CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213478Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **March 16, 2022**
From: **Hamid Shafiei, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: **To Executive Summary, IQA for Assessment # 1 of NDA 213478**

Subject: **Amendment #2: Final Recommendation of Approval**

In the original IQA review #1 dated June 24, 2020, and the amendment # 1 to IQA dated June 23, 2021, satisfactory resolutions of remaining deficiencies listed below were required before this application can be recommended for approval from the OPQ perspective.

- Facilities had not been cleared because of **pending required preapproval inspections** of TOYO Pharmaceutical Co., LTD. manufacturing facility, FEI 3016419927 which had been deferred due to the travel restrictions caused by the COVID-19 pandemic.
- The CMC issues on labels/labeling had **not** been satisfactorily resolved

The Office of Pharmaceutical Quality Assessment (OPMA) has completed the assessment of the drug product manufacturing facility, TOYO Pharmaceutical Co., using the 704(a)(4) process in lieu of the ability to perform preapproval inspection (see Appendix 1)

The CMC labels/labeling issues have been satisfactorily resolved (see Appendix 2)

Therefore, from the OPQ perspective this application is now recommended for **approval**.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

43 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

NDA Number	213478
Drug Product (DP) Name	HYFTOR (sirolimus) topical gel
Strength	0.2%
Route of Administration	Topical
NDA Applicant	Nobelpharma Co., Ltd.
Drug Product Manufacturer	TOYO Pharmaceutical Co., Ltd. Joto Plant 5-4, Tsurumi, Tsurumi-ku Osaka, Osaka, Japan
(R)LD Information (Brand Name of Product, Applicant)	RAPAMUNE (sirolimus) oral solution; RAPAMUNE (sirolimus) tablets (PF Prism CV c/o Pfizer Inc)
RLD/RS Number	NDA 21110
Proposed Indication	Treatment of angiofibroma associated with tuberous sclerosis in adults and (b) (4)
Submission pathway	505(b)(2)
Assessment Cycle Number	02

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #1 dated 22-May-2020, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see NDA 213478 Labeling R01, Section 4.0). These labeling issues have not been resolved. In addition, minor unsolicited updates for the drug product, which was concluded to be adequate in the last assessment cycle (see N213478 DP R01 dated 08-Jul-2020), on post approval stability protocol were assessed and concluded to be adequate.

RECOMMENDATION:

This application is not deemed ready for approval in its present form from the CMC labeling perspective until the issues delineated in the **List of Deficiencies** are satisfactorily resolved.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0030 (SDN-30)	12/23/2020
eCTD-0033 (SDN-33)	03/08/2021
eCTD-0034 (SDN-34)	03/10/2021
eCTD-0035 (SDN-35) (container and carton labels)	03/26/2021

I. DRUG PRODUCT

The Drug Product chapter of this NDA in the last review cycle (01) was concluded adequate with no outstanding issues. In the resubmission, the applicant provided unsolicited updates in 3.2.P.8, which are highlighted in green below. Of note, stability data for samples collected during manufacturing to support the proposed manufacturing process were assessed by Process Assessor, Khalid Khan and are not included in this assessment.

P.8 STABILITY

Table P.8.1: Primary Stability Study of Drug Product (eCTD-0030 dated 12/23/2020)

Storage Conditions	Testing Time Points	Tests	Available Data[h]
5 ± 3 °C (long-term)	0, 1, 3, 6, 9, 12, 13, 14, and 15 months	Appearance, pH, assay, related substances, apparent viscosity, drug release per USP <724>[a], elemental impurities[b], antimicrobial effectiveness per USP <51>[c], microbial limits[d], (b) (4) content[e], drug release per USP <1724>[f], seal integrity test[g]	15 months
25 ± 2°C/60±5% RH (accelerated)	0, 1, 3, and 6 months		6 months

[a] Performed only at 0, 1, and 3 months under both conditions.
[b] Performed per USP <233>, procedure 2 - ICP-MS, only at 0, 1, 6, 12, and 15 months under the long-term condition and at 0, 1, and 6 months under accelerated condition.
[c] Testing under long-term only at 0, 12, 13, 14, and 15 months and under accelerated only at 0 and 6 months
[d] Testing for 1) TAMC and TYMC per USP <61>, 2) *Staphylococcus aureus* and *Pseudomonas aeruginosa per USP <62>* under long-term only at 0, 6, 12, 13, 14, and 15 months and under accelerated only at 0 and 6 months, 3) *Burkholderia cepacia complex* per USP <60> under long-term only at 15 months.
[e] Performed under long-term only at 0, 6, 12, 13, 14, and 15 months and under accelerated only at 0 and 6 months.
[f] Performed only at 6, 9, 12, 13, 14, and 15 months under the long-term condition and at 6 months under accelerated condition.
[g] Performed only at 0 and 15 months under the long-term condition.
[h] In eCTD-0001, up to 12 months long-term data and 6 months accelerated data were provided.

Post-Approval Stability Protocol and Commitment

Table P.8.2: Stability Protocol for Commercial Batches: Routine Annual Batches (eCTD-0030)

Storage Condition	Initial	3 M	6 M	9 M	12 M	15 M
5 ± 3 °C	X, Y, Z	X	X	X	X	X,Y

X= Appearance, pH, Assay, Related Substances, Apparent Viscosity, Drug Release per USP <1724>
Y = (b) (4) Content, Seal Integrity Test, Microbial Limits
Z = Identity, Minimum Fill

Assessment: ***Adequate***

The stability protocol of the three primary stability batches (Table 1 of 3.2.P.8.1) indicates antimicrobial effectiveness test includes the 6-month time point for drug product stored at 5±3°C. However, there is no 6-month antimicrobial effectiveness test data in 3.2.P.8.3. This discrepancy has little impact on the adequacy of the NDA since antimicrobial effectiveness test at 12, 13, 14, and 15-month time points have been provided. Furthermore, t=0 time point for seal integrity test has been added in the resubmission.

The updated post-approval stability protocol is essentially the same as that provided in eCTD-0007, including testing under category "X" and "Y" to be performed at the last time point. However, testing "Y" was removed from the 12-month time point in eCTD-0030. This is acceptable since testing Y is included in the last time point (15-month).

In conclusion, these updates are minor. The Drug Product remains adequate.

II. LABELING

1.0 PRESCRIBING INFORMATION

An updated Prescribing Information labeling was submitted in eCTD-0030. However, the deficiencies identified in Quality Assessment – Labeling, Assessment Cycle #1 dated 22-May-2020 were not addressed in eCTD-0030 since these labeling issues were not conveyed to the applicant in the first review cycle. For convenience, these labeling issues, except for those applicable updates where applicable, are repeated in Section 4.0. For clarity, the recommended information for Prescribing Information and Patient Information labeling is shown below.

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.0 CARTON AND CONTAINER LABELS

The following deficiencies identified in the Labeling Assessment 01 were not conveyed to the applicant in the last review cycle, but were conveyed to the applicant on 2/26/2021, together with the comments from DMEPA.

1. Please address the following issues for both container and carton labels:
   a. Relocate the strength "0.2%" to immediately after the established name "sirolimus topical gel".
   b. The established names of inactive ingredients should be used. Revise the statement from to **"Each gram contains:** 2 mg of sirolimus solubilized in a gel consisting of alcohol %, Carbomer 940, purified water, and trolamine (to adjust pH)".
   c. Revise the storage statement from at 2 - 8°C (36 - 46°F)" to at 2° to 8°C (36° to 46°F)".

3.1 CONTAINER LABEL

Two container labels were provided in eCTD-0033 with identical information except for alcohol content, one label with "alcohol %" and the other label with "alcohol 51%". The applicant stated

(b) (4)

Conclusion: **Unsatisfactory**

In eCTD-0033, the applicant stated that (b) (4). Therefore, the alcohol content should be 51%, as calculated below.

(b) (4)

The following issues are identified and conveyed to the applicant on 3/19/2021:

1. In your amendment dated 3/8/2021 for the container and carton labels, the route of the administration and dosage form are part of the proposed proprietary name, i.e., HYFTOR (sirolimus topical gel). (b) (4) Please ensure that the proprietary name and established name are used consistently for the labeling and labels.

2. Established name, but not strength, should be provided inside the parenthesis and accompany the proprietary name. Therefore, the strength "0.2%" should be outside of the parenthesis, as shown below.

   Option 1:

   HYFTOR™
   (sirolimus topical gel) 0.2%

   Option2:

   HYFTOR™
   (sirolimus) topical gel 0.2%

See Item 1 regarding Option 1 vs. Option 2.

3. We acknowledge that you provided two sets of container and carton labels in the 3/8/2021 amendment, where identical information was provided for each set of labels, except for alcohol content (b) (4)% vs. 51%. We further acknowledge that (b) (4) Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided. Therefore, the alcohol content of 51% should be used in the labeling and labels. Please provide updated labels that list alcohol 51%.

In eCTD-0035, the revised container label was provided as shown below.

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (sirolimus topical gel)	**Acceptable** The applicant clarified that the route of the administration and dosage form are part of the proprietary name, i.e., HYFTOR (sirolimus topical gel).
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	topical	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% Each gram contains: 2 mg sirolimus	**Acceptable** Strength in metric system (2 mg sirolimus per gram) and "0.2%" are provided and are acceptable. Equivalence statement is not applicable since sirolimus is neither an acid nor a base.

Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	alcohol 51%, Carbomer 940, purified water, and trolamine (to adjust pH)	**Acceptable** Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73683-101-10	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	On crimp	**Acceptable** Due to limited space, expiration date will be displayed as YYYY MM (see eCTD-0034).
Storage conditions	Must be refrigerated, store at 2°C to 8°C (36°F to 46°F). Protect from light.	**Acceptable**
Bar code [21CFR 201.25(c)(2)]	Allocated	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	**Recommended Dosage and Administration**: See Prescribing Information	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America, LLC, Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	**To Open:** Use pointed end on cap to puncture seal. **Tamper Evident:** Do not accept if seal is broken.	**Acceptable**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol.	Alcohol content: 51%	**Acceptable** Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided.

Assessment: ***Adequate***

The issues conveyed in the 3/19/2021 Information Request have been addressed satisfactorily. The applicant adopts "HYFTOR (sirolimus topical gel)" as the proprietary name and

established name. Strength (0.2%) is located outside of the parenthesis. Alcohol 51% is included in the list of excipients. The information on the container label meets the regulatory requirements.

3.2 CARTON LABEL

Two carton labels were provided in eCTD-0033 with identical information except for alcohol content, one label with "alcohol (b) (4)%" and the other label with "alcohol 51%". The applicant stated (b) (4) (b) (4)

(b) (4)

Conclusion: Unsatisfactory

The issues listed on page 6 for the container label are also applicable to the carton label.

In eCTD-0035, the revised carton label was provided as shown below.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (sirolimus topical gel)	**Acceptable**
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	topical	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% Each gram contains: 2 mg sirolimus	**Acceptable**
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	alcohol 51%, Carbomer 940, purified water, and trolamine (to adjust pH)	**Acceptable** Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
Statement of being sterile (if applicable)	N/A	N/A
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73683-101-10	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated	**Acceptable** Expiration date will be displayed as YYYY-MM-DD (see eCTD-0034).
Storage conditions	Must be refrigerated, store at 2°C to 8°C (36°F to 46°F). Protect from light.	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]	Allocated	**Acceptable**

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	**Recommended Dosage and Administration**: See Prescribing Information	**Acceptable**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America, LLC Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	Keep away from fire	**Acceptable**

Assessment: ***Adequate***

The issues listed on page 6 for the carton label are addressed satisfactorily. The information on the container label meets the regulatory requirements.

4.0 LIST OF DEFICIENCIES:

A. Regarding Prescribing Information

a) Highlight Section

1. For the Product Title, the established name shall accompany the proprietary name, i.e., HYFTOR™ (sirolimus topical gel). Delete (b) (4)
2. The year of Initial U.S. Approval is (b) (4).
3. Dosage form in Sections 3, 11, and 16 should match the product title. In this case, "topical" is part of the dosage form.

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

4. Dosage form should be "Topical gel".
5. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
6. Add a description of the identifying characteristics of the gel and limited packaging information, i.e., "a colorless and transparent gel in 10-gram tubes".
7. Delete (b) (4) (b) (4)

Section 11: Description

8. The established name should accompany the proprietary name, i.e., HYFTOR™ (sirolimus topical gel).
9. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.

10. Use the established names of inactive ingredients. Add the amount of alcohol, i.e., 51%, in terms of percent volume of absolute alcohol at 60 °F (15.56 °C). Recommend listing inactive ingredients in alphabetical order.
11. Add a brief description for the drug substance characteristics and revise the molecular weight, i.e., 914.19 instead of 914.17, and chemical name of sirolimus.

Section 16: How Supplied/Storage and Handling

12. Revise established name to "(sirolimus topical gel)".
13. Add a description of the identifying characteristics of the gel and packaging information, i.e., "a colorless and transparent gel supplied in aluminum tubes in 10 g".
14. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
15. Revised storage temperature from "2 - 8°C (36 - 46°F)" to "2° to 8°C (36° to 46°F)". Add "Protect from light".
16. Delete (b) (4)

Section 17: Patient Counseling Information

17. Add (b) (4) at the end of Section 17.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Master Chemistry reviewer
DNDP II/ONDP
05/25/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson, Ph.D.
Division Director
OPQ/ONDP/DNDP II
05/25/2021

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/25/2021 05:10:50PM
GUID: 50816dbc000085595ca3284bbca465a8

Jane Chang

Digitally signed by Jane Chang
Date: 5/25/2021 03:57:25PM
GUID: 5034f819000053b21e2574590781f330

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
03/17/2022 09:36:27 AM

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

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

DATE: February 9, 2022

TO: Addendum of Assessment #2 of NDA 213478 Quality Assessment - Labeling

FROM: Jane Chang, Ph.D.
Master Chemistry Reviewer, OPQ/ONDP/DNDP II

THROUGH Wendy Wilson, Ph.D.
Division Director, OPQ/ONDP/DNDP II

SUBJECT: **Final Recommendation on Labeling/Labels**

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #2 dated 25-May-2021, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see N213478 Labeling R02, Section 4.0). These labeling issues have been satisfactorily resolved based on the revisions made in eCTD-0040.

RECOMMENDATION:

This application is now recommended for **Approval** from the CMC labeling/label perspective.

Assessment Notes

Assessor Comment: Labeling deficiencies from Quality Assessment were identified in Assessment Cycle #2 dated 25-May-2021 (see N213478 Labeling R02, Section 4.0). Subsequently, labeling amendments were submitted. These amendments, as listed below, are the subject of this addendum. In eCTD-0038 and eCTD-0039, issues on the product title and/or Initial U.S. Approval were identified. In eCTD-0040, these issues have been addressed.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received	Information
eCTD-0038 (SDN-38)	07/02/2021	PI and PPI
eCTD-0039 (SDN-39)	07/27/2021	PI and PPI
eCTD-0040 (SDN-40)	08/09/2021	PI and PPI
eCTD-0041 (SDN-41)	09/01/2021	Container and carton labels

1.0 PRESCRIBING INFORMATION

The information provided in eCTD-0040 dated 08/09/2021 is summarized below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	HYFTOR™ (sirolimus topical gel)	**Acceptable**
Dosage form, route of administration	Topical gel	**Acceptable** Per Labeling Review Tool (page 13, 26, 48, 59), dosage form terminology in Dosage Forms and Strengths section of Highlights (HL) and Sections 3, 11, and 16 of Full Prescribing Information (FPI) (e.g., oral solution, for oral suspension) should be identical to the dosage form terminology in the product title in HL.
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	1999	**Acceptable** The year FDA initially approved sirolimus as an NME was 1999 (NDA 21083).
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Topical gel, 0.2%: 2 mg of sirolimus per gram	**Acceptable**

Conclusion: Satisfactory

Information in HIGHLIGHTS section meets the regulatory requirements.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 3: DOSAGE FORMS AND STRENGTHS

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	Topical gel	**Acceptable** Per Labeling Review Tool (page 13, 26, 48, 59), dosage form terminology in Dosage Forms and Strengths section of Highlights (HL) and Sections 3, 11, and 16 of Full Prescribing Information (FPI) (e.g., oral solution, for oral suspension) should be identical to the dosage form terminology in the product title in HL.
Strength: in metric system	0.2%: Each gram contains 2 mg of sirolimus	**Acceptable**
Active moiety expression of strength (if applicable)	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	a colorless and transparent gel in 10-gram tubes	**Acceptable**

Conclusion: **Satisfactory**

Information in DOSAGE FORMS AND STRENGTHS meets the regulatory requirements.

1.2.2 Section 11: DESCRIPTION

(b) (4)

(b) (4)

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	HYFTOR™ (sirolimus topical gel)	**Acceptable**
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	topical gel	**Acceptable** Per Labeling Review Tool (page 13, 26, 48, 59), dosage form terminology in Dosage Forms and Strengths section of Highlights (HL) and Sections 3, 11, and 16 of Full Prescribing Information (FPI) (e.g., oral solution, for oral suspension) should be identical to the dosage form terminology in the product title in HL.
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	Each gram contains 2 mg of sirolimus (0.2%).	**Acceptable**
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of	alcohol 51%, Carbomer 940, purified water, and trolamine	**Acceptable** The titles of the USP monographs are used as the established names. Inactive ingredients are listed in alphabetical order.

alcohol in terms of percent volume of absolute alcohol		
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	an mTOR inhibitor immunosuppressant	**Acceptable**
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	provided	**Acceptable**
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

Conclusion: **Satisfactory**

Information in DESCRIPTION submitted as shown above meets the regulatory requirements.

1.2.3 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	topical gel	**Acceptable** Per Labeling Review Tool (page 13, 26, 48, 59), dosage form terminology in Dosage Forms and Strengths section of Highlights (HL) and Sections 3, 11, and 16 of Full Prescribing Information (FPI) (e.g., oral solution, for oral suspension) should be identical to the dosage form terminology in the product title in HL.
Strength of dosage form in metric system	Each gram contains 2 mg of sirolimus (0.2%).	**Acceptable**
Available units (e.g., bottles of 100 tablets)	10 g	**Acceptable**

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	a colorless and transparent gel supplied as 10 g in aluminum tubes (NDC 73683-101-10)	**Acceptable**
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Protect from light	**Acceptable**
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	refrigerated at 2° to 8°C (36° to 46°F)	**Acceptable**

Conclusion: Satisfactory

Information in HOW SUPPLIED/STORAGE AND HANDLING meets the regulatory requirements.

1.2.4 Section 17: PATIENT COUNSELING INFORMATION

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Distributed by: Nobelpharma America, LLC 4520 East-West Highway, Suite 400 Bethesda, MD 20814	**Acceptable**

Conclusion: Satisfactory

The information in Section 17 meets the regulatory expectation.

3.0 CARTON AND CONTAINER LABELS

Carton and container labels were provided in eCTD-0041 (SDN-41). The information is identical to that in eCTD-0035, which has been evaluated in N213478 Labeling R02, Section 4.0 and concluded to be adequate.

Jane Chang

Digitally signed by Jane Chang
Date: 2/09/2022 10:58:37AM
GUID: 5034f819000053b21e2574590781f330

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 2/09/2022 11:08:07AM
GUID: 50816dbc000085595ca3284bbca465a8

Memorandum

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

Date: **June 23, 2021**
From: **Hamid Shafiei, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: **To Executive Summary, IQA for Assessment # 1 of NDA 213478**

Subject: **ONDP Recommendation**

In the integrated quality assessment (IQA) dated July 24, 2020, this NDA was not recommended for approval in the form it was presented due to the following unresolved issues:

- **Insufficient** information to assess the adequacy of manufacturing process
- Facilities had not been cleared because of **pending required preapproval inspections** of TOYO Pharmaceutical Co., LTD. manufacturing facility, FEI 3016419927 which had been deferred due to the travel restrictions caused by the COVID-19 pandemic.
- The CMC issues on labels/labeling had **not** been satisfactorily resolved.

The applicant resubmitted this application on December 23, 2020 that included additional manufacturing process information. The additional manufacturing information provided in the resubmission has been reviewed by the OPMA Reviewer, Dr. Khalid Khan. Dr. Khan has found the manufacturing process described in the resubmission adequate to support the approval of this application from the manufacturing process perspective (see Attachment 1). However, labels/labeling issues have not yet been satisfactorily resolved and the inspection of the drug product manufacturing site, TOYO Pharmaceutical Co., LTD. manufacturing facility, FEI 3016419927 has been deferred until the travel restrictions are lifted.

Therefore, from the OPQ perspective, this NDA is **not** recommended for **approval** in its present form per 21 CFR 314.125(b)(6),(13).

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

40 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
06/23/2021 08:30:51 PM

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

NDA Number	213478
Drug Product (DP) Name	HYFTOR (sirolimus) topical gel
Strength	0.2%
Route of Administration	Topical
NDA Applicant	Nobelpharma Co., Ltd.
Drug Product Manufacturer	TOYO Pharmaceutical Co., Ltd. Joto Plant 5-4, Tsurumi, Tsurumi-ku Osaka, Osaka, Japan
(R)LD Information (Brand Name of Product, Applicant)	RAPAMUNE (sirolimus) oral solution; RAPAMUNE (sirolimus) tablets (PF Prism CV c/o Pfizer Inc)
RLD/RS Number	NDA 21110
Proposed Indication	Treatment of angiofibroma associated with tuberous sclerosis in adults and (b) (4)
Submission pathway	505(b)(2)
Assessment Cycle Number	02

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #1 dated 22-May-2020, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see NDA 213478 Labeling R01, Section 4.0). These labeling issues have not been resolved. In addition, minor unsolicited updates for the drug product, which was concluded to be adequate in the last assessment cycle (see N213478 DP R01 dated 08-Jul-2020), on post approval stability protocol were assessed and concluded to be adequate.

RECOMMENDATION:

This application is not deemed ready for approval in its present form from the CMC labeling perspective until the issues delineated in the **List of Deficiencies** are satisfactorily resolved.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0030 (SDN-30)	12/23/2020
eCTD-0033 (SDN-33)	03/08/2021
eCTD-0034 (SDN-34)	03/10/2021
eCTD-0035 (SDN-35) (container and carton labels)	03/26/2021

I. DRUG PRODUCT

The Drug Product chapter of this NDA in the last review cycle (01) was concluded adequate with no outstanding issues. In the resubmission, the applicant provided unsolicited updates in 3.2.P.8, which are highlighted in green below. Of note, stability data for samples collected during manufacturing to support the proposed manufacturing process were assessed by Process Assessor, Khalid Khan and are not included in this assessment.

P.8 STABILITY

Table P.8.1: Primary Stability Study of Drug Product (eCTD-0030 dated 12/23/2020)

Storage Conditions	Testing Time Points	Tests	Available Data[h]
5 ± 3 °C (long-term)	0, 1, 3, 6, 9, 12, 13, 14, and 15 months	Appearance, pH, assay, related substances, apparent viscosity, drug release per USP <724>[a], elemental impurities[b], antimicrobial effectiveness per USP <51>[c], microbial limits[d], (b) (4) content[e], drug release per USP <1724>[f], seal integrity test[g]	15 months
25 ± 2°C/60±5% RH (accelerated)	0, 1, 3, and 6 months		6 months

[a] Performed only at 0, 1, and 3 months under both conditions.
[b] Performed per USP <233>, procedure 2 - ICP-MS, only at 0, 1, 6, 12, and 15 months under the long-term condition and at 0, 1, and 6 months under accelerated condition.
[c] Testing under long-term only at 0, 12, 13, 14, and 15 months and under accelerated only at 0 and 6 months
[d] Testing for 1) TAMC and TYMC per USP <61>, 2) *Staphylococcus aureus* and *Pseudomonas aeruginosa per USP <62>* under long-term only at 0, 6, 12, 13, 14, and 15 months and under accelerated only at 0 and 6 months, 3) *Burkholderia cepacia complex* per USP <60> under long-term only at 15 months.
[e] Performed under long-term only at 0, 6, 12, 13, 14, and 15 months and under accelerated only at 0 and 6 months.
[f] Performed only at 6, 9, 12, 13, 14, and 15 months under the long-term condition and at 6 months under accelerated condition.
[g] Performed only at 0 and 15 months under the long-term condition.
[h] In eCTD-0001, up to 12 months long-term data and 6 months accelerated data were provided.

Post-Approval Stability Protocol and Commitment

Table P.8.2: Stability Protocol for Commercial Batches: Routine Annual Batches (eCTD-0030)

Storage Condition	Initial	3 M	6 M	9 M	12 M	15 M
5 ± 3 °C	X, Y, Z	X	X	X	X	X,Y

X= Appearance, pH, Assay, Related Substances, Apparent Viscosity, Drug Release per USP <1724>
Y = (b) (4) Content, Seal Integrity Test, Microbial Limits
Z = Identity, Minimum Fill

Assessment: ***Adequate***

The stability protocol of the three primary stability batches (Table 1 of 3.2.P.8.1) indicates antimicrobial effectiveness test includes the 6-month time point for drug product stored at 5±3°C. However, there is no 6-month antimicrobial effectiveness test data in 3.2.P.8.3. This discrepancy has little impact on the adequacy of the NDA since antimicrobial effectiveness test at 12, 13, 14, and 15-month time points have been provided. Furthermore, t=0 time point for seal integrity test has been added in the resubmission.

The updated post-approval stability protocol is essentially the same as that provided in eCTD-0007, including testing under category "X" and "Y" to be performed at the last time point. However, testing "Y" was removed from the 12-month time point in eCTD-0030. This is acceptable since testing Y is included in the last time point (15-month).

In conclusion, these updates are minor. The Drug Product remains adequate.

II. LABELING

1.0 PRESCRIBING INFORMATION

An updated Prescribing Information labeling was submitted in eCTD-0030. However, the deficiencies identified in Quality Assessment – Labeling, Assessment Cycle #1 dated 22-May-2020 were not addressed in eCTD-0030 since these labeling issues were not conveyed to the applicant in the first review cycle. For convenience, these labeling issues, except for those applicable updates where applicable, are repeated in Section 4.0. For clarity, the recommended information for Prescribing Information and Patient Information labeling is shown below.

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.0 CARTON AND CONTAINER LABELS

The following deficiencies identified in the Labeling Assessment 01 were not conveyed to the applicant in the last review cycle, but were conveyed to the applicant on 2/26/2021, together with the comments from DMEPA.

1. Please address the following issues for both container and carton labels:
   a. Relocate the strength "0.2%" to immediately after the established name "sirolimus topical gel".
   b. The established names of inactive ingredients should be used. Revise the statement from to **"Each gram contains:** 2 mg of sirolimus solubilized in a gel consisting of alcohol %, Carbomer 940, purified water, and trolamine (to adjust pH)".
   c. Revise the storage statement from at 2 - 8°C (36 - 46°F)" to at 2° to 8°C (36° to 46°F)".

3.1 CONTAINER LABEL

Two container labels were provided in eCTD-0033 with identical information except for alcohol content, one label with "alcohol %" and the other label with "alcohol 51%". The applicant stated

(b) (4)

Conclusion: **Unsatisfactory**

In eCTD-0033, the applicant stated that (b) (4). Therefore, the alcohol content should be 51%, as calculated below.

(b) (4)

The following issues are identified and conveyed to the applicant on 3/19/2021:

1. In your amendment dated 3/8/2021 for the container and carton labels, the route of the administration and dosage form are part of the proposed proprietary name, i.e., HYFTOR (sirolimus topical gel). (b) (4) Please ensure that the proprietary name and established name are used consistently for the labeling and labels.

2. Established name, but not strength, should be provided inside the parenthesis and accompany the proprietary name. Therefore, the strength "0.2%" should be outside of the parenthesis, as shown below.

   Option 1:

   HYFTOR™
   (sirolimus topical gel) 0.2%

   Option2:

   HYFTOR™
   (sirolimus) topical gel 0.2%

See Item 1 regarding Option 1 vs. Option 2.

3. We acknowledge that you provided two sets of container and carton labels in the 3/8/2021 amendment, where identical information was provided for each set of labels, except for alcohol content (b) (4)% vs. 51%. We further acknowledge that (b) (4) Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided. Therefore, the alcohol content of 51% should be used in the labeling and labels. Please provide updated labels that list alcohol 51%.

In eCTD-0035, the revised container label was provided as shown below.

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (sirolimus topical gel)	**Acceptable** The applicant clarified that the route of the administration and dosage form are part of the proprietary name, i.e., HYFTOR (sirolimus topical gel).
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	topical	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% Each gram contains: 2 mg sirolimus	**Acceptable** Strength in metric system (2 mg sirolimus per gram) and "0.2%" are provided and are acceptable. Equivalence statement is not applicable since sirolimus is neither an acid nor a base.

Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	alcohol 51%, Carbomer 940, purified water, and trolamine (to adjust pH)	**Acceptable** Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73683-101-10	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	On crimp	**Acceptable** Due to limited space, expiration date will be displayed as YYYY MM (see eCTD-0034).
Storage conditions	Must be refrigerated, store at 2°C to 8°C (36°F to 46°F). Protect from light.	**Acceptable**
Bar code [21CFR 201.25(c)(2)]	Allocated	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	**Recommended Dosage and Administration**: See Prescribing Information	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America, LLC, Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	**To Open:** Use pointed end on cap to puncture seal. **Tamper Evident:** Do not accept if seal is broken.	**Acceptable**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol.	Alcohol content: 51%	**Acceptable** Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided.

Assessment: ***Adequate***

The issues conveyed in the 3/19/2021 Information Request have been addressed satisfactorily. The applicant adopts "HYFTOR (sirolimus topical gel)" as the proprietary name and

established name. Strength (0.2%) is located outside of the parenthesis. Alcohol 51% is included in the list of excipients. The information on the container label meets the regulatory requirements.

3.2 CARTON LABEL

Two carton labels were provided in eCTD-0033 with identical information except for alcohol content, one label with "alcohol (b) (4)%" and the other label with "alcohol 51%". The applicant stated (b) (4) (b) (4)

(b) (4)

Conclusion: Unsatisfactory

The issues listed on page 6 for the container label are also applicable to the carton label.

In eCTD-0035, the revised carton label was provided as shown below.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (sirolimus topical gel)	**Acceptable**
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	topical	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% Each gram contains: 2 mg sirolimus	**Acceptable**
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	alcohol 51%, Carbomer 940, purified water, and trolamine (to adjust pH)	**Acceptable** Per 21 CFR 201.10(d)(2), the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) should be provided.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
Statement of being sterile (if applicable)	N/A	N/A
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73683-101-10	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated	**Acceptable** Expiration date will be displayed as YYYY-MM-DD (see eCTD-0034).
Storage conditions	Must be refrigerated, store at 2°C to 8°C (36°F to 46°F). Protect from light.	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]	Allocated	**Acceptable**

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	**Recommended Dosage and Administration**: See Prescribing Information	**Acceptable**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America, LLC Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	Keep away from fire	**Acceptable**

Assessment: ***Adequate***

The issues listed on page 6 for the carton label are addressed satisfactorily. The information on the container label meets the regulatory requirements.

4.0 LIST OF DEFICIENCIES:

A. Regarding Prescribing Information

a) Highlight Section

1. For the Product Title, the established name shall accompany the proprietary name, i.e., HYFTOR™ (sirolimus topical gel). Delete (b) (4)
2. The year of Initial U.S. Approval is (b) (4).
3. Dosage form in Sections 3, 11, and 16 should match the product title. In this case, "topical" is part of the dosage form.

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

4. Dosage form should be "Topical gel".
5. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
6. Add a description of the identifying characteristics of the gel and limited packaging information, i.e., "a colorless and transparent gel in 10-gram tubes".
7. Delete (b) (4) (b) (4)

Section 11: Description

8. The established name should accompany the proprietary name, i.e., HYFTOR™ (sirolimus topical gel).
9. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.

10. Use the established names of inactive ingredients. Add the amount of alcohol, i.e., 51%, in terms of percent volume of absolute alcohol at 60 °F (15.56 °C). Recommend listing inactive ingredients in alphabetical order.
11. Add a brief description for the drug substance characteristics and revise the molecular weight, i.e., 914.19 instead of 914.17, and chemical name of sirolimus.

Section 16: How Supplied/Storage and Handling

12. Revise established name to "(sirolimus topical gel)".
13. Add a description of the identifying characteristics of the gel and packaging information, i.e., "a colorless and transparent gel supplied in aluminum tubes in 10 g".
14. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
15. Revised storage temperature from "2 - 8°C (36 - 46°F)" to "2° to 8°C (36° to 46°F)". Add "Protect from light".
16. Delete (b) (4)

Section 17: Patient Counseling Information

17. Add (b) (4) at the end of Section 17.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Master Chemistry reviewer
DNDP II/ONDP
05/25/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson, Ph.D.
Division Director
OPQ/ONDP/DNDP II
05/25/2021

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/25/2021 05:10:50PM
GUID: 50816dbc000085595ca3284bbca465a8

Jane Chang

Digitally signed by Jane Chang
Date: 5/25/2021 03:57:25PM
GUID: 5034f819000053b21e2574590781f330

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 213478
Assessment # 1

Drug Product Name	HYFTOR® (sirolimus)
Dosage Form	Gel
Strength	0.2%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Nobelpharma Co., Ltd.
US agent, if applicable	Dana Dunn

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	02/18/2020	All
Proprietary Name Request	02/20/2020	All
Proprietary Name Request (Alternative)	02/24/2020	All
Response to Information Request - Clinical	03/09/2020	Clinical
General Correspondence	03/27/2020	Clinical
Multiple Categories	04/08/2020	Clinical
Response to Information Request - Quality	04/09/2020	Drug Product, Biopharm, and Microbiology
Labeling	04/17/2020	All
Response to Information Request - Quality	04/28/2020	Drug Product
Response to Information Request - Clinical	05/06/2020	Clinical
Labeling	05/11/2020	All
Multiple Categories	05/15/2020	Drug Product, Biopharm, and Microbiology
Response to Information Request - Clinical	05/21/2020	Clinical
Response to Information Request - Quality	06/03/2020	OPMA

Multiple Categories	06/05/2020	Clinical
Multiple Categories	06/08/2020	Drug Product and Clinical
Safety Update	06/09/2020	Clinical
Patent Exclusivity – Patent Certification	06/17/2020	All
Administrative Change	06/24/2020	All
Response to Information Request - Clinical	07/10/2020	Clinical
Response to Information Request	07/15/2020	Quality and Clinical

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Zhixing Shan, Ph.D.	Donna, Christner, Ph.D.
Drug Product	Jane Chang, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Khalid Khan, Ph.D.	Frank Wackes, Ph.D.
Microbiology	Erin Wall, Ph.D.	Laura Wasil, Ph.D.
Biopharmaceutics	Kalpana Paudel, Ph.D.	Tapash Ghosh, Ph.D.
Regulatory Business Process Manager	Melinda Bauerlien, MS	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Jane Chang, Ph.D.	Moo-Jhong Rhee, Ph.D.

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application **has** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, sirolimus, but **has not** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, HYFTOR (sirolimus) Topical Gel, 0.2%.
- Facilities have not been cleared due to **pending required preapproval inspections** of TOYO Pharmaceutical Co., LTD. manufacturing facility, FEI 3016419927 due to the current travel restrictions caused by the COVID-19 pandemic.
- The CMC issues on labels/labeling have **not** been satisfactorily resolved.
- The applicant request's for categorical exclusion from the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(1)(6),(13) until the above issues are satisfactorily resolved (see the **List of Deficiencies**).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Nobelpharma Co., Ltd. has submitted this 505(b)(2) new drug application for HYFTOR® (sirolimus) Topical Gel, 0.2% for the treatment of angiofibroma associated with tuberous sclerosis in adult and (b) (4) of age or older. However, based on the clinical data provided in the application, this drug product will only be considered for used in patients 6 years of age or older. This application was granted Orphan Drug and Fast-Track designation.

The drug substance sirolimus also known as rapamycin is an antifungal antibiotic which is also a mTOR inhibitor immunosuppressive agent. Sirolimus is produced by microbial fermentation of *streptomyces hygroscopicus*. It was first approved as an active ingredient of RAPAMUNE oral solution under NDA 21083 on September 15, 1999 and subsequently RAPAMUNE oral tablets under NDA 21110 on August 25, 2000. NDA 21110 is used as the listed drug for this application.

HYFTOR is a transparent, colorless, aqueous gel containing 2mg of sirolimus per each gram of gel as the active ingredient and (b) (4) alcohol, Carbomer 940, purified water, and trolamine as inactive ingredients. HYFTOR topical gel will be packaged as 10g in aluminum tubes with (b) (4) caps for commercial use.

HYFTOR (sirolimus) topical gel is manufactured by TOYO Pharmaceuticals Co., Ltd., Osaka, Japan for Nobelpharma Co., Ltd.

HYFTOR is to be applied topically (b) (4) to the affected skin area twice daily with a maximum daily dose (MDD) of 1.6mg of sirolimus equivalent to 800mg (0.8g) of gel.

Proposed Indication(s) including Intended Patient Population	Treatment of angiofibroma associated with tuberous sclerosis in adult and (b) (4) of age or older
Duration of Treatment	As prescribed
Maximum Daily Dose	800mg (0.8g) of gel equivalent to 1.6mg of sirolimus
Alternative Methods of Administration	N/A

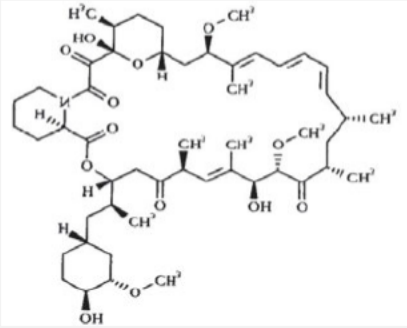
B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance sirolimus also known as rapamycin is an antifungal antibiotic which is also a mTOR inhibitor immunosuppressive agent. It is naturally occurring macrolide that is isolated from *streptomyces hygroscopicus*. Sirolimus was first approved on August 25,1999 as the active ingredient of RAPAMUNE oral solution (NDA 21083). It is a white to off-white powder that is practically insoluble in water but freely soluble in acetone, methanol, and dimethyl sulfoxide. It is non-hygroscopic with one known polymorphic form and a meting range of 180ºC – 185ºC (decomposition). Sirolimus has 15 asymmetric centers with a specific optical rotation of -146º – -160º on anhydrous basis. The structure of sirolimus has been deduced by X-ray analysis.

Sirolimus has the chemical name (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34AS)-9,10,12,13, 14,21,22,23,24,25,26,27,32,33,34,34A-hexadecahydro-9,27-dihydroxy-3-((1R)-2-((1S,3R, 4R)-4-hydroxy-3-methoxycyclohexyl)-1-methylethyl)-10,21-dimethoxy-6,8,12,14,20,26- hexamethyl-23,27-epoxy-3H-pyrido(2,1-C)-(1,4)oxaazacyclohentriacontine-1,5,11,28,29-

(4H,6H,31H)-pentone, a molecular formula of $C_{51}H_{79}NO_{13}$, a molecular weight of 914.17 and the chemical structure below:



Sirolimus drug substance for this application is manufactured in accordance to current good manufacturing practices (cGMP) by [redacted]. The information regarding the manufacture of sirolimus supplied by this manufacturer is provided in DMF [redacted]. This DMF was reviewed recently by Dr. Srinivasa Murthy on January 14, 2019 and was found to be adequate with a comment to be conveyed to the DMF holder. The DMF holder responded to Dr. Murthy's comment on February 14, 2019. Since the information in the response to Dr. Murthy's comment was also included in the NDA submission, no additional review of DMF [redacted] was needed.

Sirolimus for this application is packaged in [redacted]. It is tested and released against a drug substance specification that assures the identity, strength, purity and quality of the drug substance at release and throughout its assigned retest date of [redacted] when stored at the log-term storage condition of [redacted]°C. Sufficient stability data is provided in the DMF in support of the proposed retest date of [redacted]

Based on Dr. Murthy's review of DMF [redacted] and the review of the information provided in this application, the Drug Substance Reviewer, Dr. Zhixing Shan has recommended the approval of this application from the drug substance perspective. Dr. Shan's review is provided in the Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Adequate

HYFTOR (sirolimus) Topical Gel, 0.2% has been developed for the treatment of angiofibroma associated with tuberous sclerosis in adult and [redacted] of age or older. This drug is intended to be topically administered [redacted] to affected skin area twice daily with maximum daily dose of 800mg (0.8g) of gel equivalent to 1.6mg of sirolimus. This application was granted Orphan Drug and Fast Track designation.

HYFTOR is a transparent, colorless, aqueous gel packaged as 10g in aluminum tubes with [redacted] caps. Each gram of HYFTOR contains 2mg of sirolimus as the active ingredient and [redacted] alcohol [redacted], Carbomer 940 [redacted], purified water [redacted] and trolamine (pH modifier) as the inactive ingredients. The excipients used in the composition of the drug product are compendial materials. All inactive ingredients of the drug product are within the limit for the topical products in the FDA's inactive ingredients database.

The drug product is manufactured by TOYO Pharmaceuticals Co., Ltd., Osaka, Japan for Nobelpharma Co., Ltd. The manufacturing process steps for HYFTOR topical gel [redacted]

The drug product is tested and released against a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its currently proposed expiration dating period of 15 months. The applicant has provided sufficient stability data in the application that supports the proposed expiration dating period of 15 months when stored under the long-term storage condition of 2ºC – 8ºC.

The drug product section of this application was reviewed by the Drug Product Reviewer, Dr. Jane Chang. Dr. Chang has recommended the approval of this application from the drug product perspective. Dr. Chang's review is provided in Drug Product Chapter of IQA.

Dr. Chang has also reviewed the applicant request for the categorical exclusion from preparation of environmental assessment in accordance to 21 CFR 25.31(b). Dr. Chang has accepted the applicant's request and has granted the categorical exclusion to this application. Dr. Chang's review of the applicant's request for the categorical exclusion is also provided in the Drug Product Chapter of the IQA.

Although Dr. Chang has recommended the approval of this application from the drug product perspective, this application will be receiving complete response due to inadequate drug product manufacturing process and facility (refer to the manufacturing section of this executive summary document and the Manufacturing Chapter of the IQA).

Labeling: Inadequate

The CMC section of prescribing information (PI) labeling as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Jane Chang. Dr. Chang has identified multiple CMC labeling deficiencies in the PI as well as the immediate container and carton labels (refer to the labeling/labels deficiencies list at the end of this executive summary document). Therefore, Dr. Change has concluded that this application is not deemed ready for approval in its current form from labeling/labels perspective per 21 CFR 314.125(b)(6). Dr. Chang labeling/labels review for this application is provided in the Labeling Chapter of the IQA.

Manufacturing: Inadequate

The manufacturing process for HYFTOR (sirolimus) Topical Gel, 0.2%

(b) (4)

The manufacturing process in this application has been reviewed by the Office Pharmaceutical Manufacturing Assessment (OPMA) Reviewer, Dr. Khalid Khan. Dr. Khan has identified multiple manufacturing process deficiencies such as inadequate batch process instructions, inadequate in-process sampling procedures, inadequate equipment capability to manufacture gel product, potential for leachables from the manufacturing equipment surfaces, and unspecified hold times for the manufacturing processes. Based on these manufacturing process deficiencies, Dr. Khan **has not** recommended the approval of this application from the manufacturing process perspective (the detailed list of deficiencies for the CR letter at the end of this executive summary document).

The facilities in this applicant has also been reviewed by the OPMA reviewer Dr. Khan. Dr. Khan has stated that TOYO Pharmaceutical Co., Ltd. has not been previously inspect by the US FDA and a preapproval inspection (PAI) of this manufacturing site is required before the facilities review for this application **can be completed**. However, due to travel restriction associated with COVID-19 pandemic, this site cannot be inspected at this time. Therefore, this application cannot be approved from the facilities perspective until the inspection of TOYO Pharmaceutical Co., Ltd. is successfully performed (this issue is also included in the list of deficiencies to be conveyed in the CR letter).

In summary, Dr. Khan has recommended a **complete response** for this application as per 21 CFR 314.125(b)(1)(13). Dr. Khan review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

Based on the results from pharmaceutical development two different formulations, OSD-001 and NPC-12G gel were used in the clinical trials. OSD-001 was used in Phase 1 and Phase 2 clinical trials and NPC-12G gel was used in Phase 3 and a Long-Term Study (LTS). The applicant bridged the two different formulations by an in-vitro human skin permeability study using [redacted] (b) (4) Both formulations showed similar release profiles.

NPG-12G gel formulation 2 used in the Phase 3 and first half of LTS and NPG-12G gel formulation 3 used in the second half of LTS were manufactured at [redacted] (b) (4) and TOYO Pharmaceutical Co., Ltd., respectively. [redacted] (b) (4) [redacted] Comparative dissolution data from [redacted] (b) (4) [redacted] showed that NPC-12G formulations 2 and 3 manufactured at the two different manufacturing sites had the same in-vitro release profile. NPG-12G formulation 3 and the manufacturing site, TOYO Pharmaceutical Co., Ltd. are proposed for the commercial drug product.

Furthermore, the applicant has developed and validated IVRT method using vertical diffusion cell apparatus and has agreed to test the first three commercial batches using this IVRT method. The applicant has proposed an in-vitro release acceptance criterion of [redacted] (b) (4) $\mu g/cm^2/hr^{1/2}$. Based on the information provided in the application, the proposed in-vitro release acceptance criterion is deemed acceptable.

The biopharm information provided in this application has been reviewed by the Biopharm Reviewer, Dr. Kalpana Paudel. Dr. Paudel has recommended the approval of this application from Biopharm perspective. Dr. Paudel's review is provided in the Biopharm Chapter of the IQA.

Microbiology (if applicable): Adequate

HYFTOR (sirolimus) Topical Gel, 0.2% is a non-sterile drug product. [redacted] (b) (4) [redacted] The applicant has provided manufacturing risk assessment for BCC and tested the primary stability batches of drug product at the 15-month time-point for BCC in accordance to USP <60> to show the absence of BCC in the drug product at the end currently proposed shelf-life. The applicant has also added testing for BCC to the

drug product specification. The final proposed specification for HYFTOR topical gel includes testing and acceptance criteria for bioburden according to USP <60>, USP <61>, and USP <62> using validated methods.

The microbiology information submitted in this application has been reviewed by the Microbiology Reviewer, Dr. Erin Wall. Dr. Wall has found the information provided in the application adequate to support the approval of this application from the microbiology perspective. Dr. Wall's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Solubility of sirolimus in the gel	Assay and content uniformity	M	Assay and content uniformity are appropriately tested	Acceptable	None

D. List of Deficiencies for Complete Response

1. Labeling Deficiencies

A. Regarding PI

a) Highlight Section

1. For the Product Title, the established name shall accompany the proprietary name, i.e., HYFTOR™ (sirolimus) topical gel. Delete (b) (4)
2. The year of Initial U.S. Approval is (b) (4).

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

3. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
4. Add a description of the identifying characteristics of the gel and limited packaging information, i.e., "a colorless and transparent gel in 10-gram tubes".
5. Delete (b) (4) (b) (4)

Section 11: Description

6. The established name should accompany the proprietary name, i.e., HYFTOR™ (sirolimus) topical gel.
7. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
8. Use the established names of inactive ingredients. Add the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C). Recommend listing inactive ingredients in alphabetical order.
9. Add a brief description for the drug substance characteristics and revise the molecular weight, i.e., 914.19 instead of 914.17, and chemical name of sirolimus.

Section 16: How Supplied/Storage and Handling

10. Revise established name to "(sirolimus) topical gel".
11. Add a description of the identifying characteristics of the gel and packaging information, i.e., "a colorless and transparent gel supplied in aluminum tubes in 10 g".
12. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
13. Revised storage temperature from "2 - 8°C (36 - 46°F)" to "2° to 8°C (36° to 46°F)". Add "Protect from light".
14. Delete (b) (4)

Section 17: Patient Counseling Information

15. Add (b) (4) at the end of Section 17.

B. Regarding the Container/Carton Labels

16. Please address the following issues for both container and carton labels:
    a. (b) (4). Relocate the strength "0.2%" to immediately after the established name "sirolimus topical gel".
    b. The established names of inactive ingredients should be used. Revise the statement from (b) (4) to **"Each gram contains:** 2 mg of sirolimus

solubilized in a gel consisting of alcohol (b)(4)%, Carbomer 940, purified water, and trolamine (to adjust pH)".

c. Revise the storage statement from (b)(4) at 2 - 8°C (36 - 46°F)" to (b)(4) at 2° to 8°C (36° to 46°F)".

d. Revise the statement from (b)(4) to (b)(4) See Prescribing Information".

2. Manufacturing Deficiencies

Process:

1. The Agency acknowledges the statement that if the API assay result is outside of (b)(4) We remind you that if the API assay for a batch of sirolimus falls outside of (b)(4)%, it fails to meet the drug substance specification and cannot be use in the manufacture of the commercial drug product

2. You acknowledged in your response to Information Request 5 that, (b)(4) Please revise all manufacturing process parameters for commercial production to be either a set point or range with lower and upper limits. Those parameters should be supported by data collected from manufacturing process used for development and/or registration batches, and by adequate discussion of potential scalability issues for scale dependent parameters. Revise the pertinent section of P.3 and master batch record accordingly.

3. (b)(4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Facilities:

An inspection of the TOYO PHARMACEUTICAL CO. LTD. facility (FEI 3016419927) located in Tsurumi-Ku, Osaka, Japan; is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You

may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID-19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

Application Technical Lead:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 7/24/2020 04:15:28PM
GUID: 507d824300005f344cf8b5e5989f0057

FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	01/14/2019	Srinivasa Murthy, Ph.D.
	III			Adequate	07/08/2020	Reviewed by Jane Chang, Ph.D.

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

Document	Application Number	Description
RAPAMUNE (sirolimus) Oral Solution RAPAMUNE (sirolimus) Tablets	NDA 21110	Listed Drug

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

49 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0001 (SDN-1)	02/18/2020
eCTD-0011 (SDN-11)	05/11/2020

1.0 PRESCRIBING INFORMATION

The information in eCTD-0011 is provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	HYFTOR™ (b) (4)	**Unacceptable** The established name should be in lower case (b) (4) (b) (4)
Dosage form, route of administration	Gel, topical	**Unacceptable** The dosage form should be in lower case per Labeling Review Tool (LRT).
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	xxxx	**Unacceptable** (b) (4)
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	(b) (4) 0.2%	**Unacceptable** (b) (4) (b) (4) should be deleted. Include the strength in metric system and limited packaging information per Labeling Review Tool (LRT).
Whether the drug product is scored	N/A	N/A

Conclusion: Unsatisfactory

The proposed proprietary name, Hyftor, was assessed by DMEPA assessor, Madhuri R. Patel, on 4/29/2020 and concluded to be acceptable.

The recommended revisions are shown below:

Product Title:

HYFTOR™ (b) (4)
Initial U.S. Approval: (b) (4)

Dosage Forms and Strengths:

(b) (4) 0.2%: (b) (4)

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 3: DOSAGE FORMS AND STRENGTHS

(b) (4)

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	Gel	**Acceptable** (b) (4)
Strength: in metric system	0.2%	**Unacceptable** Add "2 mg of sirolimus per gram"
Active moiety expression of strength (if applicable)	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided	**Unacceptable** Add "colorless and transparent gel" and limited packaging information.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

(b) (4) 0.2%: a colorless and transparent gel in 10-gram tubes. Each gram contains 2 mg of sirolimus (b) (4)

(b) (4)

1.2.2 Section 11: DESCRIPTION

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	HYFTOR™ (b) (4)	**Unacceptable** (b) (4)
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Gel, topical	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	0.2%	**Unacceptable** Add strength in metric system, i.e., 2 mg per gram.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	(b) (4) , and purified water	**Unacceptable** Established names (titles of the USP monographs) should be used. List inactive ingredients in alphabetical order (recommended, but not required). The alcohol content ((b) (4) %) should be provided.
Statement of being sterile [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	N/A	N/A
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	mTOR inhibitor immunosuppressant	**Acceptable**
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	provided	**Unacceptable** See Assessment section for minor edits for chemical name and molecular weight.
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	N/A	Recommend adding a short description of the drug substance.

For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

Conclusion: **Unsatisfactory**

(b) (4)

The recommended revisions are shown below:

HYFTOR™ (sirolimus) topical gel (b) (4) 0.2% (b) (4) is an mTOR inhibitor immunosuppressant (b) (4) for topical (b) (4) use (b) (4) Each gram contains 2 mg of sirolimus, which is solubilized in a gel consisting of alcohol (b) (4)%, Carbomer 940, purified water, and trolamine.

Chemically, sirolimus is designated as (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S* (b) (4)-9,10,12,13, 14,21,22,23,24,25,26,27,32,33,34,34a (b) (4) hexadecahydro-9,27-dihydroxy-3-[(1*R*) (b) (4)-2-[(1*S*,3*R*,4*R*) (b) (4)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H* (b) (4) pyrido[2,1-c][1,4] (b) (4) oxaazacyclohentriacontine-1,5,11,28,29-((b) (4) 4*H*,6*H*,31*H*)-pentone. It has the following structural formula:

Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in chloroform, acetone and acetonitrile. Sirolimus has a molecular formula of $C_{51}H_{79}NO_{13}$ and a molecular weight of 914.19 (b) (4)

(b) (4)

1.2.3 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	gel	**Acceptable**
Strength of dosage form in metric system	0.2%	**Unacceptable** Add strength in metric system, i.e., 2 mg per gram.
Available units (e.g., bottles of 100 tablets)	Not provided	**Unacceptable** Add "supplied as 10 g in aluminum tubes".
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not provided	**Unacceptable** Add "a colorless and transparent gel" and packaging information. Include "NDC numbering pending" if NDC number is not yet available.
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Not provided	**Unacceptable** The drug product is sensitive to light. Even though the aluminum tube is adequate to protect the product from light, it is recommended adding "Protect from light" to be consistent with the container label.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	refrigerated at 2-8°C (36-46°F)	**Acceptable** See Assessment section for minor editorial edits.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with	N/A	N/A

natural rubber latex. Avoid statements such as "latex-free."		

Conclusion: Unsatisfactory

The recommended revisions are shown below:

HYFTOR™ (sirolimus) topical gel (b) (4) 0.2% is a colorless and transparent gel supplied as 10 g in aluminum tubes (NDC number pending). Each gram contains 2 mg of sirolimus.

(b) (4)

Store (b) (4) refrigerated at 2°- to 8°C (36°- to 46°F). Protect from light.

(b) (4)

1.2.4 Section 17: PATIENT COUNSELING INFORMATION

Manufacturer/distributor name was not provided.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Not provided	**Unacceptable** (b) (4) It should be relocated to Section 17.

Conclusion: Unsatisfactory

Add the following at the end of Section 17:

(b) (4)

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.0 CARTON AND CONTAINER LABELS

The information in eCTD-0001 is provided below.

3.1 CONTAINER LABEL

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (b) (4)	**Unacceptable** (b) (4) . Font size of the established name is at least half as large as the proprietary name.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	For topical use only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% (b) (4)	**Unacceptable** Strength "0.2%" is acceptable. Equivalence statement is not applicable since sirolimus is neither an acid nor a base. The location of strength should be closer to the established name.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	(b) (4) and purified water	**Unacceptable** Established names (titles of the USP monographs) should be used. List inactive ingredients in alphabetical order (recommended, but not required).

"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC number allocated	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Not indicated on the label	**Acceptable** Based on the Master Batch Record (page 57), the tubes are closed by (b) (4) with imprinting of manufacturing No and expiration date (month/year).
Storage conditions	(b) (4) at 2 - 8°C (36 - 46°F). Protect from light.	**Acceptable** See Assessment section for minor editorial changes.
Bar code [21CFR 201.25(c)(2)]	Allocated	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	(b) (4)	**Unacceptable** Recommend changing to (b) (4) See Prescribing Information"
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America LLC, Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	**To Open:** Use pointed end on cap to puncture seal. **Tamper Evident:** Do not accept if seal is broken.	**Acceptable**
Package type (for injectable products). See USP <659> for other package terms including pharmacy bulk package and Imaging bulk package.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol.	Not provided	**Unacceptable** Add " (b) (4) %" after the inactive ingredient "alcohol".

Conclusion: **Unsatisfactory**

In an email communication dated 8/9/2019 with DMEPA assessor for labeling of another NDA, the assessor stated that based on DMEPA management's involvement with the Labeling Workgroup, it was recently determined that the usual dosage statement be changed from (b) (4) (b) (4) to (b) (4) See Prescribing Information".

The recommended revisions are shown below:

1. [redacted]
   Relocate the strength "0.2%" to immediately after the established name "sirolimus topical gel".
2. The established names of inactive ingredients should be used. Revise the statement from [redacted] to "**Each gram contains:** 2 mg of sirolimus solubilized in a gel consisting of alcohol [redacted]%, Carbomer 940, purified water, and trolamine (to adjust pH)".
3. Revise the storage statement from "[redacted] at 2 - 8°C (36 - 46°F)" to "[redacted] at 2° to 8°C (36° to 46°F)".
4. Revise the statement from [redacted] to [redacted] See Prescribing Information".

3.2 CARTON LABELS

[redacted]

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (b) (4)	**Unacceptable** (b) (4) Font size of the established name is at least half as large as the proprietary name.
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	For topical use only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% (b) (4)	**Unacceptable** Strength "0.2%" is acceptable. Equivalence statement is not applicable since sirolimus is neither an acid nor a base. The location of strength should be closer to the established name.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	(b) (4) and purified water	**Unacceptable** Established names (titles of the USP monographs) should be used. List inactive ingredients in alphabetical order (recommended, but not required).
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
Statement of being sterile (if applicable)	N/A	N/A
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC number allocated	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided on Side 1	**Acceptable**
Storage conditions	(b) (4) at 2 - 8°C (36 - 46°F). Protect from light.	**Acceptable** See Assessment section for minor editorial changes.
Bar code [21 CFR 201.25(c)(2)]	Allocated on Side 2	**Acceptable**

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	(b) (4)	**Unacceptable** Recommend changing to (b) (4) See Prescribing Information"
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided on Side 2	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America LLC Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	Keep away from fire	**Acceptable**
Package type (for injectable products). See USP <659> for other package terms including pharmacy bulk package and Imaging bulk package.	N/A	N/A

Conclusion: Unsatisfactory

The recommended revisions listed on page 13 for container label are also applicable to carton label.

4.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1. For the Product Title, the established name shall accompany the proprietary name, i.e., HYFTOR™ (sirolimus) topical gel. Delete (b) (4)
2. The year of Initial U.S. Approval is (b) (4)

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

3. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
4. Add a description of the identifying characteristics of the gel and limited packaging information, i.e., "a colorless and transparent gel in 10-gram tubes".
5. Delete (b) (4) (b) (4)

Section 11: Description

6. The established name should accompany the proprietary name, i.e., HYFTOR™ (sirolimus) topical gel.
7. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.

8. Use the established names of inactive ingredients. Add the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C). Recommend listing inactive ingredients in alphabetical order.
9. Add a brief description for the drug substance characteristics and revise the molecular weight, i.e., 914.19 instead of 914.17, and chemical name of sirolimus.

Section 16: How Supplied/Storage and Handling

10. Revise established name to "(sirolimus) topical gel".
11. Add a description of the identifying characteristics of the gel and packaging information, i.e., "a colorless and transparent gel supplied in aluminum tubes in 10 g".
12. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
13. Revised storage temperature from "2 - 8°C (36 - 46°F)" to "2° to 8°C (36° to 46°F)". Add "Protect from light".
14. Delete (b) (4)

Section 17: Patient Counseling Information

15. Add (b) (4) at the end of Section 17.

B. Regarding the Container/Carton Labels

16. Please address the following issues for both container and carton labels:
    a. (b) (4) Relocate the strength "0.2%" to immediately after the established name "sirolimus topical gel".
    b. The established names of inactive ingredients should be used. Revise the statement from (b) (4) (b) (4) (b) (4) to **"Each gram contains:** 2 mg of sirolimus solubilized in a gel consisting of alcohol (b) (4)%, Carbomer 940, purified water, and trolamine (to adjust pH)".
    c. Revise the storage statement from "(b) (4) at 2 - 8°C (36 - 46°F)" to "(b) (4) at 2° to 8°C (36° to 46°F)".
    d. Revise the statement from (b) (4) (b) (4) to (b) (4) See Prescribing Information".

OVERALL ASSESSMENT:

Issues on the established name and its location, strength, lack of product description, and inactive ingredients are identified.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Senior reviewer
DNDP II/ONDP
06/03/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

I agree with Dr. Chang's assessment on the labeling and labels, and therefore, I concur with her recommendation that this application is not deemed ready for approval in its present form from the CMC labeling/label perspective until the issues delineated in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch 4
DNDP II/ONDP
06/03/2020

Jane Chang

Digitally signed by Jane Chang
Date: 6/03/2020 05:15:16PM
GUID: 5034f819000053b21e2574590781f330

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 6/03/2020 05:43:54PM
GUID: 502d0913000029f9798ca689a802fa55

BIOPHARMACEUTICS

Product Background:

NDA: NDA 213473-ORIG-1

Sirolimus Gel, 0.2% (also known as OSD-001, NPC-12G gel) is a new formulation of sirolimus designed to delivered targeted topical therapy for the treatment of angiofibroma (AF) in patients with tuberous sclerosis (TS). The drug product, sirolimus gel, 0.2% is a (b) (4) and has mammalian target of rapamycin (mTOR) inhibitory action.

Per the Applicant, sirolimus has been awarded orphan drug designation on May 17, 2017 for the treatment of angiofibroma associated with tuberous sclerosis. As a result of this designation, a Fast Track Designation (FTD) was also granted on November 27, 2018.

Drug Product Name / Strength: Sirolimus gel/ 0.2%

Indication: Treatment of angiofibroma associated with tuberous sclerosis in adults and (b) (4)

Route of Administration: Topical

Applicant Name: Nobelpharma Co., Ltd.

Review Recommendation: The submission is **ADEQUATE** from Biopharmaceutics perspective.

Review Summary:

In Vitro Release Test (IVRT) and Acceptance Criterion: ADEQUATE

The Applicant has developed and validated an IVRT method using a vertical diffusion cell apparatus. The Applicant has agreed to provide IVRT data and release profiles for the first 3 commercial batches. The Applicant's proposed in vitro release acceptance criterion (b) (4) $\mu g/cm^2/hr^{1/2}$ is acceptable.

Formulation development and bridging: ADEQUATE

Two different formulations of sirolimus gel, 0.2% were developed, OSD-001 and NPC-12G gel. OSD-001 gel formulation was used in Phase 1/2 study (a dose ranging study) and NPC-12G Gel was used in Phase 3 study, and a Long-term Study (LTS). The Applicant has used in-vitro human skin permeability study and in-vitro dissolution study (b) (4) to bridge these two formulations. Both formulations have similar release profiles from each of the methods.

Manufacturing site changes for NPC-12G gel formulation: ADEQUATE

Sirolimus gel 0.2% NPC-12G Formulation 2 (used for Phase 3 studies and the first half of long-term administration study) and NPC-12G Formulation 3 (used in the second half of long-term administration study as the final formulation) were manufactured at (b) (4) and TOYO Pharmaceutical Co., Ltd., respectively. NPC-12G Formulation 3 is the commercial formulation. Between Formulation 2 and Formulation 3, (b) (4) The Applicant provided comparative drug release profiles between Formulation 2 and Formulation 3 manufactured at different sites (b) (4) Both formulations have similar release profiles.

Biowaiver Request: Not requested
Only one strength is developed.

List of Submissions being reviewed:

Application 213478 - Sequence 0001 - 0001 (1) 02/18/2020 ORIG-1 /Multiple Categories/Subcategories

Application 213478 - Sequence 0007 - 0007 (7) 04/09/2020 ORIG-1 /Quality/Response To Information Request

Application 213478 - Sequence 0012 - 0012 (12) 05/15/2020

Application 213478 - Sequence 0014 - 0014 (14) 06/04/2020

Highlight Key Outstanding Issues from Last Cycle: The Applicant was requested to provide method development report for IVRT method and revise in vitro release acceptance criterion.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: N/A

Solubility: N/A

Permeability: N/A

Dissolution: N/A

1. Composition of proposed drug product:
The drug product, Sirolimus Gel, 0.2%, is intended for topical administration. The quantitative composition of each component of the drug product is listed in Table 1.

Table 1: Composition of the proposed drug product

Ingredient	Function	Reference to Quality Standard	Composition (mg/1g)	Percent Weight (%w/w)
Sirolimus	Active ingredient	In-house	2.0	0.20%
(b) (4)	(b) (4)	USP/NF, Ph. Eur., JPE	(b) (4)	
		USP/JP		
		JPE		
Purified Water	(b) (4)	USP/JP		
Total			1000	100.00%

(b) (4)

2. IVRT method and acceptance criterion:

It is noted that the Applicant (b) (4) throughout their development program until FDA advised them to use IVRT method at pre-NDA meeting on May 2019. The Applicant has now developed an IVRT method for Sirolimus gel 0.2% drug product using vertical diffusion cell in accordance with USP<1724> "Semisolid Drug Products - Performance Tests; Drug Release Rate Determination Using Vertical Diffusion Cell Apparatus". Models B and C are used as the test procedures for the method. The in vitro release method conditions are provided below.

Apparatus	Vertical diffusion cell (membrane permeation test apparatus, type: TP-8S) Cell volume: about 9.5 mL Effective membrane area (orifice area): 1.77 cm^2
Membrane filter	Cellulose acetate membrane (GE Healthcare, Whatman OE 67 cellulose acetate membrane, pore size: 0.45 µm, diameter: 25 mm, or equivalent)
Medium temperature	31 to 33 °C
Receptor media	0.5% Sodium dodecyl sulfate aqueous solution
Revolutions	540 - 660 rpm
Sampling time	0.5, 1, 2, 3, and 4 hr
Replenishment of test medium	The volume withdrawn is replaced with same volume of test medium at the time of each sampling.
Number of iteration times	6 times

IVRT method development

No method development report was provided in the original submission. In response to an Information Request (See IR1.3 in Appendix 1), the Applicant has submitted method development report \\cdsesub1\evsprod\nda213478\0012\m3\32-body-data\32r-reg-info\bcs181011nbp01r01-method-development-report.pdf. However, no information on the discriminating ability of the method is provided in the document. However, this is acceptable given the orphan drug designation of the drug product, and short time for the review. The risk is low.

In vitro release acceptance criterion

The Applicant plans to use IVRT method for quality control purposes (both release and stability) for the commercial batches. Since the method was developed in the late phase, there are no release data for this test in this submission. However, the following IVRT specification has been proposed for both release and stability based on stability data collected 6 to 12 months at 5°C and -20°C for batches manufactured in 2018 (Lot VLT01, VLT02 and VLT03).

(b) (4) $\mu g/cm^2/hr^{1/2}$

Based on the data provided, the Agency recommended (b) (4) $\mu g/cm^2/hr^{1/2}$ (see IR1.4 below). In response, the Applicant proposed (b) (4) $\mu g/cm^2/hr^{1/2}$ based on the mean release rate and three times standard deviation for the stability data provided in the table below. The Applicant's proposed acceptance criterion is acceptable.

Table 2: Results of IVRT for the long-term stability study and the stability study in a freezer

Test	*Storage period*	*Lot No.*	*Release rate ($\mu g/cm^2/hr^{1/2}$)*		
			Minimum	*Max*	*Mean(n=6)*
Long-term stability test at 5℃	*6M*	*VLT01*	(b) (4)		*35.2*
		VLT02			*35.8*
		VLT03			*36.2*
	9M	*VLT01*			*41.1*
		VLT02			*34.5*
		VLT03			*34.1*
	12M	*VLT01*			*35.1*
		VLT02			*33.4*
		VLT03			*34.2*
Intermediate Storage in a Freezer at -20℃	*6M*	*VLT01*			*45.9*
	9M	*VLT01*			*44.0*
	12M	*VLT01*			*35.3*
Mean					*37.1*
SD					*4.2*
Mean ± 3SD					*24.5 ~ 49.6*

Reviewer's Assessment:

- The Applicant has developed and validated an IVRT method using a vertical diffusion cell apparatus. The Applicant has provided method development report. The IVRT method is acceptable.
- The Applicant's proposed in vitro release acceptance criterion (b) (4) $\mu g/cm^2/hr^{1/2}$ is acceptable.

3. Formulation development and bridging

Table 3: Formulation of Sirolimus Gel

(b) (4)

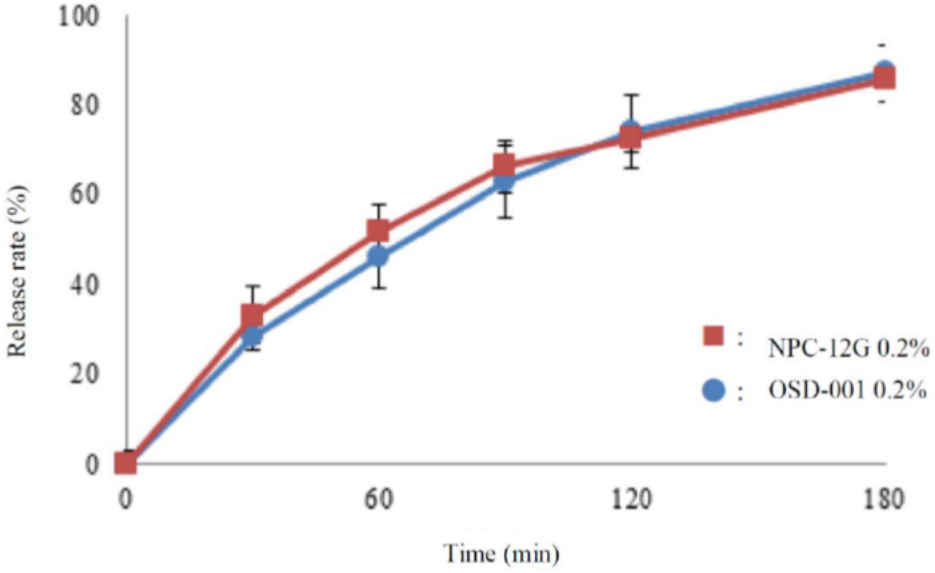
Two different formulations of sirolimus gel, 0.2% were developed, OSD-001 and NPC-12G gel. OSD-001 gel formulation was used in Phase 1/2 study (a dose ranging study) and NPC-12G Gel was used in Phase 3 study, and a Long-term Study (LTS). The Applicant used in-vitro human skin permeability study (IVPT) and in-vitro dissolution study to bridge these two formulations. The summary of these two methods are provided below.

In Vitro Dissolution study ((b) (4) Study Number G15114)

The equivalence of the proposed commercial formulation (NPC-12G gel, 0.2%) was compared to the earlier formulation OSD-001 0.2% gel using an i*n vitro* dissolution method (b) (4) The study was conducted according to the FDA guidelines, "Guideline for Bioequivalence Studies for Formulation Changes of Preparations for Topical Cutaneous Application (Semisolid Dosage and Patches (Notification No. 1101-1 of the ELD, PFSB, MHLW dated November 1, 2010. In response to an IR (See IR1.2 below), the Applicant submitted the translated document of this guidance. The Applicant also provided method validation report for the dissolution test using Apparatus as requested in IR2.1 below. The response is provided in the document \\cdsesub1\evsprod\nda213478\0014\m1\us\111-information-amendment\quality-information-amendment-03jun2020.pdf. Validation is provided in page 76 of the document. Individual dissolution data for these two dissolution profiles were also submitted by the Applicant in above document as requested by the Agency.

Figure below shows the release profiles of the two formulations, NPC-12G gel 0.2% and OSD-001 0.2% gel. This reviewer calculated the F2 similarity for these two profiles which is more than 50 (70.1), indicating release is similar.

Figure 1: Comparison of Release Profiles of NPC-12G Gel 0.2% and OSD-001 0.2% Gel Formulations



IVPT study

The Applicant has submitted *in vitro* Human Skin Permeability Study of Sirolimus Formulations in the document \\cdsesub1\evsprod\nda213478\0001\m4\42-stud-rep\422-pk\4222-absorp\b160670\b160670-pre-clinical-study-report-1.pdf The permeation profile and amount of sirolimus in the skin were evaluated after application of formulations (NPC-12G Gel 0.2% and 0.2% OSD-001) containing sirolimus at 2.5 mg/cm^2 to the human skin using diffusion cells.

Sirolimus was not detected in the receptor fluid collected between 2 and 24 hours after application of two formulations to the human skin (2 donors, n=2 each). Based on these findings, sirolimus gel, 0.2% regardless of formulation provides topical treatment with little systemic exposure.

The sirolimus concentration in the epidermis and dermis at 24 hours after application of NPC-12G Gel 0.2% was 0.3257 pmol/mg tissue (0.42% of dose). The recovery amount of sirolimus in the corneum was 2.80% of dose. The sirolimus concentration in the epidermis and dermis at 24 hours after application of 0.2% OSD-001 was 0.2740 pmol/mg tissue (0.34% of dose). The recovery amount of sirolimus in the corneum was 2.30% of dose. These results suggested that sirolimus in the formulations permeated into the epidermis and dermis via the corneum. The permeability of sirolimus was almost the same between the two formulations.

4. Manufacturing site changes for NPC-12G gel formulation

Sirolimus gel 0.2% NPC-12G Formulation 2 (used for Phase 3 studies and the first half of long-term administration study) and NPC-12G Formulation 3 (used in the second half of long-term administration study as the final formulation) were manufactured at (b) (4) and TOYO Pharmaceutical Co., Ltd., respectively. NPC-12G Formulation 3 is the commercial formulation. Between Formulation 2 and Formulation 3, (b) (4)

(b) (4) In an IR (see IR1.1) below, the Applicant was requested to provide comparative in vitro release test (IVRT) profiles for the batches manufactured at these two manufacturing sites to demonstrate drug product sameness.

In response, the Applicant provided the comparison of drug release between Formulation 2 and Formulation 3 manufactured at different sites using (b) (4) of USP<724>. As shown in the table below, both formulations release more than 80% of drug substance by 180 minutes. This reviewer calculated f2 which is more than 90 indicating similar release. As mentioned earlier, the Applicant used (b) (4) dissolution method throughout their development program until FDA advised them to use IVRT method. Hence, the release method using (b) (4) for bridging manufacturing sites is acceptable.

Table 4: Release profiles of Formulation 2 and Formulation 3 using (b) (4) method

Formulations and Manufacturing Sites	*Lot No.*	*Use*	*Released ratio (%) *1* (b) (4)
Formulation 2 (b) (4)	*NP12G1581*	*Phase 3*	
	NP12G1591	*Long-term administration*	
	NP12G1611	*Phase 3*	
	NP12G1631	*Long-term administration*	
	NP12G16X1	*Long-term administration*	
	NP12G16Y1	*Long-term administration*	
Formulation 3 *TOYO Pharmaceutical Co., Ltd.*	*NP12G1741 *2*	*Long-term administration*	
	12G1662	*PQ*	
	VJM01	*2016 PV, supportive stability*	
	VJM02	*2016 PV, supportive stability*	
	VJM03	*2016 PV, supportive stability*	
	VLT01	*2018 PV, primary stability*	
	VLT02	*2018 PV, primary stability*	
	VLT03	*2018 PV, primary stability*	

**1 Average of n=6*
**2 This lot was manufactured for Japanese market* (b) (4)

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 6/19/2020 03:23:27PM
GUID: 562e1e15002f200f35c6ccac959cdb34

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 6/19/2020 03:31:19PM
GUID: 508da7230002a2433ddcef616ca190df

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213478
Assessment Cycle Number	MR01
Drug Product Name/ Strength	HYFTOR (Sirolimus Gel 0.2%)
Route of Administration	Topical
Applicant Name	Nobelpharma America, LLC
Therapeutic Classification/ OND Division	Division of Dermatology and Dental Products
Manufacturing Site	TOYO Pharmaceutical Co., Ltd. Joto Plant 2-5-4, Tsurumi, Tsurumi-ku, Osaka, Osaka 538-0053 Japan
Method of Sterilization	N/A for a nonsterile product

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001	**2/18/2020**
0007	**4/9/2020**
0012	**5/15/2020**

Highlight Key Issues from Last Cycle and Their Resolution:

Remarks: This application provides for the marketing of a new non-sterile topical drug product, 0.2% sirolimus gel for tuberous sclerosis. This review incorporates an IR sent 4/2/2020 and the applicant response to that IR dated 4/9/2020 (Section 1.11.1 Quality Information Amendment). Per a pre-NDA meeting held in May 2019 the applicant submitted BCC testing, risk assessment and method suitability data at the mid cycle date 5/18/2020. The midcycle amendment is covered in the review below.

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug substance is not provided sterile for this nonsterile drug product, so will not be reviewed here.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section P.1 Description and Composition of the Drug Product

Description of the drug product – Topical, aqueous Sirolimus Gel 0.2% in an aluminum tube with a plastic cap.

Drug product composition -

Ingredient		
Sirolimus		0
(b) (4)		(b) (4)
(Carbomer 940) USP/NF		
(b) (4)		
Purified Water USP		

Summary Table of the proposed Container Closure System (3.2.P.7) – Section P.7 Container Closure System

Component		
Aluminum tube		(b) (4)
Cap		

Assessment: Adequate

The applicant provided a description of the drug product and container closure system that meets regulatory expectations.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

13 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Erin Wall

Digitally signed by Erin Wall
Date: 5/21/2020 12:05:16PM
GUID: 5d83ca3b009622bb24dda4b4fd39936b

Laura Wasil

Digitally signed by Laura Wasil
Date: 5/21/2020 12:10:02PM
GUID: 59b190cf009be8467b9b6b02d9543afe

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
07/24/2020 06:11:43 PM

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0001 (SDN-1)	02/18/2020
eCTD-0011 (SDN-11)	05/11/2020

1.0 PRESCRIBING INFORMATION

The information in eCTD-0011 is provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	HYFTOR™ (b) (4)	**Unacceptable** The established name should be in lower case (b) (4) (b) (4)
Dosage form, route of administration	Gel, topical	**Unacceptable** The dosage form should be in lower case per Labeling Review Tool (LRT).
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	xxxx	**Unacceptable** (b) (4)
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	(b) (4) 0.2%	**Unacceptable** (b) (4) (b) (4) should be deleted. Include the strength in metric system and limited packaging information per Labeling Review Tool (LRT).
Whether the drug product is scored	N/A	N/A

Conclusion: Unsatisfactory

The proposed proprietary name, Hyftor, was assessed by DMEPA assessor, Madhuri R. Patel, on 4/29/2020 and concluded to be acceptable.

The recommended revisions are shown below:

Product Title:

HYFTOR™ (b) (4)
Initial U.S. Approval: (b) (4)

Dosage Forms and Strengths:

(b) (4) 0.2%: (b) (4)

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 3: DOSAGE FORMS AND STRENGTHS

(b) (4)

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	Gel	**Acceptable** (b) (4)
Strength: in metric system	0.2%	**Unacceptable** Add "2 mg of sirolimus per gram"
Active moiety expression of strength (if applicable)	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided	**Unacceptable** Add "colorless and transparent gel" and limited packaging information.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

(b) (4) 0.2%: a colorless and transparent gel in 10-gram tubes. Each gram contains 2 mg of sirolimus (b) (4)

(b) (4)

1.2.2 Section 11: DESCRIPTION

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	HYFTOR™ (b) (4)	**Unacceptable** (b) (4)
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Gel, topical	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	0.2%	**Unacceptable** Add strength in metric system, i.e., 2 mg per gram.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	(b) (4) , and purified water	**Unacceptable** Established names (titles of the USP monographs) should be used. List inactive ingredients in alphabetical order (recommended, but not required). The alcohol content ((b) (4) %) should be provided.
Statement of being sterile [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	N/A	N/A
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	mTOR inhibitor immunosuppressant	**Acceptable**
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	provided	**Unacceptable** See Assessment section for minor edits for chemical name and molecular weight.
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	N/A	Recommend adding a short description of the drug substance.

For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

Conclusion: **Unsatisfactory**

(b) (4)

The recommended revisions are shown below:

HYFTOR™ (sirolimus) topical gel (b) (4) 0.2% (b) (4) is an mTOR inhibitor immunosuppressant (b) (4) for topical (b) (4) use (b) (4) Each gram contains 2 mg of sirolimus, which is solubilized in a gel consisting of alcohol (b) (4)%, Carbomer 940, purified water, and trolamine.

Chemically, sirolimus is designated as (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S* (b) (4)-9,10,12,13, 14,21,22,23,24,25,26,27,32,33,34,34a (b) (4) hexadecahydro-9,27-dihydroxy-3-[(1*R*) (b) (4)-2-[(1*S*,3*R*,4*R*) (b) (4)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H* (b) (4) pyrido[2,1-c][1,4] (b) (4) oxaazacyclohentriacontine-1,5,11,28,29-((b) (4) 4*H*,6*H*,31*H*)-pentone. It has the following structural formula:

Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in chloroform, acetone and acetonitrile. Sirolimus has a molecular formula of $C_{51}H_{79}NO_{13}$ and a molecular weight of 914.19 (b) (4)

(b) (4)

1.2.3 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	gel	**Acceptable**
Strength of dosage form in metric system	0.2%	**Unacceptable** Add strength in metric system, i.e., 2 mg per gram.
Available units (e.g., bottles of 100 tablets)	Not provided	**Unacceptable** Add "supplied as 10 g in aluminum tubes".
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not provided	**Unacceptable** Add "a colorless and transparent gel" and packaging information. Include "NDC numbering pending" if NDC number is not yet available.
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Not provided	**Unacceptable** The drug product is sensitive to light. Even though the aluminum tube is adequate to protect the product from light, it is recommended adding "Protect from light" to be consistent with the container label.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	refrigerated at 2-8°C (36-46°F)	**Acceptable** See Assessment section for minor editorial edits.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with	N/A	N/A

natural rubber latex. Avoid statements such as "latex-free."		

Conclusion: Unsatisfactory

The recommended revisions are shown below:

HYFTOR™ (sirolimus) topical gel (b) (4) 0.2% is a colorless and transparent gel supplied as 10 g in aluminum tubes (NDC number pending). Each gram contains 2 mg of sirolimus.

(b) (4)

Store (b) (4) refrigerated at 2°- to 8°C (36°- to 46°F). Protect from light.

(b) (4)

1.2.4 Section 17: PATIENT COUNSELING INFORMATION

Manufacturer/distributor name was not provided.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Not provided	**Unacceptable** (b) (4) It should be relocated to Section 17.

Conclusion: Unsatisfactory

Add the following at the end of Section 17:

(b) (4)

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.0 CARTON AND CONTAINER LABELS

The information in eCTD-0001 is provided below.

3.1 CONTAINER LABEL

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (b) (4)	**Unacceptable** (b) (4) . Font size of the established name is at least half as large as the proprietary name.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	For topical use only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% (b) (4)	**Unacceptable** Strength "0.2%" is acceptable. Equivalence statement is not applicable since sirolimus is neither an acid nor a base. The location of strength should be closer to the established name.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	(b) (4) and purified water	**Unacceptable** Established names (titles of the USP monographs) should be used. List inactive ingredients in alphabetical order (recommended, but not required).

"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC number allocated	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Not indicated on the label	**Acceptable** Based on the Master Batch Record (page 57), the tubes are closed by (b) (4) with imprinting of manufacturing No and expiration date (month/year).
Storage conditions	(b) (4) at 2 - 8°C (36 - 46°F). Protect from light.	**Acceptable** See Assessment section for minor editorial changes.
Bar code [21CFR 201.25(c)(2)]	Allocated	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	(b) (4)	**Unacceptable** Recommend changing to (b) (4) See Prescribing Information"
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America LLC, Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	**To Open:** Use pointed end on cap to puncture seal. **Tamper Evident:** Do not accept if seal is broken.	**Acceptable**
Package type (for injectable products). See USP <659> for other package terms including pharmacy bulk package and Imaging bulk package.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol.	Not provided	**Unacceptable** Add " (b) (4) %" after the inactive ingredient "alcohol".

Conclusion: **Unsatisfactory**

In an email communication dated 8/9/2019 with DMEPA assessor for labeling of another NDA, the assessor stated that based on DMEPA management's involvement with the Labeling Workgroup, it was recently determined that the usual dosage statement be changed from (b) (4) (b) (4) to (b) (4) See Prescribing Information".

The recommended revisions are shown below:

1. [redacted]
   Relocate the strength "0.2%" to immediately after the established name "sirolimus topical gel".
2. The established names of inactive ingredients should be used. Revise the statement from [redacted] to "**Each gram contains:** 2 mg of sirolimus solubilized in a gel consisting of alcohol [redacted]%, Carbomer 940, purified water, and trolamine (to adjust pH)".
3. Revise the storage statement from "[redacted] at 2 - 8°C (36 - 46°F)" to "[redacted] at 2° to 8°C (36° to 46°F)".
4. Revise the statement from [redacted] to [redacted] See Prescribing Information".

3.2 CARTON LABELS

[redacted]

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	HYFTOR (b) (4)	**Unacceptable** (b) (4) Font size of the established name is at least half as large as the proprietary name.
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	For topical use only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	0.2% (b) (4)	**Unacceptable** Strength "0.2%" is acceptable. Equivalence statement is not applicable since sirolimus is neither an acid nor a base. The location of strength should be closer to the established name.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	10 g	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	(b) (4) and purified water	**Unacceptable** Established names (titles of the USP monographs) should be used. List inactive ingredients in alphabetical order (recommended, but not required).
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
Statement of being sterile (if applicable)	N/A	N/A
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC number allocated	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided on Side 1	**Acceptable**
Storage conditions	(b) (4) at 2 - 8°C (36 - 46°F). Protect from light.	**Acceptable** See Assessment section for minor editorial changes.
Bar code [21 CFR 201.25(c)(2)]	Allocated on Side 2	**Acceptable**

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	(b) (4)	**Unacceptable** Recommend changing to (b) (4) See Prescribing Information"
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided on Side 2	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	**Distributed by:** Nobelpharma America LLC Bethesda, Maryland 20814 USA	**Acceptable**
And others, if space is available	Keep away from fire	**Acceptable**
Package type (for injectable products). See USP <659> for other package terms including pharmacy bulk package and Imaging bulk package.	N/A	N/A

Conclusion: Unsatisfactory

The recommended revisions listed on page 13 for container label are also applicable to carton label.

4.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1. For the Product Title, the established name shall accompany the proprietary name, i.e., HYFTOR™ (sirolimus) topical gel. Delete (b) (4)
2. The year of Initial U.S. Approval is (b) (4)

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

3. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
4. Add a description of the identifying characteristics of the gel and limited packaging information, i.e., "a colorless and transparent gel in 10-gram tubes".
5. Delete (b) (4) (b) (4)

Section 11: Description

6. The established name should accompany the proprietary name, i.e., HYFTOR™ (sirolimus) topical gel.
7. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.

8. Use the established names of inactive ingredients. Add the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C). Recommend listing inactive ingredients in alphabetical order.
9. Add a brief description for the drug substance characteristics and revise the molecular weight, i.e., 914.19 instead of 914.17, and chemical name of sirolimus.

Section 16: How Supplied/Storage and Handling

10. Revise established name to "(sirolimus) topical gel".
11. Add a description of the identifying characteristics of the gel and packaging information, i.e., "a colorless and transparent gel supplied in aluminum tubes in 10 g".
12. Include strength in metric system, i.e., Each gram contains 2 mg of sirolimus.
13. Revised storage temperature from "2 - 8°C (36 - 46°F)" to "2° to 8°C (36° to 46°F)". Add "Protect from light".
14. Delete (b) (4)

Section 17: Patient Counseling Information

15. Add (b) (4) at the end of Section 17.

B. Regarding the Container/Carton Labels

16. Please address the following issues for both container and carton labels:
    a. (b) (4) Relocate the strength "0.2%" to immediately after the established name "sirolimus topical gel".
    b. The established names of inactive ingredients should be used. Revise the statement from (b) (4) (b) (4) (b) (4) to **"Each gram contains:** 2 mg of sirolimus solubilized in a gel consisting of alcohol (b) (4)%, Carbomer 940, purified water, and trolamine (to adjust pH)".
    c. Revise the storage statement from "(b) (4) at 2 - 8°C (36 - 46°F)" to "(b) (4) at 2° to 8°C (36° to 46°F)".
    d. Revise the statement from (b) (4) (b) (4) to (b) (4) See Prescribing Information".

OVERALL ASSESSMENT:

Issues on the established name and its location, strength, lack of product description, and inactive ingredients are identified.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Senior reviewer
DNDP II/ONDP
06/03/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

I agree with Dr. Chang's assessment on the labeling and labels, and therefore, I concur with her recommendation that this application is not deemed ready for approval in its present form from the CMC labeling/label perspective until the issues delineated in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch 4
DNDP II/ONDP
06/03/2020

Jane Chang

Digitally signed by Jane Chang
Date: 6/03/2020 05:15:16PM
GUID: 5034f819000053b21e2574590781f330

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 6/03/2020 05:43:54PM
GUID: 502d0913000029f9798ca689a802fa55