocular suspension) 9%, for intraocular administration
Applicant	Icon Bioscience, Inc.
Application/Supplement Number	NDA 208912
Type of Application/Submission	Original
Proposed Indication	Treatment of postoperative inflammation
Date FDA Received	April 12, 2017
PDUFA Goal Date	February 12, 2018
Review Date	December 10, 2017
Reviewer	Jane Filie, M.D.
Project Manager	Diana Willard

This Associate Director for Labeling (ADL) memorandum provides recommendations for consideration by the management of the Division of Transplant and Ophthalmology Products (DTOP), on the content and format of the prescribing information (PI) to help ensure that the PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[2] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

This is an original NDA. Comments based on the review of Selected Requirements of the Prescribing Information (SRPI) were sent to the applicant on May 30, 2017 and a revised label was resubmitted by the applicant on June 9, 2017.

Labeling Related Consults

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* available at https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

[2] See *PLR Requirements for PI* website for PLR labeling guidances.

Medication Error and Proprietary Name Assessments, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed proprietary name "Dexycu". The primary reviewer, Sherly Abraham, R. Ph.D, and secondary reviewer Sarah K. Vee, Pharm.D., concluded that the proposed name is acceptable since it will not misbrand the product and does not raise safety concerns (see DMEPA review dated 07/18/17). The proprietary name "Dexycu" was granted on July 25, 2017.

DMEPA also reviewed the proposed label and labeling for Dexycu (dexamethasone intraocular suspension) to determine whether there are safety concerns with respect to preventable medication errors. The primary reviewer James Schlick, R.Ph., and secondary reviewer, Otto Townsend, Pharm.D. provided recommendations (see review dated 12/04/17). Final decisions regarding the content and formatting of the labeling are deferred to the clinical team. The recommendations from DMEPA with respect to the PI are as follows and are included in the working version of the labeling:

A. Highlights and Full Prescribing Information

1. (b) (4) DMEPA recommended stating the dose as '0.005 mL' since the syringe used to prepare and administer the dose is calibrated in mL increments."
   ADL comment: This recommendation was incorporated in the labeling.

B. Highlights of Prescribing Information

1. "In the Dosage and Administration section we recommend the statement 'See Full Prescribing Information for instructions on administration of the injectable suspension' to alert healthcare practitioners (HCP) to the instructions."
   ADL comment: See comment by Dr. Wiley Chambers in the marked version of the labeling.

C. Full Prescribing Information

1. "We recommend Section 2.2 be re-titled 'Preparation and Administration' since both occur in this section."
   ADL comment: This recommendation was incorporated in the proposed labeling.

2. "Under Section 2.2 (Administration) where the glass vial is referenced as item #1, there is no statement to alert HCPs that after preparation, 0.005 mL will be delivered. We recommend the statement 'After preparation 0.005 mL will be delivered.' to alerts HCPs that only a small portion of the drug will be given (b) (4)
   ADL comment: See comment by Dr. Wiley Chambers in the marked version of the labeling.

3. "In Section 2.2, Steps 1-11, we recommend that the person performing each step be identified. There is confusion as to who should be performing each step either the surgeon, scrub nurse, or operating room assistant."
   ADL comment: See comment by Dr. Wiley Chambers in the marked version of the labeling.

4. "In Section 2.2, Step 3, the illustration is confusing. It appears that the needle cap should be removed before placing the needle on the syringe. We recommend the Sponsor clarify the illustration."
   ADL comment: See comment by Dr. Wiley Chambers in the marked version of the labeling.

5. "In Section 2.2, Step 6, we recommend an illustration of the needle immersed in the drug near the neck of the vial. This will demonstrate that the needle should not be above the surface of the drug. Otherwise the HCP will draw up air instead of drug."
   ADL comment: See comment by Dr. Wiley Chambers in the marked version of the labeling.

6. "In Section 2.2, Step 6, we recommend the Sponsor indicate how much drug should be withdrawn from the vial into the syringe."
   ADL comment: This recommendation was incorporated in the proposed labeling.

7. "In Section 2.2, Step 6, we recommend the Sponsor add a statement to discard the unused portion of the vial after the needle is removed."
   ADL comment: This recommendation was incorporated in the proposed labeling.

8. "In Section 2.2, Step 7, we recommend the Sponsor clarify if the needle should be re-capped before removing the needle from the syringe."
   ADL comment: See comment in the marked labeling by Dr. Wiley Chambers.

9. "In Section 2.2, Step 11, we recommend adding the statement 'Discard unused portion remaining in the syringe'. This is important because after administration there will be excess drug in the syringe that should not be stored and used on other patients later."
   ADL comment: This recommendation was incorporated in the proposed labeling.

10. "In Section 3 (Dosage Forms and Strengths) we recommend adding a basic description of the package (i.e. provided as a kit to administer a single dose of 0.005 mL of 9% dexamethasone)."
    ADL comment: This recommendation was incorporated in the proposed labeling.

11. "In Section 3 (Dosage Forms and Strengths) and Section 16 (How Supplied/Storage and Handling), we recommend adding a description of the injectable suspension characteristics (i.e. white, opaque…)."
    ADL comment: According to 21 CFR 201.57 (c)(4)(ii), this section must include a description of the identifying characteristics of the dosage form when applicable. In the case of this drug product the suspension comes in an opaque vial, thus, it will not be visible to the user.

12. "In Section 16 (How Supplied/Storage and Handling) we recommend adding the NDC number."
13. "In Section 16 (How Supplied/Storage and Handling) the statement [redacted] (b) (4) is incorrect. Five microliters are equal to 0.005 mL. Thus, the statement should be corrected to prevent confusion."
14. "In Section 16 (How Supplied/Storage and Handling) the vial size, 2 mL, is included in the description. We recommend removing this information, since this will lead to confusion over how much drug volume is in the vial."
15. "In Section 16 (How Supplied/Storage and Handling) [redacted] (b) (4)
16. "In Section 16 (How Supplied/Storage and Handling), the package type is stated as [redacted] (b) (4) We recommend that the package type be clarified and we defer to OPQ for the correct package type."
    ADL comment: Section 16 has been revised to address recommendations 12 to 16 for section 16 How Supplied/Storage and Handling.

Labeling Formatting and Content

At the time of this review, the labeling of section **14 CLINICAL STUDIES** is undergoing discussion between the applicant and the clinical and statistical teams; therefore, the version of the labeling in this review does not reflect the final language, tables and figures for section 14.

Formatting and content recommendations were made with the aim of improving clarity and readability of labeling. The edits and recommendations are shown throughout the proposed labeling in track changes and comments. In the marked version of the proposed PI, the ADL recommendations are presented in track changes (red) and comments (in balloons) begin with the bolded acronym "ADL". This version of the PI includes changes proposed by DTOP Deputy Director Dr. Wiley Chambers, M.D. (purple), clinical reviewer Dr. Jennifer Harris, M.D. (aqua), the DMEPA reviewer Dr. James Schlick R.Ph. (blue), nonclinical reviewer Dr. Aaron Ruhland, Ph.D. (burgundy), product quality reviewer Dr. Xinghua Wu, Ph.D. (orange), the clinical pharmacology reviewer Dr. Abhay Joshi, Ph.D. (gray), the statistical reviewer Dr. Abel Eshete, Ph.D (blue).

The marked version does not reflect the final formatting of the labeling. Hence, a clean copy of the proposed labeling at the time of this review is included following its marked version.

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/s/

JANE FILIE
01/11/2018

RENATA ALBRECHT
01/12/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 29, 2017

To: Diana Willard
CPMS
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 208912**
DEXYCU (dexamethasone intraocular suspension) 9%, for intraocular administration

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OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling submitted for consult on May 10, 2017, for DEXYCU (dexamethasone intraocular suspension) 9%, for intraocular administration. OPDP's comments are provided directly below on the attached marked-up copy of the proposed PI. Our comments are based on the version of the proposed labeling located in Sharepoint on December 21, 2017. OPDP's comment on the proposed carton and container labeling, provided below, is based on the version located in Sharepoint on December 21, 2017, also attached.

Carton and Container Labeling

We recommend that the established name be presented in a manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
12/29/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 4, 2017
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208912
Product Name and Strength:	Dexycu (Dexamethasone) Suspension for Intraocular Injection, 9% 0.5 mg/0.005 mL
Product Type:	Single-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Icon Bioscience, Inc.
Submission Date:	April 12, 2017 and June 9, 2017
OSE RCM #:	2017-892
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD.

Reference ID: 4189751

1 REASON FOR REVIEW

As part of the approval process for Dexycu, The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B - N/A
Human Factors Study	C - N/A
ISMP Newsletters	D - N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Assessment of Overfill

Dexycu is packaged in a carton containing the following items:

- One glass **vial**: 0.5 mL of DEXYCU (dexamethasone suspension for intraocular injection, 9%)
- One sterile 1-mL **syringe**
- One sterile **syringe guide**
- One sterile **syringe ring**
- One sterile 18-gauge **needle** (1½ inches long), plastic cap attached
- One sterile 25-gauge bent **cannula** (8 mm long), plastic cap attached

The prescribed dose for Dexycu (0.005 mL) is very small, so a syringe ring and guide are required to accurately measure and administer the dose. For an illustration, see Dosage and Administration instructions in Appendix G.3. The Dexycu vial contains 0.5 mL, but the prescribed dose is 0.005 mL. Hence, there is excess volume of drug product in the vial. The excess volume of drug product in the vial is required for two reasons: (b) (4)

Reference ID: 4189751

Because of these two parameters, we find that excess volume of drug product in the vial is required for accurate preparation and administration.

Although we understand why the excess volume is required, we were concerned that if the syringe ring and guide are not used during the administration, some of the excess volume drawn into the syringe during preparation could accidentally be injected into the iris leading to an overdose. We discussed this concern with the Division of Transplant and Ophthalmology (DTOP) Clinical team to assess the clinical impact of injecting too much drug into the iris. On November 17, 2017, in response to our email, the DTOP Clinical team indicated that the to be marketed kit was used in the phase III clinical trial, and there were no preparation and dose administration errors documented by the investigators using the drug kit. Additionally, DTOP indicated that the eye can be irrigated to remove the drug if too much volume is injected into the iris. However, we identified areas in the label and labeling that can be improved to further alert health care practitioners (HCP) to the correct preparation and administration of the drug. Thus, we found additional mitigation strategies (labels and labeling) that can be incorporated to minimize the risk of an overdose.

Assessment of Prescribing Information

Our assessment identified areas of concern as follows:

A. Highlights and Full Prescribing Information
    1. The symbol 'µL' is used throughout the prescribing information. This symbol can be misread as 'mL' and lead to an overdose.
B. Highlights of Prescribing Information
    1. There is no statement in the Dosage and Administration section to alert health care practitioners (HCP) to see the Full Prescribing Information (PI) for preparation and administration instructions.
C. Full Prescribing Information
    1. Section 2.2 includes preparation and administration instructions, not just administration instructions.
    2. Under Section 2.2 (Administration) where the glass vial is referenced as item #1, there is no statement to alert HCPs that after preparation, 0.005 mL will be delivered. This statement will alert HCPs that only a small portion of the drug will be given (b) (4)
    3. In Section 2.2, Steps 1-11, There is confusion as to who should be performing each step- either the surgeon, scrub nurse, or operating room assistant.
    4. In Section 2.2, Step 3, the illustration is confusing. It appears that the needle cap should be removed before placing the needle on the syringe.
    5. In Section 2.2, Step 6, there is no close-up illustration of the needle immersed in the drug near the neck of the vial. This will demonstrate that the needle should not be above the surface of the drug. Otherwise the HCP will draw up air instead of drug. Additionally, step 6 does not indicate how munch drug volume should be withdrawn from the vial into the syringe. Lastly, step 6 does not instruct the HCP to discard the unused portion of the vial after the needle is removed.

6. In Step 7, it is unclear if the needle should be recapped before removing the needle from the syringe.
7. In Section 2.2, Step 11, the step does not include instructions to discard the unused portion remaining in the syringe. This is important because after administration there will be excess drug in the syringe that should not be stored and later used on other patients.
8. In Section 3 (Dosage Forms and Strengths) there is no basic description of the package (i.e. provided as a kit to administer a single dose of 0.005 mL of 9% dexamethasone).
9. In Section 3 (Dosage Forms and Strengths) and Section 16 (How Supplied/Storage and Handling), there is no description of the injectable suspension characteristics (i.e. white, opaque…).
10. In Section 16 (How Supplied/Storage and Handling) the NDC number is not included.
11. In Section 16 (How Supplied/Storage and Handling) the statement (b) (4) (b) (4) is incorrect. Five microliters are equal to 0.005 mL.
12. In Section 16 (How Supplied/Storage and Handling) the vial size, 2 mL, is included in the description. This could cause confusion that there is 2 mL of drug volume.
13. In Section 16 (How Supplied/Storage and Handling) (b) (4)
14. In Section 16 (How Supplied/Storage and Handling), the package type is stated as (b) (4) We defer to OPQ for the correct package type.

We provide recommendations in Section 4.1 to address these concerns.

Assessment of Container Label and Carton Labeling

We identified areas of concern that could lead to medication errors and they are as follows:

1. The established name and strength lack prominence on the container label and carton labeling.
2. The strength statement '0.5 mg dexamethasone/0.005 mL' is not included on the top panel of the carton labeling.
3. The principal display panel of the container label should include the statement 'to deliver 0.005 mL.
4. The top panel on the carton labeling does not include a statement to alert health care practitioners (HCP) to consult the preparation and administration instructions in the Prescribing Information (PI). The steps that include the syringe ring and syringe guide to prepare a dose are critical, thus a reference to read the Prescribing Information should be included on the top panel, which is the most prominent panel of the carton.

5. The storage statement [redacted] (b) (4)
6. There is no package type (i.e. single-dose) term on the carton labeling. The package type should be included on the carton labeling per the FDA guidance.[a] We defer to the Office of Pharmaceutical Quality (OPQ) on the appropriate package type term.
7. There is no statement on the carton labeling to discard the unused portion of the medication. This is important because of the excess volume in the vial and syringe after delivery of the dose.
8. The expiration date on the container label is expressed as xxxx-xx and the carton labeling (kit) expiration date is expressed as xx/xx The expiration date formats should be consistent and presented in accordance with USP <7> Labeling and FDA guidance[b] (e.g. MMMYYYY or MMMDDYYYY).
9. The Prescribing Information sheet included in the to be marketed kit sample we obtained from Icon Biosciences is small and difficult to read.

We provide recommendations in Section 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

We find the excess drug volume required to prepare the dose acceptable from a medication error perspective. We provide recommendations for the Prescribing Information (PI) in Section 4.1and recommendations for the container label and carton labeling in Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information

1. The symbol 'µL' is used throughout the Dosage and Administration, Dosage Form and Strengths, and How Supplied sections of the PI. This symbol can be misread as 'mL' and could lead to an overdose. We recommend stating the dose as '0.005 mL' since the syringe used to prepare and administer the dose is calibrated in mL increments.

B. Highlights of Prescribing Information

[a] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

[b] Safety considerations for container labels and carton labeling design to minimize medication errors. Draft guidance for industry. Apr 2013. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf [cited 24 Oct 2017]

1. In the Dosage and Administration section we recommend the statement 'See Full Prescribing Information for instructions on administration of the injectable suspension' to alert healthcare practitioners (HCP) to the instructions.

C. Full Prescribing Information

1. We recommend Section 2.2 be re-titled 'Preparation and Administration' since both occur in this section.
2. Under Section 2.2 (Administration) where the glass vial is referenced as item #1, there is no statement to alert HCPs that after preparation, 0.005 mL will be delivered. We recommend the statement 'After preparation 0.005 mL will be delivered.' to alerts HCPs that only a small portion of the drug will be given rather than 0.5 mL in the vial.
3. In Section 2.2, Steps 1-11, we recommend that the person performing each step be identified. There is confusion as to who should be performing each step- either the surgeon, scrub nurse, or operating room assistant.
4. In Section 2.2, Step 3, the illustration is confusing. It appears that the needle cap should be removed before placing the needle on the syringe. We recommend the Sponsor clarify the illustration.
5. In Section 2.2, Step 6, we recommend an illustration of the needle immersed in the drug near the neck of the vial. This will demonstrate that the needle should not be above the surface of the drug. Otherwise the HCP will draw up air instead of drug.
6. In Section 2.2, Step 6, we recommend the Sponsor indicate how much drug should be withdrawn from the vial into the syringe.
7. In Section 2.2, Step 6, we recommend the Sponsor add a statement to discard the unused portion of the vial after the needle is removed.
8. In Section 2.2, Step 7, we recommend the Sponsor clarify if the needle should be re-capped before removing the needle from the syringe.
9. In Section 2.2, Step 11, we recommend adding the statement 'Discard unused portion remaining in the syringe'. This is important because after administration there will be excess drug in the syringe that should not be stored and used on other patients later.
10. In Section 3 (Dosage Forms and Strengths) we recommend adding a basic description of the package (i.e. provided as a kit to administer a single dose of 0.005 mL of 9% dexamethasone).
11. In Section 3 (Dosage Forms and Strengths) and Section 16 (How Supplied/Storage and Handling), we recommend adding a description of the injectable suspension characteristics (i.e. white, opaque…).

12. In Section 16 (How Supplied/Storage and Handling) we recommend adding the NDC number.
13. In Section 16 (How Supplied/Storage and Handling) the statement (b) (4) is incorrect. Five microliters are equal to 0.005 mL. Thus, the statement should be corrected to prevent confusion.
14. In Section 16 (How Supplied/Storage and Handling) the vial size, 2 mL, is included in the description. We recommend removing this information, since this will lead to confusion over how much drug volume is in the vial.
15. In Section 16 (How Supplied/Storage and Handling) (b) (4)
16. In Section 16 (How Supplied/Storage and Handling), the package type is stated as (b) (4) We recommend that the package type be clarified and we defer to OPQ for the correct package type.

4.2 RECOMMENDATIONS FOR ICON BIOSCIENCES

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling

1. The established name and strength lack prominence. Increase the prominence of the established name considering all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Ensure the expiration date format on the container label and carton labeling is consistent with each other and easily understood as recommended by USP General Chapter <7> Labeling and FDA guidance (e.g. MMMYYYY or MMMDDYYYY).[c] Currently, the expiration date is expressed as xxxx-xx on the container label and xx/xx on the carton labeling (kit).

B. Carton Labeling

1. Include the strength statement '0.5 mg dexamethasone/0.005 mL' on the top panel of the carton labeling to make this critical information more prominent.
2. Include the statement 'See Full Prescribing Information for instructions on preparation and administration of the injectable suspension.' on the top panel of the carton labeling. Since a syringe ring and syringe guide are required to prepare and administer the correct volume of

[c] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

Reference ID: 4189751

medication, this alert should be included to direct HCPs to the preparation and administration instructions.

3. Revise the storage statement on the carton labeling to read (b) (4)

4. Include the statement 'Discard unused portion' on the carton labeling. This statement is important to include because of the excess volume in the vial and syringe after delivering the dose.

C. Container Label

1. The principal display panel of the container label should include the statement 'To deliver 0.005 mL. This critical statement alerts HCPs to the appropriate volume to be injected. This may require you to move or make the 'Icon' Logo smaller to provide enough room to include this statement.

D. General Comment for the Kit

1. Enlarge the font size of the Prescribing Information sheet included in the kit. The current PI sheet in your sample kit you provided us is small and difficult to read.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dexycu that Icon Bioscience, Inc. submitted on April 12, 2017.

Table 2. Relevant Product Information for Dexycu	
Initial Approval Date	N/A
Active Ingredient	Dexamethasone
Indication	[redacted] (b) (4) for the treatment of postoperative inflammation
Route of Administration	Ocular
Dosage Form	Suspension for Intraocular Injection
Strength	9%
Dose and Frequency	Inject 0.005 mL into the [redacted] (b) (4) behind the iris immediately after the completion of surgery
How Supplied	Each kit contains a single-use 2-cc glass vial with a blue cap designed to deliver 0.005 mL of 103.4 mg/mL dexamethasone
Storage	[redacted] (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS: N/A
APPENDIX C. HUMAN FACTORS: N/A
APPENDIX D. ISMP NEWSLETTERS: N/A
APPENDIX E. FDA Adverse Event Reporting System (FAERS): N/A
APPENDIX F. OTHER: N/A

APPENDIX G. LABELS AND LABELING

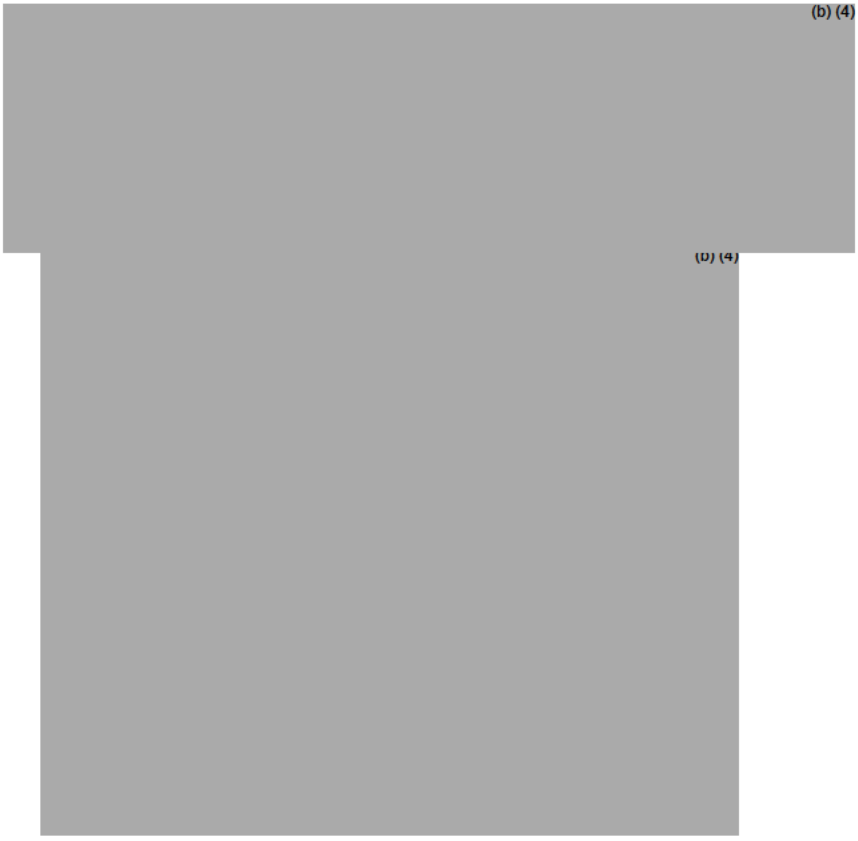
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Dexycu labels and labeling submitted by Icon Bioscience on April 28, 2017 and June 9, 2017.

- Container label - April 28, 2017
- Carton labeling - April 28, 2017
- Prescribing Information (Image not shown) - June 9, 2017
- Administration Instructions in *Dosage and Administration; Full Prescribing Information*

G.2 Label and Labeling Images

Container Label



[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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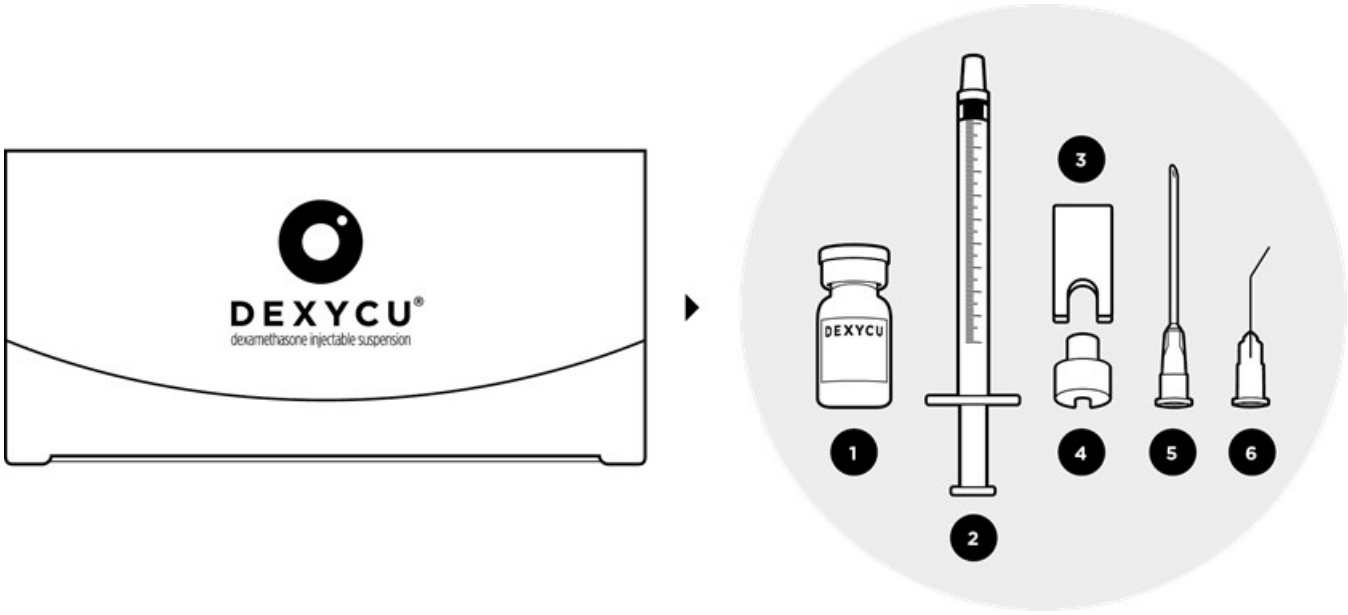
G.3 Administration Instructions in *Dosage and Administration; Full Prescribing Information*

The DEXYCU administration kit contains the following items:



1. One glass **vial**: 0.5 mL of DEXYCU [redacted] (b) (4)

2. One sterile 1-mL **syringe**

3. One sterile **syringe guide**

4. One sterile **syringe ring**

5. One sterile 18-gauge **needle** (1½ inches long), plastic cap attached

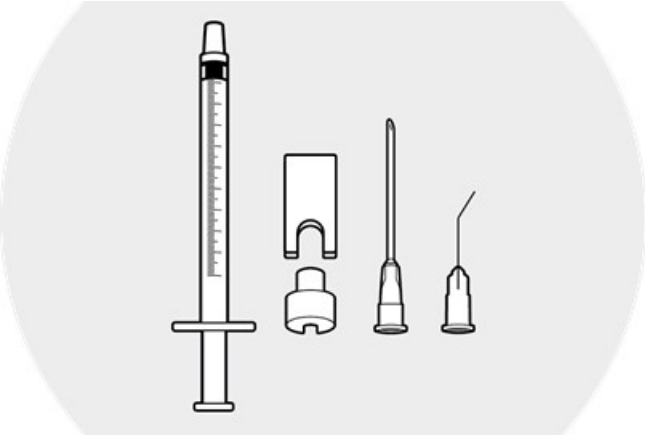
6. One sterile 25-gauge bent **cannula** (8 mm long), plastic cap attached

Step 1.

Prepare a sterile field.

Remove the components of the administration kit from their respective pouches:

- syringe
- syringe guide
- syringe ring
- needle
- cannula



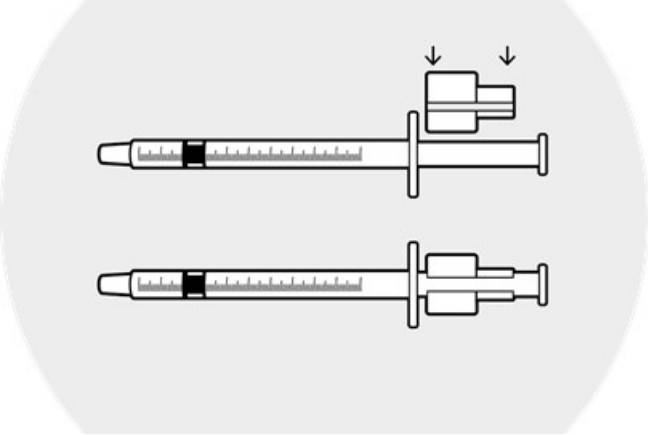
Place onto the sterile field.

Step 2.

Withdraw the syringe plunger approximately 1 inch.

Place the syringe ring on the plunger (slit facing the plunger).

Apply slight downward pressure until the syringe ring "snaps" into place.

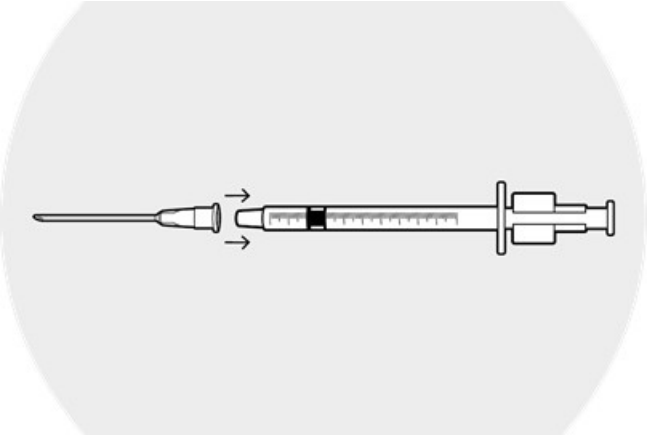


Step 3.

Place the 18-gauge needle firmly on the syringe.

Remove the cap from the needle.

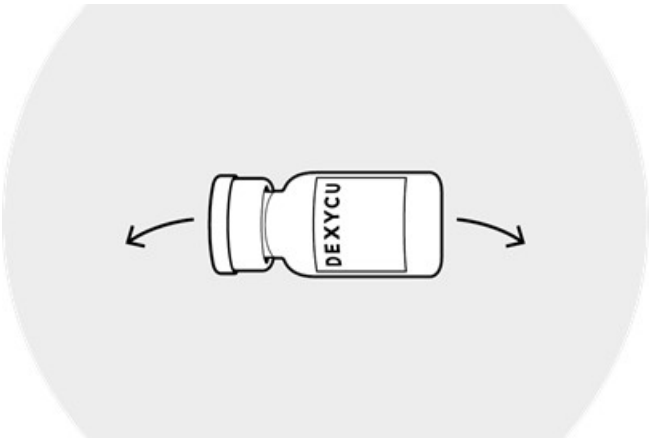
Depress the plunger completely and then withdraw the plunger to fill the syringe with air.



Step 4.

Vigorously shake the vial of DEXYCU sideways for a <u>minimum</u> of 30 seconds (b) (4)

The suspended drug material must be used immediately after shaking.



Step 5.

Remove the blue plastic flip-cap from the vial and wipe the top of rubber stopper with an alcohol pad.

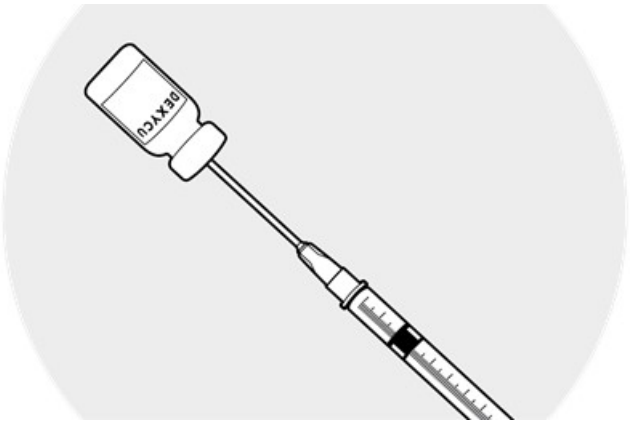
Invert the vial (b) (4)

Step 6.

Insert the needle into the vial and inject the air into the vial.

Making sure the needle tip is immersed in the drug material pooled in the neck of the inverted vial, fill the syringe by slowly withdrawing the plunger.

Remove the needle from the vial.



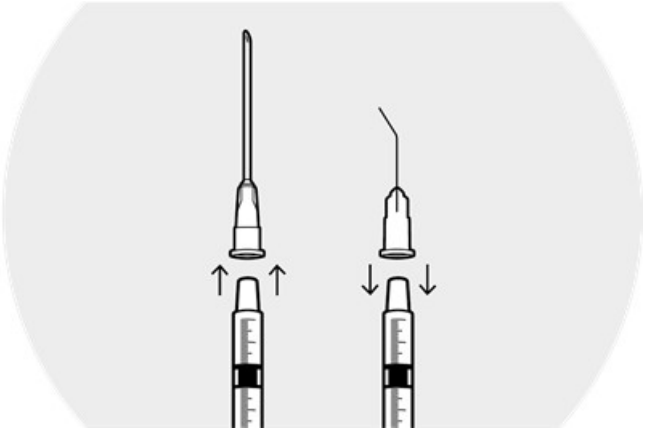
Step 7.

Remove the needle from the syringe.

Firmly place the cannula on the syringe and remove the plastic cap.

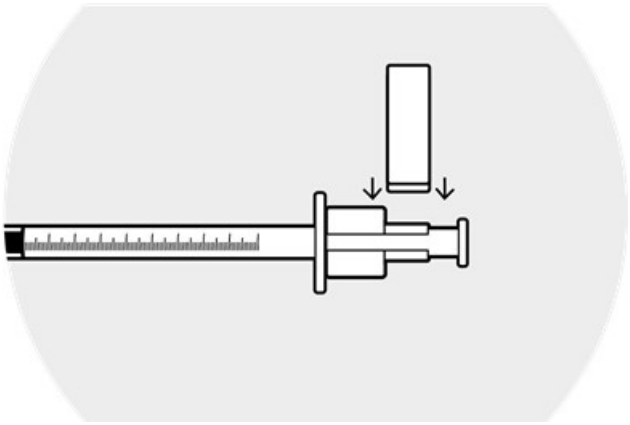
Hold the syringe vertically with the cannula pointing up.

Depress the plunger to expel air bubbles from syringe.



Step 8.

Affix the syringe guide over the syringe ring on the plunger.

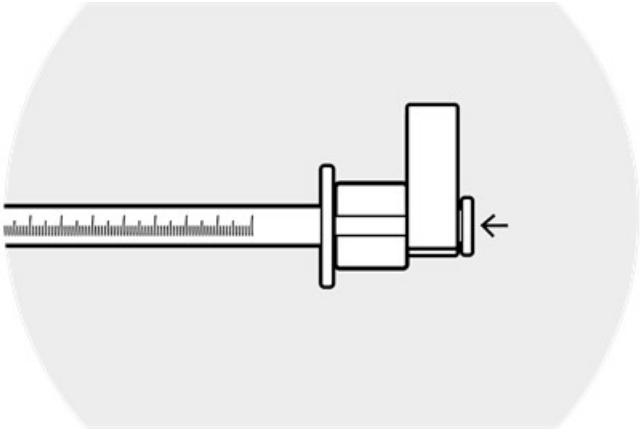


Step 9.

Depress the plunger until the syringe guide/ring mechanism comes gently into contact with the flange of the syringe.

Lightly tap/flick the barrel of the syringe to remove any excess drug from the tip of the cannula.

Do not wipe or touch the tip of the cannula to remove excess drug.

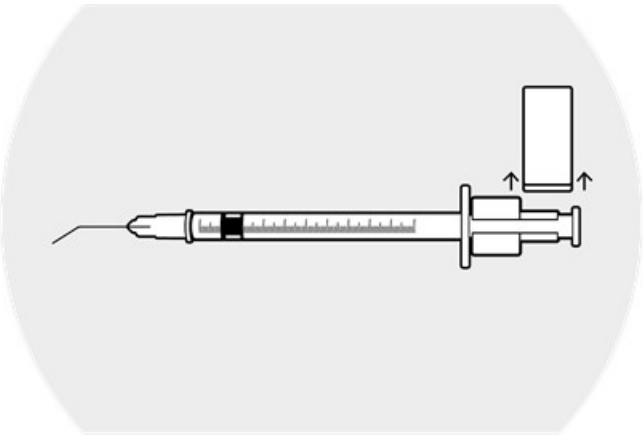


Step 10.

Remove the syringe guide, leaving the syringe ring in place.

(b) (4) **to not move the plunger**. The space between the syringe ring and the top of the plunger is the medication injection volume that will be applied to the patient's eye.

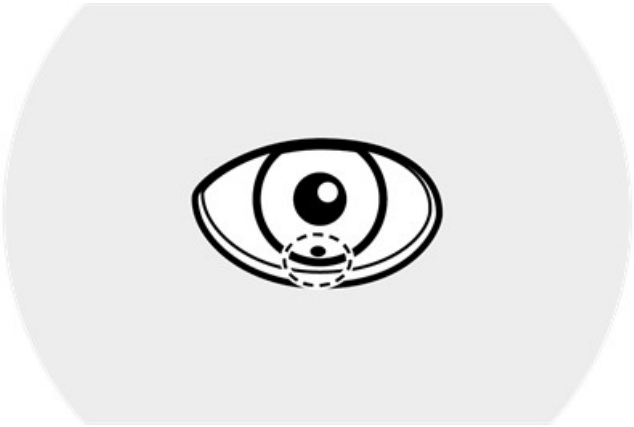
The syringe is now ready for injection.



Step 11.

In a single slow motion, inject the drug material behind the iris in the inferior (b) (4). If the sphere of administered drug after intraocular injection appears to be larger than 2 mm in diameter, excess drug material may be removed by irrigation and aspiration in the sterile surgical setting

PLEASE NOTE: Some drug material will remain in the syringe after the injection—this is necessary for accurate dosing.



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/s/

JAMES H SCHLICK
12/04/2017

OTTO L TOWNSEND
12/04/2017

Clinical Inspection Summary

Date	November 30, 2017
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	William Boyd, Clinical Team Leader Jennifer Harris, Clinical Reviewer Diana Willard, Regulatory Project Manager
NDA#	208912
Applicant	Icon Bioscience
Drug	Dexycu (dexamethasone intraocular injection)
NME	No
Review Priority	Standard Review
Proposed Indication	Treatment of postoperative inflammation (b) (4)
Consultation Request Date	June 5, 2017
Summary Goal Date	December 12, 2017
Action Goal Date	February 12, 2017
PDUFA Date	February 12, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Sampson and Nordlund were inspected in support of this NDA. Based on the results of these inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of both of these inspections was Voluntary Action Indicated (VAI).

2. BACKGROUND

The Applicant submitted this NDA to support the use of Dexycu (IBI-10090, dexamethasone intraocular injection) in the treatment of post-operative inflammation (b) (4)

Inspections were requested for the following protocol in support of this application:

Protocol C13-04, "A Phase 3, Prospective, Randomized, Double-masked, Placebo-controlled, Parallel-design, Multicenter Study to Evaluate Efficacy and Safety of IBI-10090 for the Treatment of Inflammation Associated with Cataract Surgery"

This study was conducted at 27 domestic study sites enrolling 395 subjects.

The primary objective of this study was to evaluate the efficacy of two dose levels of IBI-10090 (dexamethasone suspension for intraocular injection) in the treatment of inflammation associated with cataract surgery.

The primary efficacy endpoint was the proportion of patients with clearing of the anterior chamber cells (that is, ACC grade = 0) 8 days after surgery (that is, at POD 8).

Rationale for Site Selection

The clinical sites of Drs. Sampson and Nordlund were selected for inspection because they enrolled relatively large numbers of subjects and have not been previously inspected.

3. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
Site #09 Reginald Sampson, M.D. Hull Eye Center 1739 West Avenue Lancaster, CA 93534	C13-04 Subjects: 35	14-18 Aug 2017	VAI
Site #27 Michael L. Nordlund, M.D., Ph.D. Cincinnati Eye Institute 4760 Red Bank Expressway, Suite 108 Cincinnati, OH 45227 Cincinnati Eye Institute Ambulatory Surgery Center 945 CEL Drive Cincinnati, OH 45227	C13-04 Subjects: 24	11-18 Oct 2017	VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

1. Reginald Sampson, M.D.

At this site for Protocol C13-04, 49 subjects were screened, 35 subjects were randomized, and 34 subjects completed the study.

The records of all 35 randomized subjects were reviewed. The records reviewed for these subjects included, but were not limited to, financial disclosure forms, IRB and monitoring correspondence, informed consent forms, subject records, inclusion/exclusion criteria, monitoring records, protocol deviations, adverse events, and test article accountability.

Informed consent procedures appeared to be adequate. The primary efficacy endpoint was verifiable.

However, a Form FDA 483 was issued at the conclusion of the inspection noting that study documentation was inadequate for Subjects (b) (6). Specifically, for all four subjects, the right eye was identified as the study eye (that is, the eye to receive cataract surgery) but the test article was described as being administered to the left eye. For all four subjects, the Clinical Study Report indicated that the right eye was the eligible study eye.

(b) (6) the sub-investigator, responded to the Form FDA 483 in writing in a letter dated September 1, 2017. She stated that each of these four discrepant case histories was the result of a typographical error. Her response was adequate. These documentation errors would appear to have affected neither safety nor efficacy considerations.

2. Michael L. Nordlund, M.D., Ph.D.

At this site for Protocol C13-04, 34 subjects were screened and 24 subjects were randomized, with one subject not receiving the study drug due to complications during surgery.

The records of all 34 subjects were reviewed. The records reviewed for these subjects included, but were not limited to, regulatory documents, Form FDA-1572s, financial disclosure forms, IRB, sponsor, and monitor correspondence, staff training, informed consent forms, case report records, inclusion/exclusion criteria, electronic records, subject medical records, subject visit worksheets, study procedures, primary and secondary efficacy data, adverse events, protocol deviations, concomitant medications, and test article accountability.

Informed consent procedures appeared to be adequate. The primary efficacy endpoint was verifiable.

The EIR notes that the data listings for Subjects (b) (6) (342 mcg arm), (b) (6) (placebo arm), and (b) (5) (517 mcg arm) were erroneous for gradation of cells (1), cells (1), and flare (1), respectively, at, post-operative Day 1 (POD 1). Correct data listings would have been cells (2), cells (2), and flare (0), respectively, per post-inspection correspondence with our investigator. These discrepancies would not appear to significantly affect safety and/or efficacy considerations, especially as the primary efficacy endpoint was measured on POD 8.

A Form FDA 483 with a single observation was issued at the conclusion of the inspection noting that on 32 occasions for 11 subjects, the line listings indicate a “0” for anterior chamber flare while in the electronic medical record no value for flare was documented.

Dr. Nordlund responded to the Form FDA 483 in writing in a letter dated October 20, 2017, explaining that the sub-investigator performing this assessment did not document flare if no flare was evident. Dr. Nordlund further noted that the sub-investigator has been retrained regarding the need for appropriate documentation of positive and negative study findings. Dr. Nordlund's written response appears adequate.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\NDA 208912
DTOP\Division Director\Renata Albrecht
DTOP\Team Leader\William Boyd
DTOP\Medical Officer\Jennifer Harris
DTOP\Project Manager\Diana Willard
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
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KASSA AYALEW
12/01/2017