CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216482Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 26, 2024
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 216482
Product Name, Dosage Form, and Strength:	Myhibbin (mycophenolate mofetil oral suspension), 200 mg/mL
Applicant Name:	Liqmeds Worldwide Limited
FDA Received Date:	March 20, 2024
TTT ID #:	2022-2270-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader (Acting):	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

Liqmeds Worldwide Limited submitted revised container label and carton labeling received on March 20, 2024 for Myhibbin. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Myhibbin (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Liqmeds Worldwide Limited implemented all of our recommendations and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON MARCH 20, 2024

Container Label(s)

Carton Labeling

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[a] Vee, S. Label and Labeling Review for Myhibbin (NDA 216482). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 30. TTT ID: 2022-2270.

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/s/

SARAH K VEE
03/26/2024 10:04:27 AM

DAMON A BIRKEMEIER
03/26/2024 10:13:56 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	January 30, 2024
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 216482
Product Name, Dosage Form, and Strength:	Myhibbin (mycophenolate mofetil) oral suspension, 200 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Liqmeds Worldwide Limited
FDA Received Date:	November 1, 2023
TTT ID #:	2022-2270
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader (Acting):	Damon Birkemeier, PharmD, FISMP, NREMT

1 REASON FOR REVIEW

As part of the approval process for Myhibbin (mycophenolate mofetil) oral suspension, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Myhibbin prescribing information, carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 216482 mycophenolate mofetil oral suspension was submitted as a 505(b)(2) on March 8, 2022. The Reference Listed Drug (RLD) is NDA 050759 Cellcept (mycophenolate mofetil) for oral suspension. Cellcept is currently approved in 200 mg/mL (once reconstituted) for oral suspension for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants.

NDA 216482 received a complete response (CR) on January 6, 2023, due to a lack of risk evaluation and mitigation strategy (REMS). The Applicant submitted a response to the CR on November 1, 2023.

3 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that that the proposed mycophenolate mofetil oral suspension have the same strength, indication, and route of administration as the RLD, Cellcept. The difference is that the proposed mycophenolate mofetil will be available as ready to use oral suspension whereas the RLD Cellcept is available as for oral suspension.

We performed a risk assessment of the proposed prescribing information, container label, and carton labeling for mycophenolate mofetil oral suspension to identify areas of vulnerability that may lead to medication errors and other areas for improvement.

Our review of the proposed prescribing information, container label, and carton labeling identified other areas that may be revised to improve clarity and readability of important information. We provide recommendations for the Division and for the Applicant to address these deficiencies.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed prescribing information, container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide recommendations for the Division in Section 5.1 and the Applicant in Section 5.2 below.

5.1 RECOMMENDATIONS FOR DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE (DRTM)

A. Prescribing Information

1. Dosage and Administration Section 2.3

   a. (b) (4) Revise to read "1.5 g orally administered twice daily".

5.2 RECOMMENDATIONS FOR LIQMEDS WORLDWIDE LIMITED

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

A. General Comments (Container labels & Carton Labeling)

1. Replace the proprietary name with the conditionally acceptable name, "Myhibbin" throughout the labels and labeling and resubmit for review.
2. Per the Drug Supply Chain Security Act (DSCSA), the "smallest saleable unit" must include the NDC in both human-readable and machine-readable forms. See *Guidance for Industry Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers (June 2021)*.[a] Include the machine-readable forms of the NDC.

[a] https://www.fda.gov/media/116304/download.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Myhibbin received on November 1, 2023 from Liqmeds Worldwide Limited.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Myhibbin</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>mycophenolate mofetil</td></tr>
<tr><td>Indication</td><td>for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>oral suspension</td></tr>
<tr><td>Strength</td><td>200 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><td>ADULTS</td><td>DOSAGE</td></tr>
<tr><td>Kidney Transplant</td><td>1 g orally twice daily</td></tr>
<tr><td>Heart Transplant</td><td>1.5 g orally twice dail</td></tr>
<tr><td>Liver Transplant</td><td>1.5 g orally twice daily</td></tr>
<tr><td>PEDIATRICS</td><td></td></tr>
<tr><td>Kidney Transplant</td><td>600 mg/m^2 orally twice daily, up to maximum of 2 g daily</td></tr>
<tr><td>Heart Transplant</td><td>600 mg/m^2 orally twice daily (starting dose) up to a maximum of 900 mg/m2 twice daily (maximum daily dose of 3 g or 15 mL of oral suspension)</td></tr>
<tr><td>Liver Transplant</td><td>600 mg/m^2 orally twice daily (starting dose) up to a maximum of 900 mg/m2 twice daily (maximum daily dose of 3 g or 15 mL of oral suspension)</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>175 mL of suspension in 225 mL bottle</td></tr>
</table>

Table 2. Relevant Product Information for Myhibbin	
Storage	Store at 20°C to 25°C (68° F to 77° F); excursions permitted to 15°C to 30°C (59° F to 86° F) [See USP Controlled Room Temperature]. Do not freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 19, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "mycophenolate". Our search identified two previous reviews[b,c], and we confirmed that our previous recommendations were implemented.

[b] Vee, S. Label and Labeling Review for mycophenolate mofetil oral solution (NDA 216482). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 09. OSE RCM No.: 2022-497.

[c] Vee, S. Label and Labeling Review for mycophenolate mofetil oral solution (NDA 216482). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 01. OSE RCM/TTT No.: 2022-497-1/2022-2270-1.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Myhibbin labels and labeling submitted by Liqmeds Worldwide Limited.

- Container label received on December 20, 2022
- Carton labeling received on December 20, 2022
- Prescribing Information (Image not shown) received on December 20, 2022, available from \\CDSESUB1\evsprod\NDA216482\0022\m1\us
- Medication Guide received on December 20, 2022, available from \\CDSESUB1\evsprod\NDA216482\0022\m1\us

F.2 Label and Labeling Images

Container label

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

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/s/

SARAH K VEE
01/30/2024 03:28:46 PM

DAMON A BIRKEMEIER
01/30/2024 03:33:24 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 1, 2022
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 216482
Product Name and Strength:	(b) (4) (mycophenolate mofetil) oral suspension, 200 mg/mL
Applicant/Sponsor Name:	Liqmeds Worldwide Limited
OSE RCM #/TTT #:	2022-497-1/2022-2270-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 23, 2022 for (b) (4). The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for (b) (4) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. Statements, (b) (4) (b) (4) ", were not removed and are redundant.

3 RECOMMENDATIONS FOR LIQMEDS WORLDWIDE LIMITED

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

A. Delete the statements, " (b) (4) since these are redundant.

[a] Vee, S. Label and Labeling Review for (b) (4) (NDA 216482). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 09. OSE RCM No.: 2022-497.

B. The proposed proprietary name [redacted] (b) (4) " was found conditionally acceptable. If you intend to have a proprietary name for your product, update your container label and carton labeling and submit for review.

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/s/

SARAH K VEE
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12/01/2022 11:50:53 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 29, 2022
To:	Saharat Patanavanich Regulatory Project Manager **Division of Rheumatology and Transplant Medicine (DRTM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Mycophenolate Mofetil Oral Suspension
Dosage Form and Route:	for oral use
Application Type/Number:	NDA 216482
Applicant:	Liqmeds Worldwide Limited

1 INTRODUCTION

On March 7, 2022, Liqmeds Worldwide Limited submitted for the Agency's review an original New Drug Application (NDA) 216482 for mycophenolate mofetil oral suspension, for oral use. The Applicant proposes the indication for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart or liver transplants, and should be used in combination with other immune-suppressants.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine (DRTM) on June 13, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for mycophenolate mofetil for oral suspension.

2 MATERIAL REVIEWED

- Draft Mycophenolate Mofetil Oral Suspension MG received on March 7, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on November 14, 2022.
- Draft Mycophenolate Mofetil Oral Suspension MG received on March 7, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on November 21, 2022.
- Draft Mycophenolate Mofetil Oral Suspension Prescribing Information (PI) received on March 7, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on November 14, 2022.
- Draft Mycophenolate Mofetil Oral Suspension Prescribing Information (PI) received on March 7, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on November 21, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MARY E CARROLL
11/29/2022 08:33:56 AM

KYLE SNYDER
11/29/2022 09:44:57 AM

MARCIA B WILLIAMS
11/29/2022 10:09:54 AM

LASHAWN M GRIFFITHS
11/29/2022 10:47:47 AM

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

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

Memorandum

Date: November 28, 2022

To: Saharat Patanavanich, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for Mycophenolate Mofetil Oral Suspension, for oral use

NDA: 216482

Background:

In response to DRTM's consult request dated June 10, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for Mycophenolate Mofetil Oral Suspension, for oral use.

PI/PPI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 21, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on November 28, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
11/28/2022 04:50:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

From: Shamir Tuchman, MD, MPH, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, Deputy Director
DPMH, ORPURM, OND

To: Division of Rheumatology and Transplant Medicine (DRTM)

Subject: Pediatric safety assessment of excipient content in a ready-to-use (RTU) mycophenolate mofetil oral suspension.[1]

Applicant: Liqmeds Worldwide, LTD[2]

Application number: NDA 216482

Drug: Mycophenolate mofetil RTU oral suspension

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[1] This review will refer to the drug product as "mycophenolate mofetil RTU oral suspension"

[2] This review will refer to "Liqmeds Worldwide, LTD" as the "Applicant"

Drug Class:	Immunosuppressant
Proposed Pediatric Indication:	Prophylaxis of organ rejection in recipient 3 months of age and older with allogenic kidney, heart, and liver transplants
Proposed Dosage Forms:	RTU suspension
Route of administration:	Oral

Consult Request:
On August 16, 2022, DRTM consulted DPMH to provide an evaluation of a RTU oral suspension dosage form for mycophenolate mofetil submitted by the Applicant through a 505(b)(2) pathway for marketing approval. DRTM notes that 6 inactive ingredients differ in the submitted drug product from those founds in the Listed Drug (LD) and all other approved generic drug products of the LD. DRTM asks DPMH to opine on the potential of these inactive ingredients and their combination to precipitate adverse GI tolerability effects in the proposed pediatric population for the indication submitted in the NDA.

Materials Reviewed/Referenced:

- The following documents entered into DARRTS under NDA 216482
  - Cover Letter, Response to Information Request, Module 1.2, dated August 23, 2022 (eCTD# 10)
  - DPMH Consult Request Form, dated August 16, 2022
  - Filing Review Issues Identified Letter, dated May 25, 2022
  - Clinical Filing Review, dated May 25, 2022
  - General Consult Request, dated April 28, 2022
  - Cover Letter, Module 1.2, dated March 8, 2022 (eCTD# 1)
  - Draft Labeling Text, Module 1.14.1.3, dated March 8, 2022 (eCTD#1)
  - Control of Inactive ingredients/Summary of Inactive ingredients, Module 3.2.P.4, dated March 8, 2022 (eCTD# 1)
- The following documents entered into DARRTS under NDA 050759
  - Approval Letter, dated October 1, 1998
- The following documents entered into DARRTS under NDA 214047
  - DPMH consult review, dated December 8, 2020
  - Approval Letter, dated November 30, 2020

I. Background

The Applicant submitted a New Drug Application (NDA) on March 8, 2022 for a new ready to use (RTU) oral suspension dosage form of mycophenolate mofetil. The Applicant is seeking approval under the 505(b)(2) pathway of the Federal Food, Drug, and Cosmetic Act (FD&C), and the NDA contains pivotal in-vivo relative bioavailability data from two studies in healthy adult male volunteers (Study CL-155-18 and Study CL-156-18) to bridge to FDA's previous finding of safety and effectiveness for Cellcept oral suspension 200 mg/mL (NDA 050759 originally approved on October 1, 1998) as the LD. The LD is a powder dosage form which must be reconstituted with water into a 200 mg/mL suspension prior to administration.[3]

II. Drug Product

Mycophenolate mofetil RTU oral suspension and the LD are both single-ingredient products containing mycophenolate mofetil as the active ingredient, but compared to the LD, mycophenolate mofetil RTU oral suspension contains 6 inactive ingredients not found in the LD. These 6 inactive ingredients and their concentrations are shown in **Table 1**.

Table 1: Inactive ingredients in Mycophenolate Mofetil RTU Oral Suspension not found in the LD

Inactive ingredients Not Present in LD	Concentration (mg/mL)
(b) (4) Simethicone Emulsion	(b) (4)
Polysorbate 80	
Sodium Phosphate, Monobasic, Dihydrate	
Sodium Phosphate, Dibasic, Dihydrate	
Glycerin	
Propylparaben	0.560

Source: adapted by this reviewer from the DRTM Clinical Filing Review dated May 25, 2022

[3] Prescribing information found under Cellcept (NDA 050759) at Drugs@FDA.gov

Although the individual amount of these 6 inactive ingredients have previously been qualified and do not exceed amounts found in the inactive ingredient database (IID), the safety and tolerability of all 6 inactive ingredients in the amounts proposed within a single product are unknown. The combination of these inactive ingredients along with mycophenolate mofetil has the potential to cause worse gastrointestinal (GI) intolerance, particularly in pediatric patients, for the following reasons:

- Four (monosodium phosphate, dibasic sodium phosphate, simethicone, and glycerin) of the 6 inactive ingredients can cause GI adverse effects independently
- Mycophenolate mofetil is known to cause GI adverse effects as reflected in Section 6.1 of LD labeling.
- Younger pediatric patients are more susceptible to mycophenolate mofetil's GI adverse effects. Under a *Pediatrics* sub-heading in Section 6.1, LD labeling includes the following information related to GI adverse events:

  "The type and frequency of adverse events in a clinical study for prevention of kidney allograft rejection in 100 pediatric patients 3 months to 18 years of age dosed with CELLCEPT oral suspension 600 mg/m^2 twice daily (up to 1 g twice daily) were generally similar to those observed in adult patients dosed with CELLCEPT capsules at a dose of 1 g twice daily with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, leukopenia, and anemia, which were observed in a higher proportion in pediatric patients."

Decreased GI tolerability from use of the proposed drug product due to these 6 inactive ingredients could lead to non-adherence and inconsistent immunosuppression, which could affect graft function and survival for the intended pediatric kidney, heart, and liver allograft population. Because the mycophenolate mofetil RTU oral suspension is a pediatric-friendly dosage form, the proposed product has the potential to be used off-label in patients less than 6 years of age, in whom the consequences of GI intolerance could be more severe.

In a May 25, 2022 Filing Review Issues Identified Letter to the Applicant, the Division conveyed their concern regarding the potential for pediatric patients to develop GI intolerance from the novel combination of inactive ingredients in the proposed drug product and requested that the Applicant provide a justification supporting the GI tolerability of the proposed dosage form in the pediatric population.

In the August 23, 2022 response, the Applicant provided the following information justifying the pediatric safety of the 6 inactive ingredients in the proposed product:

1) A comparison of functionality of inactive ingredients between the mycophenolate mofetil RTU oral suspension and the LD. (b) (4)
(b) (4)
2) The demonstrated chemical stability of the final drug product formulation. The Applicant contends stability data reflect that the inactive ingredients do not cross react or interact with mycophenolate mofetil and remain in their original chemical states; (b) (4)
3) The 6 inactive ingredients alone or in combination are classified under the category "generally recognized as safe (GRAS)" as per the FDA in pharmaceutical preparations for currently marketed drug products.[4]
4) The Applicant stipulates that no reports of GI toxicity related to these inactive ingredients, either alone or in combination, have been described in the literature or reported to its pharmacovigilance database. The Applicant provided literature references supporting the safety of the inactive ingredients in approved drug products when found at or above the concentration contained in the proposed drug product. The Applicant noted that simethicone is an active ingredient in an approved drug product at a concentration well-above that contained as an inactive ingredient in the proposed drug product.
5) All inactive ingredients, with the exception of the raspberry flavor, are inactive ingredients within the prespecified levels in IID and used in oral dosage forms.

Reviewer Comment: The Applicant's response to the Filing Review Issues Identified Letter provides supportive information for the safety of each inactive ingredient relative to the GRAS classification and exposures noted in the IID. The functionality of each inactive ingredient and demonstrated chemical stability of the final drug product likely has minimal bearing on the potential GI tolerability. The Applicant does not provide justification that the combination of the inactive ingredients in this drug product would not lead to adverse GI tolerability.

[4] Found at https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras

III. Review of Inactive Ingredients

The DRTM Pharmacology-Toxicology (pharm-tox) reviewers undertook an analysis of each of the 6 inactive ingredients to compare the potential exposures relative to the IID database thresholds using the maximum daily dose (MDD) in adult and pediatric patients. The pharm-tox reviewers assumed a 20 kg weight for pediatric patients for the dosing calculations.

Because the IID maximum exposure thresholds are not specific for pediatric patient populations, this reviewer undertook further analyses to better approximate the maximum daily dose of each inactive ingredient (mg/kg) based on the maximum dosage being proposed by the Applicant for pediatric patients 3 months of age and older. The Applicant is proposing the same pediatric dosing approved in the LD labeling:

- 600 mg/m^2/dose twice daily up to a maximum dose of 1 gram twice daily for the prophylaxis of allogenic kidney transplant rejection in pediatric patients 3 months of age and older.
- 600 mg/m^2/dose twice daily up to a maximum dose of 900 mg/m^2/dose twice daily (1.5 grams twice daily) for the prophylaxis of allogenic heart and liver transplant rejection in pediatric patients 3 months of age and older.

In order to capture values representative of the wide spectrum of ages, weights, and body surface areas (BSAs), this reviewer analyzed the maximum daily dose of the 6 inactive ingredients in the mycophenolate mofetil RTU oral suspension that differ from the LD based on the following scenarios:

1) The smallest potential pediatric patients set as the lowest weight and height (e.g., 5^{th} percentile) 3-month old patient.
2) The highest weight and height (e.g., 95^{th} percentile) for a 3-month old patient.
3) The lowest weight pediatric patient who could potentially receive a dose just below the maximum dose of 1 gram twice daily (e.g., BSA < 1.7 m^2 with a height at the 95%ile).
4) The tallest pediatric patient (e.g., 95^{th} percentile) who weighs 20 kg (e.g. highest potential BSA for a patient weighing 20 kg).

The results of these analyses as well as those provided by the DRTM pharm-tox reviewers are shown in **Table 2.**

Table 2: Potential Inactive Ingredient Exposures in the Proposed Pediatric Allogenic Kidney, Heart, and Liver Transplant Population

Inactive ingredients Not Present in LD	Conc. (mg/mL)	Excipient Dose (mg) at maximum approved daily adult dose (mg/kg)[a]	BSA-based daily dosing volume (mg) for a 3-month old pediatric patient at the 5th Percentile for height and weight	BSA-based daily dosing volume (mg) for a 3-month old pediatric patient at the 95th Percentile height and weight	Maximum approved dose (1.5 g BID) for an adolescent patient at the 95th Percentile for height	BSA-based daily max MMF Dose for 20 kg patient at the 95th Percentile for height	MDE in mg (mg/kg)[a]
Simethicone						(b) (4)	150 (2.5 mg/kg)
Polysorbate 80							432 (7.2 mg/kg)
Sodium Phosphate, Monobasic, Dihydrate							140 (2.3 mg/kg)
Sodium Phosphate, Dibasic, Dihydrate							137[b] (2.4 mg/kg)
Glycerin							31,536 (525.6 mg/kg)
Propylparaben	0.560	8.4 mg (0.14 mg/kg)	2.3 mL (1.26 mg) 0.29 mg/kg	3.2 mL (1.77 mg) 0.26 mg/kg	15 mL (8.4 mg) 0.15 mg/kg	8.1 mL (4.5 mg) 0.23 mg/kg	17[c] 0.3 mg/kg

Abbreviations: MDD = Maximum Daily Dose; MDE = Maximum Daily Exposure

[a] From the FDA Inactive Ingredient Database information for the oral route of administration. Calculated dose/exposure in mg/kg using 60 kg as standard adult weight, per Starting Dose Guidance

[b] 143 mg is the oral MDE reported for Sodium Phosphate, Dibasic (not specifically the dihydrate). The oral MDE reported for the dihydrate is 18 mg. However, a difference in toxicity between Sodium Phosphate, Dibasic and Sodium Phosphate, Dibasic, Dihydrate is not expected, and thus the MDE for Sodium Phosphate, Dibasic is considered adequate to cover the excipient level.

[c] 17 mg is the oral MDE reported for Propylparaben Sodium. The oral MDE reported for Propylparaben (not sodium) is 4 mg. However, a difference in toxicity between Propylparaben Sodium and Propylparaben is not expected, and thus the MDE for Propylparaben Sodium is considered adequate to cover the excipient level.

The exposure, on a mg/kg basis, for the 6 inactive ingredients for potential pediatric patients receiving the maximum proposed BSA-based dosage falls below those calculated from the IID for an adult weighing 60 kg. Most of the potential excipient exposures calculated for pediatric patients of the lowest and highest potential BSAs fall well below the IID thresholds with the exception of propylparaben which is near but remains below the Maximum Daily Exposure (MDE).

Comparison of the maximum mg/kg amount of simethicone likely to be delivered with the mycophenolate mofetil RTU oral suspension when dosed as proposed is (b) (4) less than that with approved drug products containing simethicone as an active ingredient and (b) (4) of that in the IID. Simethicone is approved as an over-the-counter (OTC) drug product under the OTC monograph for treatment of gas retention in the GI tract.[5] The approved maximum dosages for pediatric patients less than 2 years of age, 2 to 12 years of age, and older than 12 years of age are 240 mg, 480 mg, and 500 mg respectively. For a term neonate, 2-year old patient, and 12-year old patient at the 5th percentile weight this represents maximum dosing of 96 mg/kg, 47 mg/kg, and 14.5 mg/kg, respectively.[6] The primary adverse effect reflected in OTC labeling for Simethicone is loose stools.

Comparison of the maximum mg/kg amount of sodium phosphate likely to be delivered with the mycophenolate mofetil RTU oral suspension when dosed as proposed is more than (b) (4) less than that delivered with provision of drug products containing sodium phosphates as active ingredients at the maximum approved adult dose. OSMOPREP is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults.[7] It contains sodium phosphate dibasic anhydrous and sodium phosphate monobasic monohydrate as active ingredients. The approved adult dosage is 30 grams (6 grams every 15 minutes) in the evening before colonoscopy and 18 grams (6 grams every 15 minutes) on the morning of colonoscopy. The most common adverse reactions from two, randomized, investigator-blinded, active controlled trials in adult patients included bloating, nausea, abdominal pain, and vomiting. Diarrhea, as part of the efficacy of OSMOPREP, was not defined as an adverse event in these trials.

Comparison of the maximum mg/kg amount of glycerin delivered with the mycophenolate mofetil RTU oral suspension when dosed as proposed is (b) (4) less than that delivered with approved drug products containing glycerin as an inactive ingredient. The safety of glycerin(glycerol) as an inactive ingredient was the focus of a DPMH

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[5] OTC labeling found under Mylicon, Gas X at https://dailymed.nlm.nih.gov

[6] 5th percentile weights from CDC Clinical Growth Tables at https://www.cdc.gov/growthcharts/clinical_charts.htm

[7] Prescribing information found under OSMOPREP (NDA 021892) at Drugs@FDA.gov at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021892s014lbl.pdf

clinical memorandum for THYQUIDITY (NDA 214047) on November 30, 2020.[8] THYQUIDITY is approved for the treatment of congenital and acquired hypothyroidism in pediatric patients down to birth. THYQUIDITY is a RTU levothyroxine sodium oral solution. The DPMH memorandum notes that the IID does not account for the duration of inactive ingredient exposure with chronic drug product use and does not specify whether the highest amount of an inactive ingredient per unit dose is applicable specifically to a pediatric population.[9] As a RTU drug formulation, the memorandum notes that THYQUIDITY would likely appeal to prescribers and parents/caregivers over existing products. DPMH calculated the maximum daily glycerol exposure with administration of THYQUIDITY in the first 3 months of life and noted a maximal exposure of (b) (4) mg/kg. A safe level of glycerol exposure is not established in pediatric patients from either juvenile animal studies or pediatric studies. Given its hyperosmolar properties, glycerin has the potential to cause local GI toxicity with fluid shifts which can present with emesis, diarrhea, and poor feeding. The DPMH memorandum noted that there are two drug products (RAVICTI, NDA 203284 and ORFADIN NDA 206356) containing glycerin as an excipient that are approved down to birth where the USPI describes the glycerin content. The memorandum recommended implementing post-approval safety surveillance in the form of an enhanced pharmacovigilance surveillance program. Ultimately, the Division of General Endocrinology (DGE) opted to inform prescribers of the theoretical concern of glycerin exposures from drug product use in pediatric patients from birth to 3 months of age in labeling in the Pediatric Use Section (8.4). The following language was added to Section 8.4:[10]

"Glycerol has the potential to cause gastrointestinal irritation resulting in vomiting and/or osmotic diarrhea. Patients in the first 3 months of life may be particularly susceptible to serious fluid and electrolyte complications from glycerol-induced gastrointestinal irritation. Closely monitor patients from birth to 3 months of age receiving THYQUIDITY for signs and symptoms of gastrointestinal irritation."

IV. Conclusion

Because a safe pediatric threshold for each inactive ingredient is unknown and the safety of this combination of inactive ingredients has not been previously evaluated, the theoretical risk remains for worse GI intolerance with use of this product compared to the LD. At least 3 of the inactive ingredients (glycerin and the two sodium phosphates) are

[8] Pediatric Review entered into DAARTS under NDA 214047 on November 30, 2020.

[9] Ibid

[10] Approved Labeling for THYQUIDITY found under NDA 214047 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214047s000lbl.pdf

known to be associated with GI irritation and symptoms of nausea, abdominal pain, vomiting, and diarrhea as either potential safety or efficacy findings in labeling. This theoretical safety concern cannot be addressed with the data included in this 505(b)(2) NDA submission containing only pivotal bioavailability data to bridge to the LD.

However, the maximum amount of each inactive ingredient likely to be administered to the intended pediatric population falls below available thresholds from the IID and approved drug products.[11] The maximum mg/kg amount is even lower when compared to the maximum labeled dosage for products containing one or more of these excipients as an active ingredient in an approved drug product.[12,13]

Mycophenolate mofetil, as an active ingredient, is known to have potential GI tolerability adverse effects. As such, delineating whether the 6 inactive ingredients are contributing to adverse GI tolerability using post-approval safety surveillance would be difficult to interpret given the overlap in adverse effects with the active ingredient.

V. Recommendations

- The theoretical concern of the inactive ingredients and/or their combination causing adverse GI tolerability effects should not preclude approvability of the product down to 3 months of age.
- The use of post-marketing surveillance or a post-marketing safety study to assess this safety concern is unlikely to adequately assess this concern.
- Consider providing cautionary language in subsection 8.4 of labeling to caution prescribers about the theoretical possibility that use of this product may be associated with GI tolerance because of the novel inactive ingredient combination. There is precedent for this approach with at least one other recently approved product.
- Add the following language after the Pediatric Use statement in Section 8.4:

The combination of inactive ingredients (e.g. simethicone, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, glycerin) in Mycophenolate Mofetil Oral Suspension have the potential to impact gastrointestinal tolerability. Monitor pediatric patients receiving Mycophenolate Mofetil Oral Suspension for signs and symptoms of gastrointestinal intolerance"

[11] Adjusted for a standard 60 kg adult body weight

[12] Approved Labeling for OSMOPREP found under NDA 214047 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021892s014lbl.pdf

[13] OTC labeling for Simethicone found under Mylicon, Gas X at https://dailymed.nlm.nih.gov

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	September 9, 2022
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 216482
Product Name, Dosage Form, and Strength:	mycophenolate mofetil oral suspension, 200 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Liqmeds Worldwide Limited
FDA Received Date:	March 8, 2022
OSE RCM #:	2022-497
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for mycophenolate mofetil oral suspension, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

NDA 216482 mycophenolate mofetil oral suspension was submitted as a 505(b)(2) on March 8, 2022. The Reference Listed Drug (RLD) is NDA 050759 Cellcept (mycophenolate mofetil) for oral suspension. Cellcept is currently approved in 200 mg/mL (once reconstituted) for oral suspension for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants.

We note that that the proposed mycophenolate mofetil oral suspension have the same strength, indication, and route of administration as the RLD, Cellcept. The difference is that mycophenolate mofetil will be available as ready to use oral suspension whereas the RLD Cellcept is available as for oral suspension.

We performed a risk assessment of the proposed prescribing information, container label, and carton labeling for mycophenolate mofetil oral suspension to identify areas of vulnerability that may lead to medication errors and other areas for improvement.

Our review of the proposed container label and carton labeling identified other areas that may be revised to improve clarity and readability of important information. We provide recommendations for the Applicant to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed mycophenolate mofetil prescribing information is acceptable from a medication error perspective. We conclude that the proposed container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide recommendations for the Applicant in Section 4.1 below.

4.1 RECOMMENDATIONS FOR LIQMEDS WORLDWIDE LIMITED

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

A. General Comments (Container labels & Carton Labeling)

1. To ensure consistency with the Prescribing Information, revise the statements, (b) (4) to read "Recommended Dosage: See prescribing information.
2. Relocate the route of administration, "For oral use only" to the principal display panel.
3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.
4. Revise the beyond-use statement (b) (4) and include a space for the patient to write the date the bottle was first opened. For example, "Date of first opening __/__/__. Discard unused portion 60 days after opening".

   We recommend "Date of first opening" so patients won't have to calculate the "Discard after" date. Additionally, the "__/__/__" statement will alert the users to write a complete date (month, day, and year) on the container label and carton labeling.

B. Container Labels

1. Add the net quantity statement "175 mL" to the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for mycophenolate mofetil received on March 8, 2022 from Liqmeds Worldwide Limited, and the listed drug (LD).

Table 2. Relevant Product Information for mycophenolate mofetil and the Listed Drug

Product Name	**Mycophenolate mofetil**	**Cellcept**[a] (NDA 050759)
Initial Approval Date	N/A	October 1, 1998
Active Ingredient	mycophenolate mofetil	
Indication	for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart or liver transplants, (b) (4) in combination with other immunosuppressants	for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants.
Route of Administration	oral	
Dosage Form	oral suspension	For oral suspension
Strength	200 mg/mL	200 mg/mL upon reconstitution
Dose and Frequency	**ADULTS** / **DOSING** Kidney Transplant: 1 g twice daily, (b) (4) Heart Transplant: 1.5 g twice daily (b) (4) (b) (4) Liver Transplant: 1.5 g twice daily (b) (4) **PEDIATRICS** Kidney Transplant: 600 mg/m^2 orally twice daily, up to maximum of (b) (4)	**ADULTS** / **DOSAGE** Kidney Transplant: 1 g twice daily, orally or intravenously (IV) over no less than 2 h (2.2) Heart Transplant: 1.5 g twice daily orally or IV, over no less than 2 h (2.3) Liver Transplant: 1.5 g twice daily orally or 1g twice daily IV over no less than 2 h (2.4) **PEDIATRICS** Kidney Transplant: 600 mg/m^2 orally twice daily, up to maximum of 2 g daily (2.2) Heart Transplant: 600 mg/m^2 orally twice daily (starting dose) up to a maximum of 900 mg/m^2 twice daily (3 g or 15 mL of oral suspension) (2.3) Liver Transplant: 600 mg/m^2 orally twice daily (starting dose) up to a maximum of 900 mg/m^2 twice daily (3 g or 15 mL of oral suspension) (2.4)
How Supplied	175 mL (b) (4)	225 mL bottle with bottle adapter and 2 oral dispensers

[a] Cellcept [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2022 AUG 10. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/050722s049s051,050723s049s051,050758s047s049,050759s054s056lbl.pdf

Storage	(b) (4) excursions permitted to 15°C to 30°C (59°F to 86°F).	• Store dry powder at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). • Store constituted suspension at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) for up to 60 days. Storage in a refrigerator at 2°C to 8°C (36°F to 46°F) is acceptable. Do not freeze.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following mycophenolate mofetil labels and labeling submitted by Liqmeds Worldwide Limited.

- Container label received on March 8, 2022
- Carton labeling received on March 8, 2022
- Prescribing Information (Image not shown) received on March 8, 2022, available from \\CDSESUB1\evsprod\nda216482\0001\m1\
- Medication Guide received on March 8, 2022, available from \\CDSESUB1\evsprod\nda216482\0001\m1\

G.2 Label and Labeling Images

Container Label

(b) (4)

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

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

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M E M O R A N D U M

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

DATE: 8/1/2022

TO: Division of Rheumatology and Transplant Medicine (DRTM)
Office of Immunology and Inflammation (OII)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216482

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in April 2022 , which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs non-responsive .

The final classification for the inspections was No Action Indicated (NAI).

OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4), which falls within the surveillance interval. The RRA was conducted under the following submissions: ANDAs non-responsive .

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	Alkem Laboratories, Ltd.	Department of Bioequivalence, C-6/1, C-6/2, and C-17/7, MIDC Industrial Estate, District Raigad, Taloja, Navi Mumbai, Maharashtra, India
Analytical	(b) (4)	

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