CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207154Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **February 17, 2016**
From: **Yichun Sun, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 207154

Subject: Final Approval Recommendation for NDA 207154

At the time when the CMC review #1 was written, resolution of issues on Labels and Labeling was pending.

Label/Labeling

On February 11, 2016, the NDA applicant submitted an amendment providing the finalized mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now satisfactorily resolved. The review of the CMC sections of the final package insert, and mock up container and carton labels was conducted by Dr. Hitesh Shroff is attached (**Attachment - 1**).

Recommendation:

The revised package insert and mock-up container and carton labels are acceptable from the CMC perspective. Therefore, from the ONDP's perspective, this NDA is recommended for **APPROVAL**. An expiration dating period of 24 months is granted for the drug product of NDA 207154.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
2/17/2016

Yichun Sun -S

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Date: 2016.02.17 14:21:13 -05'00'

Attachment - 1 (Review of CMC Sections of the Finalized Labeling and Labels)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **February 17, 2016**

From: **Hitesh Shroff**
Senior CMC Reviewer
DNDP II/ONDP

Hitesh N. Shroff -S

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Date: 2016.02.17 12:20:39 -05'00'

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
DNDP II/ONDP

To: **CMC Review #1 of NDA 207154**

Subject: **Final Approval Recommendation**

The CMC review #1 has noted the following pending issues:

- The label/labeling issues were not completely resolved.

Because of these deficiencies, in the CMC review #1, this NDA was not recommended for approval from the CMC perspective.

The package insert and the container and carton labels have been revised and submitted on February 11, 2016. The labels/labeling are revised satisfactorily from the CMC perspective (**Attachment 1**).

Recommendation:

This NDA is now recommended for approval from the ONDP perspective.

1. *Package Insert*

(a) "Highlights" Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACZONE® Gel, 7.5% safely and effectively. See full prescribing information for ACZONE® Gel, 7.5%.

ACZONE® (dapsone) Gel, 7.5%, for topical use
Initial U.S. Approval: 1955

DOSAGE FORMS AND STRENGTHS
Gel, 7.5% (3).

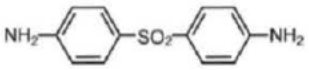
(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

3 DOSAGE FORMS AND STRENGTHS
Gel, 7.5%. Each gram of **ACZONE** Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel with suspended particles.

#11. Description

11 DESCRIPTION
ACZONE (dapsone) Gel, 7.5%, contains dapsone, a sulfone, in an aqueous gel base for topical dermatologic use. **ACZONE** Gel, 7.5% is an off-white to yellow gel with suspended particles. Chemically, dapsone has an empirical formula of $C_{12}H_{12}N_2O_2S$. It is a white or slightly yellow-white, crystalline powder that has a molecular weight of 248.30. Dapsone's chemical name is 4-[(4-aminobenzene) sulfonyl] aniline and its structural formula is:



Each gram of **ACZONE** Gel, 7.5%, contains 75 mg of dapsone, USP, in a gel of diethylene glycol monoethyl ether, methylparaben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80, and purified water.

#16 How Supplied/storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

ACZONE Gel is an off-white to yellow gel with suspended particles. It is supplied in an airless pump containing a polypropylene bottle with a high density polyethylene piston.

ACZONE (dapsone) Gel, 7.5%, is supplied in the following sizes:

NDC 0023-5206-30	30 gram pump
NDC 0023-5206-60	60 gram pump
NDC 0023-5206-90	90 gram pump

Storage: Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. Protect from freezing.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Recommendation:
This 505(b)(1) NDA is not deemed ready for approval as of this review in its present form per 21 CFR 314.125(b)(6).

NDA 207154
Review #1

Drug Name/Dosage Form	Dapsone/Gel
Strength	7.5%
Route of Administration	For topical use only
Rx/OTC Dispensed	Rx
Applicant	Allergan, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA submission	4/28/2015	All disciplines of the review team
Amendment	6/1/2015	Facility
Amendment	7/15/2015	Biopharmaceutics
Amendment	7/31/2015	Quality microbiology
Amendment	8/21/2015	Drug product
Amendment	9/15/2015	Drug product
Amendment	9/15/2015	Drug product manufacturing process
Amendment	9/30/2015	Biopharmaceutics
Amendment	10/14/2015	Biopharmaceutics

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	Branch II/Division of New Drug API
Drug Product	Hitesh Shroff	Branch V/Division of New Drug Products II
Process	Yuesheng Ye	Branch VIII/Division of Process Assessment III
Microbiology	Elizabeth Bearr	Branch I/Division of Microbiology Assessment
Facility	Sherry (Xiaohui) Shen	Branch III/Division of Inspection Assessment
Biopharmaceutics	Vidula Kolhatkar	Branch II/Division of Biopharmaceutics
Regulatory Business Process Manager	Maria Cowan	Branch I/Division of Regulatory and Business Process Management
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II
ORA Lead	Paul Perdue, Jr	Division of Medical Products & Tobacco Operations
Environmental Assessment (EA)	Hitesh Shroff	Branch V/Division of New Drug Products II

Table of Contents

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	15-Dec-2015	Reviewed by Dr. Martin Haber
	Type III			N/A	Not reviewed	Adequate information provided in NDA
	Type III			N/A	Not reviewed	Adequate information provided in NDA
	Type IV			Adequate	14-DEC-2015	Reviewed by Dr. Hitesh N. Shroff

1 Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
EOP2 meeting minutes	IND 054440	Discussion of the development plan for dapsone gel, 7.5% for the treatment of acne Vulgaris.
Advice letter	IND 054440	Comments and recommendations regarding the proposed dosage form.
Pre-NDA meeting minutes	IND 054440	Discussion of the development plan for dapsone gel, 7.5%.
Cross reference letter	NDA 21794	Providing the location of chemistry, manufacturing, and controls information previously submitted to NDA 21794 for ACZONE (dapsone) Gel, 5% and specifically referenced by this application.

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility has issued an "Approval" recommendation for the facilities involved in this application (See the **Attachment B**).

However, the issues on labels/labeling are not completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved (See the **List of Deficiencies** on pp. 100-101).

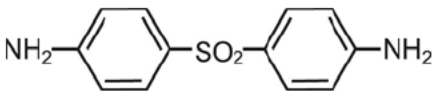
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The drug substance/active pharmaceutical ingredient (API) used in the drug product, (dapsone gel), is dapsone. The drug substance is chemically produced. The chemical name of dapsone is: 4-[(4-aminobenzene)sulfonyl]aniline. It has the following structural formula:



Dapsone is a white or slightly yellow-white, crystalline powder that has an empirical formula of $C_{12}H_{12}N_2O_2S$ and a molecular weight of 248.30. Dapsone melts in the temperature range of 175 – 181°C. Dapsone is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids. The amine groups on the aminobenzene rings have calculated pKa_1 of 0.5 and calculated pKa_2 of 1.2, respectively.

(b) (4)

(b) (4)

B. Drug Product [Established Name] Quality Summary

The drug product, ACZONE (dapsone) Gel, is an off-white to yellow gel with suspended dapsone particles. The strength of dapsone gel is 7.5% (w/w). Dapsone is a sulfone indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. Each gram of ACZONE contains 75 mg of dapsone in a gel of diethylene glycol monoethyl ether, methylparaben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80, and purified water.

ACZONE (dapsone) Gel, 7.5%, is packaged in an airless pump container closure system in 3 different sizes (30 g, 60 g and 90 g). The airless pump contains a polypropylene bottle with a high density polyethylene piston. Additionally, 3 g professional samples packaged in an (b) (4) laminated tube are also available.

The dapsone gel is prepared by (b) (4)

(b) (4)

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. An in vitro release test (IVRT) of dapsone gel has been developed but not fully validated. The facility review team from the Office of Process and Facilities has provided an Overall Acceptable recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on the 12-month long-term and 6-month accelerated stability data obtained from 3 registration batches of the drug product.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Aczone
Non Proprietary Name of the Drug Product	Dapsone gel
Non Proprietary Name of the Drug Substance	Dapsone
Proposed Indication(s) including Intended Patient Population	Dapsone gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.
Duration of Treatment	N/A
Maximum Daily Dose	Approximately a pea-sized amount of Aczone gel, 7.5%, in a thin layer to the entire face once daily or other affected areas once daily.
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: N/A
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: N/A
   - IVIVC: N/A
   - IVRT:

   An IVRT method has been developed by the NDA applicant. However, the IVRT method has not been fully validated. The applicant proposed to validate the IVRT method before it can be used to test to-be-marketed batches of the gel. Additionally, acceptance criteria of the IVRT method will be set until sufficient data with validation lots (t = 0 and stability data) are available. The Agency agrees with the applicant's approach for establishing in vitro release specifications. The following comments were conveyed to the applicant in a general advice letter on December 23, 2015:

   - Submit the IVRT method validation report, and provide your proposed in vitro release acceptance criteria based on the data

from at least 6 production batches, to the Agency at your earliest convenience, but by the first Annual Report at the latest.

E. Novel Approaches
N/A

F. Any Special Product Quality Labeling Recommendations
Protect from freezing.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
1/11/2016

Yichun Sun -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yichun Sun -S, 0.9.2342.19200300.100.1.1=1300393310
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ASSESSMENT OF THE BIOPHARMACUETICS

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

    In the 74-day letter, the Agency recommended that the applicant develop an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for the proposed drug product to be used at release and during stability as a quality control parameter.

Applicant's Response: On July 14, 2015 a teleconference was held between the Agency and the applicant to clarify the recommendation received in the 30 June 2015 Filing Communication letter. During the teleconference, the following items were agreed upon:

- Allergan committed to develop and validate an IVRT method as recommended by the Agency.
- Allergan agreed to provide a status update on method development and validation by the end of September 2015.
- The Agency agreed that if there are difficulties with completing the validation or justifying the specifications, the method validation and specifications can be set as a post-marketing commitment.

The applicant submitted a status report about in vitro release method development on September 30, 2015 as agreed at the teleconference.

(b) (4)

[redacted]

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(b) (4)

[redacted]

Reviewer's Assessment: IVRT method is acceptable.

The applicant has stated that the IVRT method will be validated prior to testing of to-be-marketed batches and specifications will be included as 'report' until sufficient data with validation lots (t = 0 and stability) are available.

The applicant's approach for the in vitro release specifications is acceptable.

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

    The commercial formulation was used in two pivotal Phase 3 studies and four Phase 1 studies.

Applicant's Response: N/A

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature: IVRT method is acceptable.
The applicant has stated that the IVRT method will be validated prior to testing of to-be-marketed batches and specifications will be included as 'report' until sufficient data with validation lots (t = 0 and stability) are available. The Agency agrees with the applicant's approach for establishing in vitro release specifications. The following comments were conveyed to the applicant in a general advice letter on December 23, 2015:

Submit the IVRT method validation report, and provide your proposed in vitro release acceptance criteria based on the data from at least 6 production batches, to the Agency at your earliest convenience, but by the first Annual Report at the latest.

Reviewer's Signature
Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
01/05/2016

Vidula R. Kolhatkar -S

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Date: 2016.01.11 11:29:13 -05'00'

Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics Assessment, and I concur with the Reviewer's assessment and comments to convey to the Applicant.

Supervisor's Signature
Kelly Kitchens, Ph.D.
QAL, Branch II
Division of Biopharmaceutics/ONDP
01/05/2016

Kelly M. Kitchens -S

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Date: 2016.01.11 11:31:55 -05'00'

ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response:
ACZONE (dapsone) Gel, 7.5% is a gel for cutaneous use. This is an aqueous, multiple dose product.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use) and comply with the agency's request that the drug product should not contain *Burkholderia cepacia*. These limits include a total combined yeasts and molds count (TYMC) of NMT (b) (4) CFU/g, total aerobic microbial count (TAMC) of NMT (b) (4) CFU/g, and the absence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *B. cepacia*.

Applicant states that the test for *B. cepacia* is based on principles derived from USP <62>. The test method requires a 1:100 dilution (for TAMC) and 1:10 dilution (for TYMC) of the test material in tryptic soy broth with 4% polysorbate 20 and 0.5% lecithin. If any organisms are detected, the identity of the organism will be determined. The submission dated 04/28/2015 did not provide validation studies to document that the test method can detect *B. cepacia* in the drug product.

The following information request was sent to the firm on 06/30/2015:

Section 3.2.P.5.2 of the application outlines the test for the absence of Burkholderia cepacia in the drug product. Provide the following:
a. A detailed description of the test method that specifies the growth conditions (i.e., growth medium, incubation time and temperature).

In their response dated 07/31/2015, the applicant described the following test method.

(b) (4)

The following information was requested from the firm on 06/30/2015:

b. Validation studies to confirm that the test method is suitable for detection of B. cepacia in the drug product. Include pre-incubation conditions for the B. cepacia test strain and enumeration of inoculated organisms.

The applicant responded to the request on 07/31/2015 with the following information.

B. cepacia ATCC 25416 used for inoculation of the test group and control group is prepared by the following procedure.

(b) (4)

Following the above procedure, method suitability was demonstrated using 3 lots of Aczone 7.5%. The results are summarized in Table 1 copied from the submission.

Table 1 Method Suitablity using 3 Lot of Aczone 7.5%

Test Sample Lot#	Selective Media	Test Group (Product)	Positive Control	Negative Control	Viability Control, Average # of CFU
ENA-1C	MacConkey	Growth	Growth	No growth	(b) (4)
FHL-C	MacConkey	Growth	Growth	No growth	
FHK-C	MacConkey	Growth	Growth	No growth	

The microbial limits test methods for TYMC, TAMC, and absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* provided in the submission dated 04/28/2015 were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The product is tested for preservative content at release and as part of the stability program. The lower limit of the specification for preservative content is (b) (4) % w/w (b) (4) (b) (4). Antimicrobial effectiveness testing of a lot formulated with (b) (4) % w/w was performed using methods described in USP <51> and all lots met USP criteria for Category 2 products.

The drug product will also be tested for microbial limits as part of the post-approval stability protocol.

Reviewer's Assessment:

The microbial limits specification for ACZONE (dapsone) Gel, 7.5% is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

2.3.P.7 Container/Closure System

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

Applicant's Response: N/A

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

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

Applicant's Response: N/A

Reviewer's Assessment: N/A

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

Applicant's Response: N/A

Reviewer's Assessment: N/A

QUALITY ASSESSMENT

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The microbial limits specification for ACZONE (dapsone) Gel, 7.5% is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Reviewer's Signature
Elizabeth Bearr, Ph.D.
Branch I
Division of Microbiology Assessment/OPF
01/05/2016

Elizabeth R. Bearr -A
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Date: 2016.01.12 08:21:36 -05'00'

Secondary Review Comments and Concurrence:
I concur.

Supervisor's Signature
Erika Pfeiler, Ph.D.
Quality Assessment Lead, Branch I
Division of Microbiology Assessment/OPF
01/05/2016

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ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

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

Applicant's Response:
The action increases the use of 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. No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

QUALITY ASSESSMENT

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The claimed categorical exclusion from the preparation of an Environmental Assessment (EA) per 21 CFR 25.31 (b) is acceptable.

Reviewer's Signature
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP
12/18/2015

Hitesh N. Shroff -S

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Date: 2016.01.11 11:45:13 -05'00'

Secondary Review Comments and Concurrence:

I concur.

Supervisor's Signature
Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II/ONDP
12/18/2015

Moojhong Rhee -S

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Date: 2016.01.11 11:56:55 -05'00'

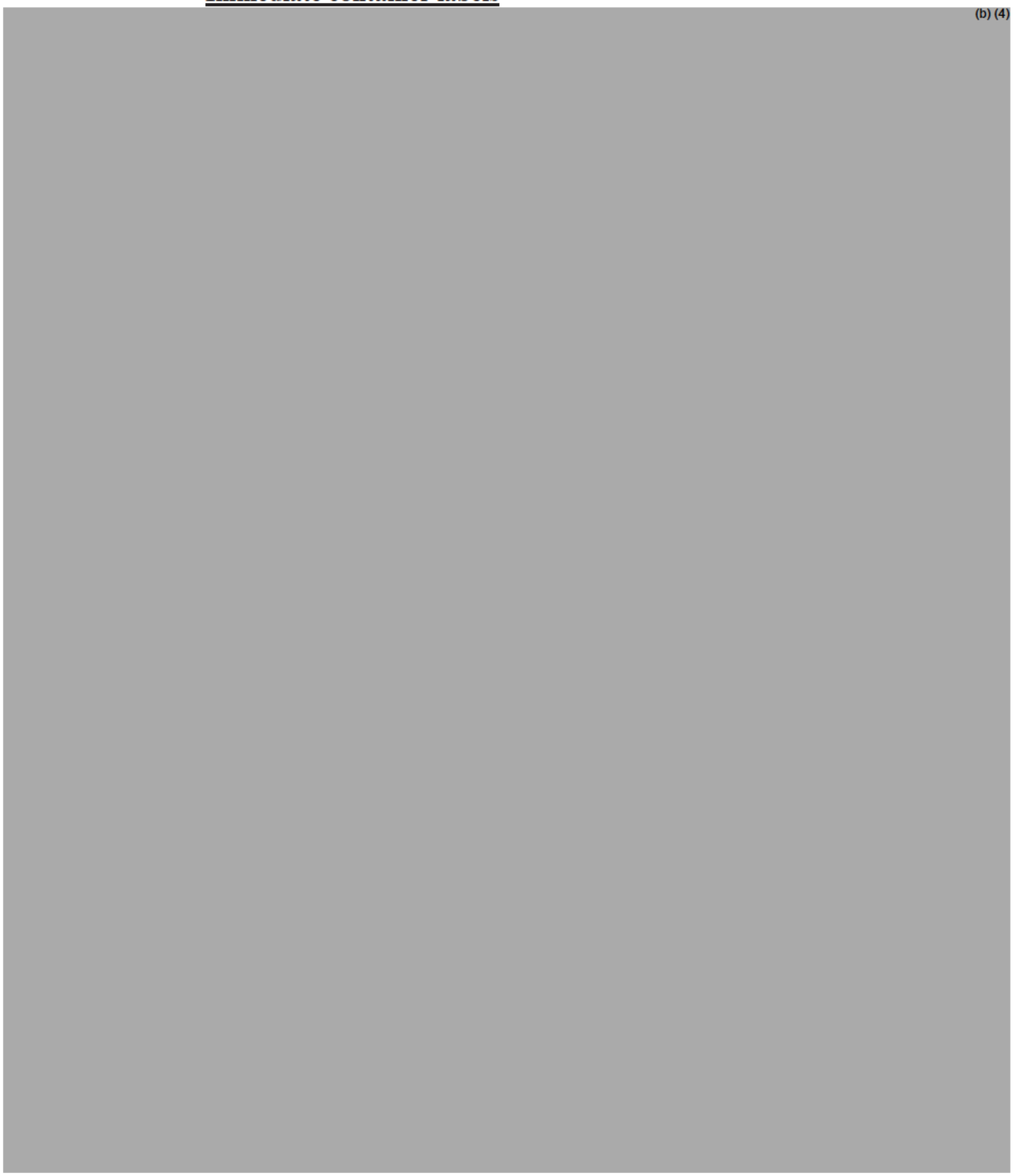
I. Review of Common Technical Document-Quality (CDd-Q) Module 1

A. Labeling & Package Insert

Carton and Container Labels

Immediate container labels

(b) (4)



(b) (4)

[redacted]

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The drug name is presented correctly. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Displayed as 7.5 % **Satisfactory**
Net contents (21 CFR 201.51(a))	Net content properly displayed as 30 g, 60 g and 90 g **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC numbers are indicated properly. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Not displayed **Not Satisfactory**
Storage conditions	Storage condition is not displayed properly **Not Satisfactory**
Bar code (21CFR 201.25)	Barcode is not displayed. **Not Satisfactory**
Name of manufacturer/distributor	The names of manufacturer and distributor are displayed correctly. **Satisfactory**
List of Ingredients	Incorrect ingredients are listed. **Not Satisfactory**

Evaluation: **Not adequate.** The 30 g, 60 g and 90 g pump labels should be revised to include the following information:

- Display "Lot:" and "Exp:"
- Display a barcode
- Add the following statement in the storage condition description "[See USP Controlled Room Temperature]"
- List ingredients as shown below:
  "Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water."

The 3 g sample tube labels should be revised to include the following information:

- Display "Lot:" and "Exp:"
- Add the following statement in the storage condition description "[See USP Controlled Room Temperature]"

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name and established name are correctly described. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	Displayed as 7.5 % **Satisfactory**
Net quantity of dosage form (21 CFR 201.51(a))	Correctly Displayed on the carton. **Satisfactory**
"Rx only" displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is displayed on the carton. **Satisfactory**
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	Lot and Exp are displayed. **Satisfactory**
Storage conditions	Storage condition is not described adequately on the carton. **Not Satisfactory**
Bar code (21CFR 201.25)	Bar code displayed correctly **Satisfactory**
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	NDC number displayed correctly **Satisfactory**
Manufacturer/distributor's name 21CFR201.1(a)	The names of manufacturer and distributor are displayed correctly. **Satisfactory**
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	Incorrect ingredients are listed. **Not Satisfactory**
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information" (21 CFR 201.55)	This statement is correctly displayed as "See package insert for dosage information" **Satisfactory**
"Keep out of reach of children" (Required for OTC but Optional for Rx drugs)	Displayed **Satisfactory**
Route of Administration (21 CFR 201.100(b)	Described as "for tropical use only" **Satisfactory**

Evaluation: Not Adequate.

The 8 x 3 g sample tubes, 30 g, 60 g and 90 g carton labels should be revised to include the following information:

- Add the following statement in the storage condition description

"[See USP Controlled Room Temperature]"

- List ingredients as shown below:

"Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water."

The 8 x 3 g sample tube carton labels should be revised to include the following information:

- Display "Lot:" and "Exp:"

Labeling Review

The following is a summary of the labeling review.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACZONE® Gel, 7.5% safely and effectively. See full prescribing information for ACZONE® Gel, 7.5%.

ACZONE® (dapsone) Gel, 7.5%
For topical use only
Initial U.S. Approval: 1955

---------DOSAGE FORMS AND STRENGTHS---------
Gel, 7.5%. Each gram of **ACZONE®** Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel (3).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name Dosage form, route of administration Controlled drug substance symbol (if applicable)	ACZONE (dapsone) gel N/A	The drug product title is described correctly. **Satisfactory** Dosage form is displayed correctly. The route of administration is not displayed. **Not Satisfactory**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Gel, 7.5%. Each gram of **ACZONE®** Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel	The dosage form and strength are described correctly. However, the description should be deleted. **Not Satisfactory**
Whether the drugproduct is scored (If the product is not scored, do not say		The product is not scored. **Satisfactory**

Evaluation: Not adequate. This section should be revised as follows:

- Display the drug product title as shown below:
  ACZONE (dapsone) gel, for topical use
- Delete the following statement:

Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel

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

3 DOSAGE FORMS AND STRENGTHS
Gel, 7.5%. Each gram of ACZONE® Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	gel	Dosage form is described correctly. **Satisfactory**
Strengths: in metric system	7.5%	The strength is described correctly. **Satisfactory**
Description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white yellow gel.	The dosage form is described correctly. **Satisfactory**

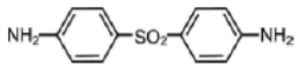
Evaluation: Not adequate. This section should be revised as follows:

- Revise the dosage form description as shown below:

  Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel with suspended particles.

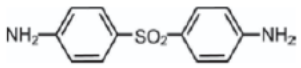
#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION
ACZONE® Gel, 7.5%, contains dapsone, a sulfone, in an aqueous gel base for topical dermatologic use. ACZONE® Gel, 7.5% is an off-white to yellow gel with suspended drug particles. Chemically, dapsone has an empirical formula of $C_{12}H_{12}N_2O_2S$. It is a white or slightly yellow-white, crystalline powder that has a molecular weight of 248. Dapsone's chemical name is 4,4'-diaminodiphenylsulfone and its structural formula is:



Each gram of ACZONE® Gel, 7.5%, contains 75 mg of dapsone, USP, in a gel of; diethylene glycol monoethyl ether; methylparaben; acrylamide/sodium acryloyldimethyl taurate copolymer; isohexadecane; polysorbate 80; and purified water.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	ACZONE Gel, 7.5%	The proprietary name is correct, however, the established name is not displayed. **Not Satisfactory**

Dosage form and route of administration	Gel , for topical dermatologic use	Dosage form and route of Administration are displayed correctly. **Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not applicable	**Not applicable**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	diethylene glycol monoethyl ether; methylparaben; acrylamide/sodium acryloyldimethyl taurate copolymer; isohexadecane; polysorbate 80; and purified water.	Information for inactive ingredients is provided correctly. **Satisfactory**
Statement of being sterile (if applicable)	Not applicable	**Not applicable**
Pharmacological/ therapeutic class	Sulfone	The Pharmacological/ therapeutic class displayed correctly **Satisfactory**
Chemical name, structural formula, molecular weight	Chemical Name: 4,4'-diaminodiphenylsulfone Molecular formula: $C_{12}H_{12}N_2O_2S$ Molecular weight: 248 molecular structure is: 	The chemical name is not the IUPAC name. The MW is not precise. **Not Satisfactory**
If radioactive, statement of important nuclear characteristics.		Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	An off-white to yellow gel with suspended drug particles. (Dapsone) It is a white or slightly yellow-white, crystalline powder.	The DP and DS described correctly. **Satisfactory**

Evaluation: No adequate. This section should be revised as follows:

- Revise the drug product title as shown below:
  ACZONE (dapsone) gel, 7.5%
- Replace the chemical name with the following IUPAC name:
  4-[(4-aminobenzene)sulfonyl] aniline
- The molecular weight of dapsone should be revised to "248.30"

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

16 HOW SUPPLIED/STORAGE AND HANDLING
ACZONE® (dapsone) Gel, 7.5%, is supplied in the following sizes:

NDC 0023-5206-30
30 gram airless pump polypropylene bottles

NDC 0023-5206-60
60 gram airless pump polypropylene bottles

NDC 0023-5206-90
90 gram airless pump polypropylene bottles

Storage: Store at controlled room temperature, 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F). Protect from freezing.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	7.5%	The strength is described correctly. **Satisfactory**
Available units (e.g., bottles of 100 tablets)	30 g, 60 g and 90 g airless pump propylene bottles	This information should be revised **Not Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not provided	This information is not provided. **Not Satisfactory**
Special handling (e.g., protect from light, do not freeze)	Protect from freezing	Special storage condition is provided.
Storage conditions	Store at controlled room temperature, 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F).	Information not provided correctly. **Not Satisfactory**

Evaluation: Not adequate. How Supplied and Handling section should be revised as follows:

- The following drug product and container closure description should be added
  ACZONE gel is an off-white to yellow gel with suspended particles It is supplied in airless pumps containing polypropylene bottles with high density polyethylene pistons.
- The following statement should be added to the storage condition
  [See USP Controlled Room Temperture]

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: Allergan, Inc. Irvine CA 92612, U.S.A. By: DPT Laboratories, Ltd. San Antonio, TX 78215 U.S.A.	Information is correctly provided. **Satisfactory**

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: NOT Adequate.

The applicant has provided preliminary labeling and package insert and request for their revision will be conveyed to the applicant, and labels and labeling have not been finalized as of this review.

Reviewer's Signature
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP
12/18/2015

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2016.01.11 11:47:28 -05'00'

Secondary Review Comments and Concurrence:

I concur with Dr. Hitesh Shroff's assessment on the labels and labeling.

Supervisor's Signature
Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II/ONDP
12/18/2015

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.01.11 11:57:49 -05'00'

I. List of Deficiencies To Be Communicated

The following comments should be conveyed to the applicant.

A. Regarding Label/labeling

Immediate container labels:

The 30 g, 60 g and 90 g pump labels should be revised to include the following information:

- Display "Lot:" and "Exp:"
- Display a barcode
- Add the following statement in the storage condition description "[See USP Controlled Room Temperature]"
- List ingredients as shown below:
  "Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water."

The 3 g sample tube labels should be revised to include the following information:

- Display "Lot:" and "Exp:"
- Add the following statement in the storage condition description
  "[See USP Controlled Room Temperature]"
- Include "Manufactured for: and by:" same as pump labels.

Carton labels:

The 8 x 3 g sample tubes, 30 g, 60 g and 90 g carton labels should be revised to include the following information:

- Add the following statement in the storage condition description
  "[See USP Controlled Room Temperature]"
- List ingredients as shown below:
  "Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water."

The 8 x 3 g sample tube carton labels should be revised to include the following information:

- Display "Lot:" and "Exp:"

PI

"Highlights" Section

This section should be revised as follows:

- Display the drug product title as shown below:
  ACZONE (dapsone) gel, for topical use
- Delete the following statement:
  "Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel"

"Dosage Forms and Strength" Section

This section should be revised as follows:

- Revise the dosage form description as shown below:
  "Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel with suspended particles."

#11 Description

This section should be revised as follows:

- Revise the drug product title as shown below:
  ACZONE (dapsone) gel, 7.5%
- Replace the chemical name with the following IUPAC name:
  4-[(4-aminobenzene)sulfonyl] aniline
- The molecular weight of dapsone should be revised to "248.30"

#16 How supplied/storage and handling

This section should be revised as follows:

- The following drug product and container closure description should be added.
  "ACZONE gel is an off-white to yellow gel with suspended particles It is supplied in airless pumps containing polypropylene bottles with high density polyethylene pistons."
- The following statement should be added to the storage condition
  "[See USP Controlled Room Temperature]"

II. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

Risk assessment of dapsone gel, 7.5%

Product Attribute/CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	Life-Cycle Consideration/ Comments
Assay (Dapsone)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	During the DP manufacturing process dapsone assay is an in-process-control. Also it is determined by an in-house validated HPLC method at release.	Low to None	None
Dapsone Related Substances	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	The dapsone related impurities are fully characterized and controlled in dapsone specification. The impurities are also controlled by DP specification. The impurities are assessed by an in-house validated HPLC method.	Low to None	None
Preservative content (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	The preservative concentration is confirmed to meet the specification by an in-house validated HPLC method at release.	Low to None	None
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	High	(b) (4) is added to control microbial contamination. Microbial limit tests and (b) (4) test are included in the DP specification.	Low to None	None
Apparent pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Moderate	The pH of the DP is controlled during the manufacturing as IPC and it is also controlled by DP specification.	Low to None	None
Apparent Viscosity (cps)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Moderate	The viscosity is determined to meet the DP specification at release by a validated analytical method.	Low to None	None
Within-Container Uniformity, USP <3>	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Moderate	Conforms to USP <3> and dapsone assay is determined to meet the DP specification.	Low to None	None
Minimum Fill	• Process parameters • Scale/equipment • Site	Low	Minimum fill is determined per USP <755>.	Low to None	None
Particle Size of API	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Moderate	The particle size is determined by an in-house validated method at release to meet the specification.	Lot to None	None
Pump Functionality: 1. Number of actuations to Prime 2. Amount dispensed per Actuation 3. Total amount drug product dispensed	• Formulation • Raw materials • Process parameters	Low	The pump is not a metered dose release pump. Pump functionality tests are included in the DP release specification.	Lot to None	None

B. **Facility Recommendation:** "Approve" recommendation was entered in Panorama on Dec 9, 2015.

Facility Status View for NDA 207154

Displays information for the facilities that are associated to NDA 207154. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.
Time run: 1/8/2016 12:18:46 PM

Overall Manufacturing Inspection Recommendations for NDA 207154

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 207154-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	ALLERGAN INC	Approve	Complete	12/9/2015

OPF Facility Recommendations for Facilities on NDA 207154

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
(b) (4)							
NDA 207154-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	3002606285	219682291	ALLERGAN PHARMACEUTICALS IRELAND	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	9/22/2015
NDA 207154-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	1643525	967467379	ALLERGAN SALES LLC	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	12/9/2015
(b) (4)							