NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) NDA
Application Number(s)	216482
Priority or Standard	Standard
Submit Date(s)	March 8, 2022
Received Date(s)	March 8, 2022
PDUFA Goal Date	January 8, 2023
Division/Office	Division of Rheumatology and Transplant Medicine
Review Completion Date	January 5, 2023
Established/Proper Name	Mycophenolate mofetil
(Proposed) Trade Name	(b) (4)
Pharmacologic Class	Immunosuppressant
Code name	N/A
Applicant	Liqmeds Worldwide LTD
Doseage form	Oral suspension
Applicant proposed Dosing Regimen	Adults: Kidney Transplant 1 g twice daily (b) (4) Heart Transplant 1.5 g twice daily (b) (4) Liver Transplant 1.5 g twice daily (b) (4) Pediatric: Kidney Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 2g daily Heart Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 900 mg/m^2 twice daily (maximum daily dose of 3g daily or 15 ml oral suspension) Liver Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 900 mg/m^2 twice daily (maximum daily dose of 3g daily or 15 ml oral suspension)
Applicant Proposed Indication(s)/Population(s)	Prophylaxis of organ rejection in adult and pediatric recipients 3 months and older of allogenic kidney, heart, or liver transplants in combination with other immunosuppressants
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Prophylaxis of organ rejection in adult and pediatric recipients 3 months and older of allogenic kidney, heart, or liver transplants in combination with other immunosuppressants
Recommended Dosing Regimen	Adults: Kidney Transplant 1 g twice daily (b) (4) Heart Transplant 1.5 g twice daily (b) (4) Liver Transplant 1.5 g twice daily (b) (4) Pediatric: Kidney Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 2g daily Heart Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 900 mg/m^2 twice daily (maximum daily dose of 3g daily or 15 ml oral suspension) Liver Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 900 mg/m^2 twice daily (maximum daily dose of 3g daily or 15 ml oral suspension)

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Saharat Patanavanich
Nonclinical Reviewer	Dana Lauterstein, Ph.D.
Nonclinical Team Leader	Carol Galvis, Ph.D.
Office of Clinical Pharmacology Reviewer(s)	Amer Al-Khouja, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, MD, Ph.D.
Clinical Reviewer	Nadia Chaudhri, MD
Clinical Team Leader	Ergun Velidedeoglu, MD
Associate Director for Labeling	Jane Filie, MD
Cross-Disciplinary Team Leader	Jianmeng Chen, MD, Ph.D.
Office Director (or designated signatory authority)	Ozlem Belen, MD, MPH

Additional Reviewers of Application

OPQ	Leah Falade/Tapash Ghosh
Microbiology	Koushik Paul, Ph.D./ Jesse Wells, Ph.D.
OPDP	Kyle Snyder
OSIS	James J Lumalcuri
OSE/DEPI	Marie Bradley/Mingfeng Zhang
OSE/DMEPA	Sarah Vee/Idalia Rychlik
OSE/DRM	Brian Caruth PharmD, BCPS/Yasmeen Abou-Sayed, PharmD/Laura Zendel, PharmD

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSIS=Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Dana Lauterstein, Ph.D.	OND/OII/DPT-II	Sections: 5	**Select one:** __X_ Authored ___ Approved
	Signature: Dana Lauterstein -S Digitally signed by Dana Lauterstein -S Date: 2023.01.04 12:22:00 -05'00'			
Nonclinical Supervisor	Carol Galvis, Ph.D.	OND/OII/DPT-II	Sections: 5	**Select one:** ___ Authored _X__ Approved
	Signature: Carol Galvis -S Digitally signed by Carol Galvis -S Date: 2023.01.04 12:24:36 -05'00'			
Clinical Pharmacology Reviewer	Amer Al-Khouja, Ph.D.	OCP/DIIP	Section: 6, 15.4	**Select one:** _X_ Authored ___ Approved
	Signature: Amer Al-khouja -S Digitally signed by Amer Al-khouja -S Date: 2023.01.04 13:31:50 -05'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen, MD, Ph.D.	OCP/DIIP	Section: 1, 6, 15.4	**Select one:** ___ Authored _x_ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S Date: 2023.01.04 12:06:23 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Nadia Chaudhri, MD	OND/OII/DRTM	Sections:1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 15.2,15.2	**Select one:** _X_ Authored ___ Approved
	Signature: Nadia N. Chaudhri -S Digitally signed by Nadia N. Chaudhri -S Date: 2023.01.04 12:57:17 -05'00'			
Clinical Team Leader	Ergun Velidedeoglu, MD	OND/OII/DRTM	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 15.1, 15.2	**Select one:** ___ Authored _X__ Approved
	Signature (Dr. Ozlem Belen to sign on behalf of Dr. Ergun Velidedeoglu): Ozlem A. Belen -S Digitally signed by Ozlem A. Belen -S Date: 2023.01.04 17:15:34 -05'00'			
Deputy Division Director (Clinical)	Ozlem Belen, MD, MPH	OND/OII/DRTM	Sections: All	**Select one:** ___ Authored _X_ Approved
	Signature: Ozlem A. Belen -S Digitally signed by Ozlem A. Belen -S Date: 2023.01.04 12:38:09 -05'00'			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PERC	Pediatric Review Committee
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1.Product Introduction

Liqmeds Worldwide Limited, herein referred to as "Applicant" in this review, submitted a 505 (b)(2) new drug application (NDA) for MMF ready-to-ingest oral suspension 200 mg/ml. The listed drug is CELLCEPT (Mycophenolate Mofetil) for oral suspension (NDA 050759). Mycophenolate mofetil (MMF) is an antimetabolite immunosuppressant that is indicated for the prevention of organ rejection in adult and pediatric recipients 3 months of age and older of allogenic kidney, heart or liver transplant recipients in combination with other immunosuppressants. CELLCEPT is available in the following dosage forms:

- Capsules, 250 mg (NDA 50-722)
- Tablets, 500 mg (NDA 50-723)
- For injection, 500 mg single dose vial for intravenous (IV) administration (NDA 50-758)
- For oral suspension, powder for reconstitution, 200 mg/mL after reconstitution (NDA 50-759)

The Applicant is seeking licensure for the same indications at the same dosage as CellCept for oral suspension 200 mg/ml. These indications include prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogenic kidney, heart or liver transplants in combination with other immunosuppressants.

Following administration, MMF is metabolized to the active moiety, mycophenolic acid (MPA), and selectively and reversibly inhibits (inosine monophosphate dehydrogenase) IMPDH, the committed step in de novo guanosine nucleotide biosynthesis. MMF leads to cell cycle arrest and disrupts T and B cell proliferation, because T and B cells cannot utilize nucleotide salvage pathways.

Mycophenolate drug products are associated with an increased risk of first trimester pregnancy loss (miscarriage) and congenital malformation (birth defects) if administered during pregnancy. On September 25, 2012, the U.S. Food and Drug Administration (FDA) approved a shared system (SS) Risk Evaluation and Mitigation Strategy (REMS) for all mycophenolate drug products.[1] A REMS acceptable to the Agency is required for all mycophenolate product NDAs and ANDAs. Applicants can either join the already established mycophenolate SS REMS or submit a separate REMS proposal for the Agency's review. See **section 1.2** of this review for further information.

[1] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-fda-approves-single-shared-risk-evaluation-and-mitigation-strategy-rems

Please note that no clinical efficacy or safety studies were submitted with this application, so several sections of this unireview are not applicable and are not completed.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Conclusion: For this 505(b)(2) NDA the Applicant demonstrated bioequivalence (BE) of MMF oral suspension 200 mg/ml to the listed drug, CellCept for oral suspension 200 mg/ml, under fasting and fed conditions. Therefore, the Applicant can rely on the Agency's previous findings of safety and effectiveness of MMF for the listed drug, CellCept powder for oral suspension (NDA 50759). The application is not approvable because the Applicant did not fulfill the REMS requirement.

Summary of BE determination for MMF ready-to-ingest oral suspension

The Applicant submitted two studies, CL-155-18 and CL-156-18, under fasting and fed conditions, respectively, to demonstrate bioequivalence of MMF Oral Suspension 200 mg/mL to the listed drug. Both studies enrolled 48 healthy male subjects each. Across both studies, subject age ranged from 20 to 43 years, and BMI ranged between 19.1 and 29.2 kg/m^2.

In studies CL-155-18 and CL-156-18, the Applicant collected PK data for MPA, the pharmacologically active metabolite, and MMF, the parent drug. BE determinations were made based on MPA data only because MMF PK parameters are not described in the listed drug (CellCept for oral suspension) labeling. MPA PK data from 40/48 (83.3%) and 42/48 (87.5%) subjects that completed all dosing periods in the fasting and fed studies, respectively, were evaluated. The order of receiving the reference or test product for each subject during each period was determined based on a randomization schedule. In CL-155-18, doses were administered after an overnight fast of at least 10 hours. In CL-156-18, doses were administered 30 minutes after a high-fat, high-calorie breakfast. Across both studies, the washout period between periods of drug administration varied between 10 and 13 days (acceptable based on MPA half-life of 18 hours).

According to the Clinical Pharmacology (CP) reviewer's analysis, a comparison of PK data generated from studies CL-155-18 and CL-156-18 suggest that there is a food effect impacting exposure to MPA. The magnitude in decrease of C_{max} appears to be greater than what is reported in the CellCept labeling. Nonetheless, MPA PK for all parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}) of the proposed product were determined to be BE to the listed drug under both fasting and fed conditions (see Table 10), irrespective of the magnitude of the food effect. Therefore, the Clinical reviewer agrees with the Clinical

Pharmacology reviewer that no new management strategy is required for food-drug interactions. The results of CP reviewer's independent analysis is consistent with the analysis conducted by the Applicant and the criteria for BE (i.e., 90% confidence interval of geometric mean ratio within 80-125%) were met. The CP reviewer determined that BE is established between MMF oral suspension 200 mg/ml and the listed drug, and the Clinical reviewer agrees with this conclusion.

REMS requirement for mycophenolate NDAs / ANDAs

Mycophenolate-containing medicines are associated with an increased risk of first trimester pregnancy loss and congenital malformations if taken during pregnancy. The current list of mycophenolate-containing medicines includes CellCept (mycophenolate mofetil available as an oral capsule, oral tablet, oral suspension, and injection), Myfortic (mycophenolic acid available as an oral delayed-release tablet), and any generic mycophenolate mofetil or mycophenolic acid products. On September 25, 2012, the FDA established a shared system REMS (SS REMS) for mycophenolate products due to post-marketing reports of increased first trimester pregnancy loss and congenital malformations. Complete information regarding this REMS can be found at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=37. Information about the pregnancy registry is available at: www.MycophenolatePregnancyRegistry.com. A REMS is required for all applications of mycophenolate products and applicants are directed to join either the SS REMS or submit a separate REMS proposal for FDA's review.

The Applicant has not complied with the REMS requirement at the time of this review. Several information requests (IRs) were relayed to the Applicant explaining the ramifications of not complying with this requirement. Therefore, a complete response (CR) letter will be issued. A CR letter indicates that the review cycle for an application is complete and that the application is not ready for approval.[2]

[2] https://www.fda.gov/drugs/laws-acts-and-rules/complete-response-letter-final-rule

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment

MMF ready-to-ingest oral suspension 200 mg/ml is a mycophenolate mofetil product submitted as a new dosage form under a 505(b)(2) NDA application. This ready-to-ingest formulation differs from the approved product, CellCept for oral suspension, which requires reconstitution by the pharmacist prior to dispensing. The purported benefit for the proposed drug product is potentially fewer dosing errors because reconstitution is not required. The Applicant is seeking the same indications at the same dosage as the approved product: the prophylaxis of organ rejection in adults and pediatric recipients 3 months and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants. The target population is pediatric patients or adults who cannot swallow solid oral formulations (e.g., capsules or tablets). This mycophenolate NDA, however, is not approvable because the Applicant did not submit an acceptable risk evaluation and mitigation strategy (REMS) which is explained further below.

Adult and pediatric kidney, heart, or liver transplantation is a life-saving therapeutic option that improves survival and quality of life for patients whose native organs are failing or have failed. To maintain this life-sustaining allograft, a combination of immunosuppressants is required which are associated with a risk of malignancies, infections and other adverse drug reactions. MMF is one component of the standard of care immunosuppression regimen for the majority of patients. SRTR/OPTN data from 2020 indicate that almost 90 % of adult and pediatric heart and kidney transplant recipients and almost 50 % of liver transplant recipients are on an MMF containing regimen. Outcomes are also noted to be excellent with five-year graft survival for kidney, heart and liver transplant recipients transplanted between 2013-2015 at approximately 80% across all age groups. These facts and outcomes indicate a benefit for the use of MMF in the standard immunosuppressive regimen.

The availability of alternative formulations of CellCept and mycophenolate products that are reliably safe and effective is a benefit to patients who may not be able to tolerate an approved formulation or may need to substitute with an alternative formulation. The 505(b)(2) pathway permits drug development without requiring duplicative studies to demonstrate what is already known about a drug by “scientifically bridging” to the approved drug. As BE was established between the proposed product and the listed drug under both fasting and fed condition (Study CL-155-18 and CL-156-18), the Applicant can rely on the Agency’s previous findings of safety and effectiveness of MMF for the listed drug, CellCept powder for oral suspension (NDA 50759). It is unclear at this time if the proposed ready-to-ingest formulation will result in fewer dosing errors.

MMF is associated with embryo-fetal toxicity and congenital malformations. On September 25, 2012, to mitigate these risks, the FDA established a risk evaluation and mitigation strategy (REMS) requirement for mycophenolate products to be submitted at the time of

NDA/ANDA submission. The FDA relayed several information requests to the Applicant, but they did not comply within an acceptable timeframe. Thus, this NDA is not approvable without this essential requirement.

A safety concern was also identified during the review, related to GI tolerability of the product due to a new combination of inactive ingredients. Six of the inactive ingredients in the MMF ready-to-ingest oral suspension are noted to be different from the approved product (CellCept for oral suspension) and approved generic drug formulations (approved generics have the same inactive ingredients as the listed drug). In addition, some of the inactive ingredients are marketed as active ingredients in approved drugs (e.g., simethicone and monosodium phosphate and dibasic sodium phosphate) and are associated with nausea, vomiting, and diarrhea. The active ingredient in this product, mycophenolate mofetil, is also known to cause adverse GI effects. Moreover, younger pediatric patients are more susceptible to these effects, as identified in section 6.1 of CellCept labeling. The concern arose that a potentially increased GI intolerance because of the new inactive ingredients in this new formulation may lead to nonadherence, dosing interruptions, and consequently suboptimal and/or inconsistent immunosuppressant exposure that may adversely impact allograft survival. This safety concern is not addressed by the studies submitted with this 505(b)(2) NDA, which contain data to bridge to the approved product. Following internal discussions involving different review divisions including DPMH, the Division of Gastroenterology (DG), and the OII leadership, the FDA decided this theoretical concern of possible adverse GI tolerability of this product due to the new combination of inactive ingredients should not preclude approvability of the product in kidney, heart, and liver transplant recipients down to patients 3 months of age. Nonetheless, to address this risk and to caution prescribers, as recommended by DPMH, cautionary language in subsection 8.4 of labeling will be included when the NDA is approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Adult heart and liver transplantation and pediatric kidney, heart and liver transplantation are considered rare conditions as there are <200000 patients living with one of these solid organ transplants. • Kidney, heart, and liver transplantation are life-saving treatment options for adult and pediatric patients with end-stage organ disease. • 1-year and 5-year patient survival for adult and pediatric kidney, heart and liver transplant recipients transplanted between 2013-2015 are reported at ≥ 90% and ≥ 80%, respectively, according to 2020 SRTR data for each solid organ transplant.	• It is clinically established that recipients of kidney, heart or liver allografts have improved quality of life and survival benefits compared to patients with end-stage kidney, heart or liver disease. As pediatric kidney, heart and liver transplantations are increasing, more children will be living with these allografts, and demand for pediatric friendly formulations will increase.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Almost 90% of heart and kidney transplant center regimens and 50% of liver transplant centers use an MMF containing IS regimen.	• MMF, in combination with approved IS agents, and other advances in transplantation have contributed to excellent patient and graft survival outcomes.

Current Treatment Options	• According to 2020 SRTR/OPTN data:
	  • For adult and pediatric kidney, heart, or liver transplantation, the two most common maintenance IS regimens include tacrolimus (tac), MMF, and steroids or tac and MMF.
	  • Since its initial approval in 1995, MMF has become more commonly used in IS regimens for all solid organ transplantations and is the anti-metabolite of choice in the majority of these populations, according to SRTR data.
	  • Transplant outcomes have steadily improved since the initial approval of CellCept with 5-year graft survival at >80% for both adult and pediatric kidney, heart, and liver transplant populations.
	• Please see section 2.2 for additional treatment options.
	• There is an oral suspension formulation of CellCept and generics of mycophenolate mofetil, but these are all powders that require reconstitution by a pharmacist.
	• Section 505 of the FDC Act allows for an alternative path to approval for applicants to develop additional formulations of drugs where at least some of the information comes from studies not conducted by the applicant and for which the applicant has not obtained right of reference (section 505 (b)(2)).
		• MMF is a contributing factor in the improved transplant outcomes since the initial approval.
		
		• Increasing access to different formulations can provide alternative therapeutic options to patients who may not tolerate a particular formulation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant submitted a 505(b)2 NDA application for approval with the listed drug identified as CellCept for oral suspension 200 mg/ml. • The Applicant submitted two studies in healthy adult males, one under fasting (CL-155-18) and one under fed (CL-156-18) conditions, to demonstrate BE as a bridge to the listed drug. • In studies CL-155-18 and CL-156-18, PK data for MPA, the pharmacologically active metabolite, and MMF, the parent drug were collected. BE determinations were made based on MPA data. • A comparison of PK data generated from studies CL-155-18 and CL 156-18 suggest there is a food effect impacting exposure to MPA and MMF, with level of decrease of C_{max} greater than what is reported in CellCept (listed drug) labeling.	• MMF oral suspension 200 mg/ml is developed as a ready-to-ingest liquid that does not require reconstitution by the pharmacist. • Improving access to additional formulations and increasing therapeutic options is of benefit to patients. • Irrespective of the magnitude of the food effect, all MPA PK parameters of the proposed product in both studies met BE criteria to listed drug under both fasting and fed conditions. • No new management strategy is needed for food-drug interactions.
Risk and Risk Management	• Most common risks associated with CellCept include myelosuppression, risk of infection, gastrointestinal toxicities and embryo-fetal toxicity. • This formulation contains six inactive ingredients that have not been assessed clinically in the intended population (i.e., pediatric kidney, heart, and liver transplant recipients).	• The safety profile of CellCept is well established and the risks are described in the labeling. • A SS REMS was established on September 25, 2012, as a requirement for approval of mycophenolate product applications to address and mitigate the risk of embryo-fetal toxicity. Please section 12 of this review regarding REMS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Inactive ingredients in the IID have not been specifically assessed for safety in pediatric populations. • Some of the inactive ingredients are active ingredients in marketed products (e.g., simethicone, monosodium diphosphate, disodium phosphate) and are associated with nausea, vomiting, and diarrhea. • If GI tolerability of MMF ready-to-ingest oral suspension is worse, then it may lead to nausea, vomiting, and/or diarrhea which could result in medication non-adherence and inconsistent immunosuppressant exposures.	• Inconsistent immunosuppressant exposure may precipitate allograft rejection and adversely impact graft survival. • A clinical study to assess the GI tolerability of the inactive ingredients of MMF oral suspension would be difficult to interpret as the active ingredient, MMF, is also associated with adverse GI effects. • The FDA decided that the unknown GI tolerability of this new proposed formulation can be addressed in subsection 8.4 of product labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Kidney, heart, and liver transplantation are lifesaving therapeutic options for patients with end-stage renal, heart and liver disease. Renal replacement therapy is a readily available option for adult and pediatric patients with end-stage renal disease, but patients note a fair to poor quality of life on hemodialysis or peritoneal dialysis. Both dialytic therapies are associated with significant comorbidities including cardiovascular disease. End-stage heart and liver disease are considered terminal conditions with a very poor quality of life and have very limited replacement therapy options. Transplantation offers a second-chance to live a nearly normal life for these patients and improves survival.

Adult and pediatric heart and liver transplantation and pediatric kidney transplantation are considered rare conditions because fewer than 200000 people are living with these allografts.

Patients who undergo kidney, heart or liver transplantation require chronic immunosuppressant medications to sustain their allografts. In 2020, SRTR/OPTN data indicate that more than 90% of kidney and heart transplant center regimens used an MMF containing immunosuppression (IS) regimen and close to 50% of liver transplant centers used an MMF containing IS regimen. Outcomes are excellent with 1-year and 5-year patient survival among adult and pediatric kidney, heart and liver transplant recipients at approximately 90% and 80%, respectively. These outcomes are due to various factors including improvements in surgical techniques and donor-recipient matching, but one of these factors is related to IS regimens, most of which include mycophenolate mofetil.

2.2. Analysis of Current Treatment Options: oral suspension formulations available

Table 1: Listed Drug (LD) and Approved Generics of Mycophenolate Mofetil (for Oral Suspension).

Listed Drug				
Product Name / NDA or ANDA	**Relevant Indication**	**Year of Approval**	**Strength**	**Dosing / Administration**

CellCept for oral suspension (NDA 050759)	Prophylaxis of organ rejection in adult and pediatric recipients 3 months and older of allogenic kidney, heart, or liver transplants in combination with other immunosuppressants	1998	200 mg/ml upon reconstitution	Adults: Kidney Transplant 1 g twice daily, orally Heart Transplant 1.5 g twice daily orally Liver Transplant 1.5 g twice daily orally Pediatric: Kidney Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 2g daily Heart Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 900 mg/m^2 twice daily (maximum daily dose of 3g daily or 15 ml oral suspension) Liver Transplant: 600 mg/m^2 orally twice daily, up to a maximum of 900 mg/m^2 twice daily (maximum daily dose of 3g daily or 15 ml oral suspension)
Approved Generics				
Mycophenolate Mofetil (ANDA 203005)	Same as for LD	2014	200 mg/ml upon reconstitution	Same as for LD
Mycophenolate Mofetil (ANDA 210370)	Same as for LD	2019	200 mg/ml upon reconstitution	Same as for LD
Mycophenolate Mofetil (ANDA 214525)	Same as for LD	2021	200 mg/ml upon reconstitution	Same as for LD
Mycophenolate Mofetil (ANDA 214871)	Same as for LD	2021	200 mg/ml upon reconstitution	Same as for LD
Mycophenolate Mofetil (ANDA 211272)	Same as for LD	2022	200 mg/ml upon reconstitution	Same as for LD

3. Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

Summary of 505(b)(2) regulatory pathway for approval

The FDA Guidance for Industry, *Applications covered by section 505 (b)(2)*[3], states that a "505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval 'were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted' (21 U.S.C. 355(b)(2))." The guidance also specifies that an applicant can rely upon the FDA's finding of safety and effectiveness for an approved drug and published literature that contains information necessary to the approval of the application. Section III of this guidance provides examples of changes to approved drugs for which 505 (b)(2) applications are applicable, including:
"*Dosage Form:* An application for a change of dosage form, such as a change from a solid oral dosage form to a transdermal patch, that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug."

In pre-IND (pIND# 140359) discussions with the Applicant at the time, Alkem Ltd, the FDA confirmed that, " 'oral suspension' and 'for oral suspension' are considered different dosage forms."[4] The FDA also stated that the 505 (b)(2) regulatory pathway was appropriate for the proposed drug product, MMF ready-to-ingest oral suspension 200 mg/ml. According to the FDA guidance, *Applications covered by section 505 (b) 2,*[1] 505 (b)(2) NDA applications should include a "bioavailability/bioequivalence study comparing the proposed product to the listed drug."

Additionally, the FDA Guidance for Industry, *Statistical Approaches to Establishing Bioequivalence,*[5] provides advice on BE study design and the criteria that should be met to determine BE of a test product to the listed drug (LD), including:
"… a standard in vivo BE study design [should] be based on the administration of either single or multiple doses of the (test) T and (reference) R drug products to healthy subjects on separate occasions, with random assignment to the two possible sequences of drug product administration ….statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (C_{max}), [should] be based on the *two one-sided tests procedure* to determine whether the average values for the pharmacokinetic measures determined after administration of the T and R products were comparable. This approach is termed average bioequivalence and involves the calculation of a 90%

[3] *Guidance for Industry: Applications Covered by Section 505 (b) 2,* FDA Draft Guidance October 1999.
[4] Pre-IND 140359 Meeting Minutes (COR-MEET-03) entered into DARRTS on September 19, 2018.
[5] *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence,* FDA Guidance January 2001.

confidence interval for the ratio of the averages (population geometric means) of the measures for the T and R products. To establish BE, the calculated confidence interval should fall within a BE limit, usually 80-125% for the ratio of the product averages.[3]

The pIND 140359 meeting minutes[2] also specified that if the Applicant chose to establish strict bioequivalence between the proposed drug product and the LD product, then the Applicant should apply the BE criteria of 80-125%.

The Applicant submitted a 505(b)(2) NDA 216482 for MMF ready-to-ingest oral suspension 200 mg/ml. This product is not marketed anywhere in the world.

CellCept oral capsule 250 mg was the first formulation of mycophenolate mofetil approved on May 3, 1995 for the prophylaxis of organ rejection and treatment of refractory organ rejection in patients receiving an allogeneic kidney transplant. CellCept for oral suspension 200 mg/ml was approved under NDA 50-759 on October 1, 1998 based on bioequivalence to CellCept Oral Capsules.

In 2007, section 505-1 of the Food and Drug Cosmetics Act (FDC Act)[6] authorized the FDA to require a REMS, if the FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. Due to post-marketing reports of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate mofetil during pregnancy, the FDA determined a REMS was necessary for all MPA products to ensure the benefits of mycophenolate outweigh the risks. The FDA approved the Mycophenolate shared system (SS) REMS for all mycophenolate products on September 25, 2012. See **section 12 REMS** for more information regarding the SS Mycophenolate REMS.

3.2. Summary of Presubmission/Submission Regulatory Activity

Presubmission Activity

A pre-IND meeting was held between the Applicant and the FDA on September 7, 2018 to discuss the Applicant's (at that time, Alkem Ltd) plan to submit an NDA Application via the 505 (b)(2) regulatory pathway for mycophenolate mofetil ready-to-ingest oral suspension 200 mg/ml.

Meeting minutes were relayed to the Sponsor on September 19, 2018. FDA responses from the meeting minutes are highlighted below:

- 505(b)(2) pathway is appropriate for the planned NDA submission
- CellCept for oral suspension 200 mg/ml (NDA 50-759) is the appropriate LD
- PREA applies to the planned 505 (b)(2) NDA submission and that the Applicant

[6] Section 505-1(a) of the FD&C Act.

should submit an initial pediatric study plan (iPSP) prior to NDA submission
- Two studies in healthy subjects alone may not be adequate to support a future 505(b)(2) NDA and additional clinical safety and/or efficacy studies in transplant patients may be required, if the BA/BE studies did not establish comparable systemic exposure to MPA and/or MMF
- The inactive ingredients seemed reasonable.

The Applicant submitted an iPSP on November 20, 2020 and, after several correspondences, an agreed upon iPSP was finalized March 8, 2021. The agreed upon iPSP consisted of a partial waiver for studies in pediatric kidney transplant recipients less than 3 months old because such studies would be highly impractical due to the small numbers of patients in this population. It also included a deferral for studies in pediatric heart and pediatric liver transplant recipients for 10 years, as CellCept had not been approved in these populations at the time of iPSP discussions.

A pre-NDA meeting was not requested by the Applicant prior to submission of the NDA.

Submission Regulatory Activity

PeRC:
This application was presented at PeRC on November 29, 2022 because additional indications were approved for the LD in the interim between the agreed upon iPSP and NDA submission. The agreed upon iPSP from March 8, 2021 included a partial waiver for studies in pediatric kidney transplant recipients less than 3 months old and a deferral for studies in pediatric heart and pediatric liver transplant recipients. On June 6, 2022 CellCept was approved for use in pediatric heart and pediatric liver transplant recipients 3 months and older. The Applicant verified intent to seek approval for all the same indications for which CellCept is approved. DRTM proposed to PeRC that the FDA grant a partial waiver for the indications of pediatric kidney, heart, and liver transplant recipients less than 3 months old for the new formulation similar to the LD because of the small numbers of patients in these populations, making studies impractical or impossible. PeRC agreed with DRTM's recommendation to grant a partial waiver for pediatric kidney, heart, and liver transplant recipients less than 3 months old and to approve MMF oral suspension in pediatric recipients of kidney, heart, and liver transplant 3 months and older. PeRC did not require the Applicant to submit a new iPSP reflecting this change.

REMS:
The Applicant failed to submit an approvable REMS at the time of NDA submission. DRM conveyed several IRs encouraging the Applicant to submit a REMS proposal or to join the established SS REMS program for mycophenolate products. The Applicant failed to meet this requirement for approval. See **section 12 REMS** for additional details.

Clinical Team Safety Concern of Possible Adverse GI Tolerability of Drug Product:

The Clinical team conveyed an IR to the Applicant in the Filing Review Issues Identified letter (see DARRTS entry May 25, 2022) regarding the concern of possible adverse GI tolerability of this new combination of inactive ingredients. In addition, a discussion was convened with the Division of Gastroenterology (DG) and the Clinical team. Consults were also submitted to OND Policy and DPMH. The Applicant submitted a response to the IR on August 23, 2022, which did not adequately address the theoretical risk of adverse GI effects associated with this new combination of inactive ingredients and is discussed in more detail in **section 8.2.3**. The DG and OND Policy agreed with the validity of DRTM's concern and deferred potential solutions to DRTM.

DPMH conducted a review of the safety concern for potential adverse GI tolerability of this new drug formulation as it relates to a pediatric population, the intended target population. DPMH acknowledged that the safety of this combination of inactive ingredients has not been previously evaluated and the theoretical risk for worse GI tolerance with this product compared to the LD. They concluded that a post-marketing study to evaluate this concern would be difficult to interpret given the active ingredient can also cause adverse GI effects. DPMH suggested adding cautionary language to subsection 8.4 of labeling to caution prescribers about the theoretical possibility that use of this product may be associated with adverse GI tolerance because of the novel inactive ingredient combination. After interdisciplinary discussions and discussion with Office of Immunology and Inflammation (OII) Director, Dr. Julie Beitz, DRTM agreed that this suggestion was an acceptable resolution to address this potential safety risk.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1.Office of Scientific Investigations (OSI)

The review team requested an inspection of the clinical and analytical sites for studies CL-155-18 and CL-156-18 from the Office of Study Integrity and Surveillance (OSIS). The inspection request was denied as the clinical and analytical sites had been inspected within the surveillance interval. The inspections were classified as “No Action Indicated” and it was determined that the data from the reviewed studies were reliable.

4.2.Product Quality

Adequate. See separate multi-disciplinary review entered into DARRTS 11/23/2022 by Dr. Craig Bertha.

4.3.Clinical Microbiology

Adequate. See separate multi-disciplinary review entered into DARRTS 11/23/2022 by Dr. Craig Bertha.

4.4. Devices and Companion Diagnostic Issues

Adequate. See separate multi-disciplinary review entered into DARRTS 11/23/2022 by Dr. Craig Bertha.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

5.1.1. Introduction

Liqmeds Worldwide Limited submitted New Drug Application (NDA) 216482 via the 505(b)(2) pathway on March 8, 2022, for Mycophenolate Mofetil (MMF) Oral Suspension, 200 mg/mL. The proposed indication is 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. The Listed Drug (LD) is NDA 50759, CellCept® (powder for oral suspension, 200 mg/ml).

All excipients contained in the MMF formulation are below those listed in the FDA Inactive Ingredient Database (IID) for approved oral drug products. However, the MMF formulation contains 6 excipients that are not present in the LD, and the Clinical team raised concern that the cumulative effect of these inactive ingredients coupled with the active ingredient (MMF) may adversely affect gastrointestinal tolerability in pediatric populations. In addition, the Applicant provides specification limits for two drug product degradants that exceed the qualification threshold of ICH Q3B, (b) (4) This review is a nonclinical safety evaluation of excipients, impurities/degradants, (b) (4) identified in the proposed drug product.

5.1.2. Brief Discussion of Nonclinical Findings

The nonclinical safety evaluation consisted of assessments on the following:

1) Excipients not contained in the LD (i.e., (b) (4) simethicone emulsion, polysorbate 80, monosodium phosphate dihydrate, dibasic sodium phosphate dihydrate, glycerin, and propylparaben)
2) Specification limits for two drug product degradants that exceed the qualification threshold of ICH Q3B (i.e., (b) (4))
3) Specification limits (b) (4)

Although there is no way to identify excipients by pediatric and non-pediatric use in the IID, the reviewer converted the maximum daily dose (MDD) levels of MMF excipients to mg/kg for pediatric populations and the maximum daily exposure (MDE) levels (or maximum potency) reported in the IID to mg/kg for adults to enable some comparison. While comparison has limitations, it provides support that the MMF product excipient levels do not present a safety concern, from a toxicological perspective.

The Applicant's specification limit of (b) (4) is not of toxicological concern. While it exceeds the Q3B qualification threshold, (b) (4). The Applicant provided impurity qualification studies for (b) (4) Two in vitro genotoxicity studies were conducted and yielded negative results. In addition, a 28-day oral study was conducted, where rats were exposed to a test item containing the impurity. An information request (IR) identifying several issues with the 28-day rat study was sent to the Applicant. Overall, the information submitted by the Applicant is sufficient to indicate that the specification limit of (b) (4) is not of toxicological concern.

The reviewer evaluated support for the Applicant's use of (b) (4) specification limit for (b) (4) and found that the potential maximum exposure (b) (4) are not of toxicological concern.

5.1.3. Labeling

For this 505(b)(2) submission, the Sponsor utilized the labeling of the LD, CellCept® (powder for oral suspension, 200 mg/ml), as the basis for the proposed product labeling. There are no changes to the relevant nonclinical sections. The reviewer finds this appropriate and does not have any recommendations.

5.2.Drug Information

5.2.1. Drug

Code Name(s): MMF

CAS Registry Number(s): 128794-94-5

Generic Name: Mycophenolate Mofetil

Chemical Name:

4-Hexanoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3 oxo5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl) ethyl ester, (*E*)-

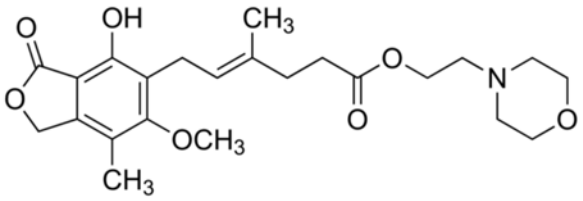
or

2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthanlanyl)-4-methyl-4-hexenoate

Molecular Formula/Molecular Weight: $C_{23}H_{31}NO_7$/ 433.49 g/mol

Structure or Biochemical Description:

Figure 1. Structure of MMF



Pharmacologic Class: Antimetabolite Immunosuppressant

5.2.2. Relevant INDs, NDAs, BLAs and DMFs

- NDA 50759 (LD): CellCept® (powder for oral suspension, 200 mg/ml)
- DMF (b) (4) (Drug Substance): (b) (4)

5.2.2.1. Drug Formulation

The LD, CellCept®, is a powder for oral suspension that needs to be reconstituted by the pharmacist prior to dispensing to the patient. The current proposed product is intended to be a new, ready-to-use liquid formulation of MMF.

Table 2. MMF Drug Product Composition

Ingredients	Quality Standard	Function	% w/v	Quantity/mL (mg/mL)
Mycophenolate Mofetil	USP	Active Pharmaceutical Ingredient	20.00	200.000
Methylparaben, NF (b) (4)	NF	(b) (4)	0.252	2.520
Propylparaben, NF (b) (4)	NF	(b) (4)	0.056	0.560
Xanthan Gum	NF	(b) (4)		
Glycerin	USP			
Sorbitol Solution (b) (4)	USP			
(b) (4) Simethicone Emulsion	USP			
Polysorbate 80	USP			
Monosodium phosphate dihydrate	NF			
Di Sodium Hydrogen Phosphate Dihydrate	USP			
Raspberry flavour	N/A			
Purified Water	(b) (4)			

Table 3. Composition of Raspberry flavor (b) (4)

Component	% w/w
(b) (4)	

5.2.3. Comments on Novel Excipients

All excipients contained in the MMF formulation are below those listed in the Inactive Ingredient Database (IID)[7] for approved oral drug products. However, the MMF formulation contains 6 excipients that are not present in the RLD (i.e., (b) (4) simethicone emulsion, polysorbate 80, monosodium phosphate dihydrate, dibasic sodium phosphate dihydrate, glycerin and propylparaben). The Clinical team raised concern that the combined effect of these inactive ingredients coupled with the active ingredient (MMF) may adversely affect gastrointestinal tolerability in pediatric populations. Thus, the reviewer conducted a toxicological evaluation of each of the excipients.

Table 4 (below) compares the MMF oral suspension product excipient levels (not present in the RLD) to those reported for the oral route in the IID. Although there is no way to identify excipients by pediatric and non-pediatric use in the IID[8], the reviewer converted the MDD levels of MMF excipients to mg/kg for pediatric populations (using 20 kg as standard pediatric weight per Starting Dose Guidance) and the MDE levels (or maximum potency) reported in the IID to mg/kg for adults (using 60 kg as standard adult weight) to enable some comparison. However, it is noted that while these comparisons are informative, they cannot be considered absolute as the patient population for excipients in the IID is unknown (the comparison relies on the assumption that excipients in the IID are for non-pediatric use and, thus, there is a high level of uncertainty).

Table 4. MMF Formulation: Levels of Excipients Not Present in the RLD

Excipients Not Present in RLD	Quantity/Dose (mg/mL)	Quantity (mg) per MDD (15 mL)	FDA Inactive Ingredient Database Information for Oral Route		% of MDE	% of Max Potency [c]
			MDE (mg) [a]	Max Potency (per unit drug use) (mg) [b]		
(b) (4) Simethicone Emulsion	(b) (4)		72 (1.2 mg/kg adult)	350 (5.8 mg/kg adult)	(b) (4)	
Calculation for (b) (4) Simethicone Emulsion						
			432	-		

[7] https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-approved-drug-products-search-frequently-asked-questions#purpose

[8] There is no way to identify excipients by pediatric and non-pediatric use in the Inactive Ingredient Database. The Draft Guidance for Industry: Using the Inactive Ingredient Database states, "*The Agency may consult the IID when performing regulatory filing reviews of applications and during the technical review of applications as part of an evaluation of whether the levels of excipients in drug product formulations are acceptable or require additional documentation to support the proposed level. The IID, however, does not currently provide information regarding the different exposure models (e.g., maximum daily intake based on the dosing recommendations indicated in the labeling, safety in pediatric populations, acute versus chronic use) that may be needed during such a technical review, nor does inclusion of an excipient at a level described in the IID necessarily satisfy the requirements in FDA regulations with respect to maximum allowable limits for specific categories of products.*"

Polysorbate 80	(b) (4)		(7.2 mg/kg adult)		(b) (4)	
Sodium Phosphate, Monobasic, Dihydrate			140 (2.3 mg/kg adult)	-		-
Sodium Phosphate, Dibasic, Dihydrate			143 [f] (2.4 mg/kg adult)	-		-
Glycerin			31,536 (525.6 mg/kg adult)	-		-
Propylparaben	0.560	8.4 (0.42 mg/kg peds)	17 [g] (0.3 mg/kg adult)	-	49.4 (140)	-

Highlighted = Calculated dose in mg/kg using 20 kg as standard pediatric weight and 60 kg as standard adult weight, per Starting Dose Guidance

[a] MDE is the total amount of the excipient that would be taken or used in a day based on the MDD of the drug product in which it is used. MDE is calculated as the dosage unit level of the excipient multiplied by the maximum number of dosage units recommended per day (excipient (mg) x number units).
[b] Only reported for excipients with levels not covered by the reported MDE in the Inactive Ingredient Database.
[c] Only calculated for excipients with levels not covered by the reported MDE in the Inactive Ingredient Database.
[d] Pediatric MDD (mg/kg based on 20 kg child) percentage of adult MDE (mg/kg based on 60 kg adult).
[e] Pediatric MDD (mg/kg based on 20 kg child) percentage of adult Maximum Potency (mg/kg based on 60 kg adult).
[f] 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.
[g] 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.

Table 4 shows that the pediatric MDD may exceed the adult MDE for two excipients: (b) (4) simethicone emulsion and propylparaben. Though, given the limitations discussed above and available information for these excipients (discussed below), the MMF product excipient levels do not present a safety concern from a toxicological perspective.

(b) (4) **Simethicone Emulsion:** Per 21CFR332.10, the MDD of simethicone is 500 mg and there is no dosage limit for professional labeling in OTC oral antiflatulent products (e.g., Mylicon, Phazyme, Gas X Extra Strength, Gas X Softgels, Gas X Thin Strips, Children's Gas X Tongue Twisters Thin Strips, Gas X, PediaCare Infant's Gas Relief Drops). To treat gas retention in the GI tract of children at ages <2, 2-12, and >12 the doses are not to exceed 240, 480, and 500 mg/day (i.e., 12, 24, and 25 mg/kg based on 20 kg child), respectively.[9] The MDD of simethicone in OTC products for pediatric and non-pediatric use exceeds the pediatric MDD of (b) (4) mg/kg in the MMF product for this excipient. A review of the therapeutic use of simethicone in gastroenterology examined clinical studies with safety reporting for approximately 2,000 adults and 200 infants that received simethicone as a monotherapy (Meier & Steuerwald, 2007[10]). The authors reported that simethicone compared favorably with placebo in terms of effects/adverse events, serious adverse events, and withdrawals due to side effects/adverse events.

[9] https://reference.medscape.com/drug/mylicon-phazyme-simethicone-342005#0
[10] Available from: https://www.karger.com/Article/Pdf/286002

Propylparaben: In 2015, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) published a reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use (EMA/CHMP/SWP/272921/2012[11]). The EMA CHMP conducted a risk assessment with focus on possible endocrine-disrupting effects in humans considering previous evaluations that determined propylparaben should be excluded from the acceptable daily intake (ADI) of 0-10 mg/kg established for parabens used in food due to identification of adverse reproductive organ effects in male rats given dietary doses of propylparaben without a clear NOEL/NOAEL (EFSA, 2004[12]; JECFA, 2006[13]). The EMA CHMP identified studies relevant for pediatric populations published after the EFSA and JECFA evaluations and determined a NOEL for propylparaben. Their evaluation states, "*On basis of a NOEL for propylparaben of 100 mg/kg/d derived in the Pouliot study (2013), a permitted daily exposure (PDE) for adults and paediatric patients can be calculated according to the method outlined in ICH Q3C1. The following uncertainty factors are used: F1=5 (rat), F2=10 (interindividual variation), F3=1 (exposure that covers juvenile period), F4=1 (lack of severity) and F5=1 (NOEL available). This calculation gives rise to a PDE for propylparaben in adults and paediatric patients of 2 mg/kg/d.*" The PDE of 2 mg/kg established for propylparaben by EMA CHMP is approximately 4.8-fold higher than the pediatric MDD of 0.42 mg/kg in the MMF product for this excipient. The pediatric MDD in the MMF product is also similar to the propylparaben MDD of (b) (4) mg/kg (based on 20 kg child) in Zovirax (NDA 019909; as well as related ANDAs for acyclovir) for the treatment of chickenpox in children ≥2 years of age that have a body weight of <40 kg. (b) (4) While the RLD only contains methylparaben, (b) (4) [14]

Overall, none of the individual MMF product excipient levels present a safety concern, from a toxicological perspective.

5.3. Comments on Impurities/Degradants of Concern

There are two drug product degradants that exceed the qualification threshold of ICH Q3B (with a 3 g daily dose the threshold is 0.15%). Specifically, the Applicant notes that the specification limits are NMT (b) (4) (b) (4)

[11] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-methyl-propylparaben-excipients-human-medicinal-products-oral-use_en.pdf
[12] Available from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2004.83
[13] Available from: WHO TRS 940
(b) (4)

5.3.1. (b) (4)

From a toxicological perspective, the specification limit (b) (4) does not raise concern. While (b) (4)

5.3.2. (b) (4)

Two in vitro genotoxicity studies (Study Nos. (b) (4) /0920/G/T105 and (b) (4) /1020/G/T111) were submitted by the applicant; both yielded negative results. In addition, a 28-day oral study (Study No. (b) (4) /0419/G/T043) was conducted, where rats were exposed to a test item (b) (4)

Study No. (b) (4) /0920/G/T105: Bacterial Reverse Mutation Test of (b) (4) Using Salmonella Typhimurium and Escherichia Coli Tester Strains

Methods

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Drug, lot #, and % purity: (b) (4)

Strains: *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, and *Escherichia coli* strain WP2uvrA

Concentrations in definitive study: 156.25, 312.5, 625, 1250, 2500, and 5000 µg/plate

Basis of concentration selection: The test item was dosed at a range of concentrations up to the standard limit of 5000 µg/plate. The concentrations were separated by a factor of approximately half log dilution (3.16-fold).

Negative control: DMSO (vehicle control)

Positive control:

Strain	Positive Control	
	-S9	+S9
TA1535	(b) (4)	
TA1537		
TA98		
TA100		
WP2uvrA		

(b) (4)

Formulation/Vehicle: DMSO

Incubation & sampling time:	All the treated plates were incubated at 37°C for 63 hours for mutagenicity and confirmatory assays. Following incubation, all the plates were observed under microscope for background lawn inhibition, presence of precipitation on the plates and were recorded along with the revertant counts for each test concentration. Revertant colonies were counted manually and verified for variation in the plate.
Comment on Study Validity:	The mean spontaneous revertant frequency of respective vehicle controls fell within the range of in-house historical control data. Mean revertant colony counts in positive control groups exhibited multifold increase (>3 fold).

Sponsor's Evaluation of Results: For a test item to be considered positive, it must produce at least a 2-fold increase in the mean revertants per plate of at least one of tester strains, TA 98, TA 100 and *E.coli* WP2 *uvrA*, over the mean revertants per plate of respective vehicle and at least a 3-fold increase in the mean revertants per plate in one or both tester strains, TA1535 and TA1537, in comparison with the appropriate vehicle control.

Results

During colony counting, no precipitation of test item was observed from 156.25 to 5000 µg/plate doses in all the five tester strains (±S9). Test item elicited thinning of background lawn at 5000 µg/plate in absence of metabolic activation with all five tester strains. No reduction in revertant colony counts were observed in all tester strains at all the tested concentrations in presence (5%) and absence of metabolic activation, in comparison to respective vehicle controls.

Based on the results, it is concluded that [redacted] (b) (4) is not mutagenic to *Salmonella typhimurium* and *E.Coli* WP2 *uvrA* tester strains both in the presence (5 and 10% S9) and absence of metabolic activation under the tested conditions.

Study No. [redacted] (b) (4) /1020/G/T111: In Vitro Mammalian Chromosome Aberration Test of [redacted] (b) (4) in Cultured Human Peripheral Blood Lymphocytes

Methods

Conducting laboratory and location:	[redacted] (b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	[redacted] (b) (4)
Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	Short term (±S9): 10, 20, and 40 µg/mL

	Continuous exposure (-S9): 0.00625, 0.0125, 0.025, 0.05, and 0.1 µg/mL
Basis of concentration selection:	Based on the results obtained in the cytotoxicity assays, test item concentration of 40 µg/mL for short term treatment and 0.1 µg/mL for continuous treatment were selected as high doses.
Negative control:	DMSO (vehicle control)
Positive control:	(b) (4)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Assays were conducted with an exposure time of ~4 hours (short exposure) both in the presence and absence of metabolic activation system and with an exposure time of ~ 22 hours (continuous exposure) in the absence of metabolic activation. Cultured human peripheral lymphocytes suspended in ~7.4 mL of serum free culture media for treatment with S9 mix and 7.9 mL of culture media supplemented with 15% FBS for treatment without S9 mix. For presence of metabolic activation, 0.5 mL of S9 mix per culture was added. Medium Change (4-Hour Treatment Only): Cultures were washed with plain media to remove the test item after 4 hours of treatment incubation and fresh culture medium supplemented with 15% FBS was added. Harvesting, Metaphase Preparation, and Staining: About 0.1 mL Colchicine was added to all the cultures to arrest cells at the metaphase stage of mitosis, ~2 hours before harvesting. After mitotic arrest, at ~22 hours, cultures were centrifuged, and the supernatant was discarded. The residual cell pellet was suspended in 6 mL of 0.075 M potassium chloride by gentle vortexing and incubated for 20 minutes at 37°C for hypotonic treatment. Following hypotonic treatment, the cells were centrifuged, supernatant removed, and fixed in ~6 mL of chilled methanol: glacial acetic acid (3:1 v/v) solution, with gentle mixing. The fixation and removal steps were repeated 3x until the cell pellets appeared off white in color. After the last centrifugation, the supernatant was discarded from each culture tube, leaving the pellet in a small volume of supernatant. The resultant cell suspension was dropped onto a clean chilled slide from a height of ~30 cm and placed for drying on a slide warmer. Slides were prepared in duplicate for each culture. After drying, the slides were stained for 8 minutes with 5% giemsa stain in Sorenson's buffer (pH 6.8). All the slides were mounted with DPX, and a quality control check of the slides was carried out before microscopic evaluation. At least 1000 cells were analyzed for mitotic index (MI) from each

	culture in the test item, vehicle, and positive control cultures.
Comment on Study Validity:	The incidences of structural aberrant cells in vehicle control groups were within the historical control data; positive controls exhibited statistically significant increases in cells with structural chromosome aberrations compared to vehicle controls.

Sponsor's Evaluation of Results: The following criteria were used in the interpretation of the results:

- **A positive response** is indicated by a significant increase ($p \leq 0.05$) in the number of cells with chromosome aberrations observed at one or more test concentration levels tested.

- **A negative result is** indicated if the test item meets none of the above criteria under all experimental conditions.

Results
For 4-hour treatment, the highest dose level selected was 40 µg/mL in the presence and absence of S9 mix. In the presence of S9 mix, the percentage reduction in MI for the high dose was 36.71%. The mean percentage aberrations observed in cells with structural aberrations excluding gaps were 0.67, 1.33, 1.00, and 1.33 for vehicle control,
10, 20, and 40 µg/mL, respectively. In the absence of S9 mix, the percentage reduction in MI for the high dose was 47.13%. The mean percentage aberrations observed in cells with structural aberrations excluding gaps were 1.33, 1.00, 1.00, and 0.00 for vehicle control, 10, 20, and 40 µg/mL, respectively (Table 5).

For 21-hour treatment, the highest dose level selected was 0.1 µg/mL in the absence of S9 mix. The percentage reduction in MI for the high dose was 43.62%. Out of five doses tested, the 3 highest doses which exhibited <50% reduction in MI were analyzed for chromosome aberrations (i.e., 0.025, 0.05, and 0.1 µg/mL). The mean percentage aberrations observed in cells with structural aberrations excluding gaps were 1.00, 1.00, 0.67, and 0.67 for vehicle control, 0.025, 0.05, and 0.1 µg/mL, respectively (Table 5).

Based on the results, it is concluded that (b) (4) is non-clastogenic to cultured human peripheral blood lymphocytes up to (b) (4) µg/mL in short term and (b) (4) µg/mL in continuous exposure under the tested conditions.

Table 5. Summary of Results: In Vitro Mammalian Chromosome Aberration Test

Presence of Metabolic Activation **Exposure Duration:-4 h**

Test item Treatment concentration (µg/ml)	Total metaphases with Aberrations		Mean % Metaphases with Aberrations (-g)	Mean of % Numerical Aberrations	Mean % Total Aberrations (-g)
	Including Gaps	Excluding Gaps			
VC (DMSO)	2	2	0.67	0.00	0.67
10 (T1)	4	4	1.33	0.00	2.00
20 (T2)	3	3	1.00	0.34	1.67
40 (T3)	4	4	1.33	0.00	2.00
PC (b) (4)	29	29	9.67	0.34	20.67

Absence of Metabolic Activation **Exposure Duration:-22 h**

Test item Treatment concentration (µg/ml)	Total metaphases with Aberrations		Mean % Metaphases with Aberrations (-g)	Mean of % Numerical Aberrations	Mean % Total Aberrations (-g)
	Including Gaps	Excluding Gaps			
VC (DMSO)	3	3	1.00	0.00	0.83
0.025 (T3)	3	3	1.00	0.00	0.50
0.05 (T4)	2	2	0.67	0.00	0.33
0.1 (T5)	2	2	0.67	0.00	0.33
PC (b) (4)	31	31	10.34	0.00	19.67

Absence of Metabolic Activation **Exposure Duration:-4 h**

Test item Treatment concentration (µg/ml)	Total metaphases with Aberrations		Mean % Metaphases with Aberrations (-g)	Mean of % Numerical Aberrations	Mean % Total Aberrations (-g)
	Including Gaps	Excluding Gaps			
VC (DMSO)	4	4	1.33	0.00	2.00
10 (T1)	3	3	1.00	0.34	2.00
20 (T2)	3	3	1.00	0.67	1.00
40 (T3)	0	0	0.00	0.00	0.00
PC (b) (4)	35	35	11.66	0.00	34.33

Note: CYP = Cyclophosphamide, MMC = Mitomycin C, T1 to T5 = Low to high concentrations of test item in DMSO, VC = Vehicle control (DMSO), -g= excluding gaps, PC - Positive Control, % Total aberrations = (total number of aberration types observed/total metaphases scored)×100.

Study No. (b) (4) /0419/G/T043: Repeated Dose (28 Days) Oral Toxicity Study of Mycophenolate Mofetil Oral Suspension with Unknown Impurity At (b) (4) in Wistar Rats

In the 28-day oral study, rats were exposed to a test item containing MMF, (b) (4) (b) (4) (referred to as unknown impurity at (b) (4) in the study report) at three doses (referred to as groups G2, G3, and G4; Table 6).

Table 6. 28-Day Rat Study (Study No. (b) (4) /0419/G/T043) Dose Groups

Group	Impurity# Dose (mg/kg b.w.)	API@ Dose (mg/kg b.w.)	(b) (4) Impurity Dose (mg/kg b.w.)	Strength (mg/mL)	Dose Volume (mL/kg/ animal)	No. of Rats	Sex	Animal Number	
								From	To
G1 (Vehicle Control)	NA	NA	NA	0	4.82	6	M	T043/001	T043/006
						6	F	T043/007	T043/012
G2 (Low Dose)	(b) (4)	0.08	(b) (4)	(b) (4)	0.46	6	M	T043/013	T043/018
						6	F	T043/019	T043/024
G3 (Mid Dose)		0.41		0.18@	2.29	6	M	T043/025	T043/030
						6	F	T043/031	T043/036
*G4 (High Dose)		0.82			4.58	6	M	T043/037	T043/042
						6	F	T043/043	T043/048
G5 (Reference-1 High Dose)	NA	0.82	NA	0.17@	4.82	6	M	T043/049	T043/054
						6	F	T043/055	T043/060
G6 (Reference-2 High Dose)	NA	NA	(b) (4)	(b) (4)	4.46	6	M	T043/061	T043/066
						6	F	T043/067	T043/072

Note: NA= Not Applicable, # = Unknown Impurity at (b) (4) @ = Mycophenolate mofetil, $ = (b) (4) * = G4 group was terminated on Day 6 of the study, due to mortalities and toxic clinical signs.

Methods

Study initiation date: April 19, 2019

Conducting laboratory and location: (b) (4)

GLP compliance: No

Drug, lot #, and % purity: MMF (sample for unknown impurity at (b) (4) (b) (4) MYCL1055 (supernatant), N/A

Doses: See Table 6, above

Frequency of dosing: Once daily

Number/Sex/Group: 6/sex/group

Dose volume: See Table 6, above

Formulation/Vehicle: Placebo (unknown composition)

Route of administration: Oral gavage

Species: Rat

Strain: Wistar Han

Age / Sexual Maturity: 7 to 8 weeks at start of acclimatization

Comment on Study Design and Conduct:	The study report indicates that there were no study plan deviations recorded throughout the study. The formulation of the vehicle is unclear, and the study has numerous limitations/deficiencies, outlined in the discussion below.
Dosing Solution Analysis:	No information is provided on concentration/homogeneity testing or acceptance criteria for any of the test articles.

At the high dose of the impurity ((b) (4); group G4), 2/6 males and all females (6/6) were found dead between days 5 and 6 of the treatment period (these animals were necropsied after they were found). Numerous microscopic findings were seen in the mid- and high-dose groups (G3 and G4, respectively) including decreased cellularity in the femur and bone marrow of all males and females. Limited findings (only multifocal tingle body macrophages in the thymus) were reported for the low-dose group (G2), but it is noted that this study has several limitations including insufficient animal numbers and a lack of concentration and homogeneity testing or acceptance criteria for all test articles. The study report concludes that the low dose ((b) (4)) is the NOAEL. This equates to a human equivalent dose (HED) of (b) (4), which is below the (b) (4) of impurity potentially yielded from the (b) (4) specification. However, the Applicant submitted an amendment to the study report indicating that the study was originally conducted considering unknown impurity at (b) (4) and post-completion of the study they were able to synthesize and characterize the impurity. Based on this analysis they edited the COA for the test item using an updated relative response factor (RRF) of (b) (4) to yield a NOAEL of (b) (4) which would equate to a HED of (b) (4).

The following issues identified for the 28-day oral study, were conveyed to the Applicant in a Nonclinical IR on September 9, 2022 (DARRTS ID: 5043300):

We are reviewing your submission dated March 8, 2022, for mycophenolate mofetil (MMF) oral suspension. You conducted a 28-day oral toxicity study in rats (Study No. (b) (4)/0419/G/T043) to provide justification for the specification limit of NMT (b) (4) of (b) (4) impurity (b) (4) (also referred to as unspecified unknown impurity at (b) (4) in your finished MMF oral suspension product. We identified several issues in your study, and have the following comments:

1. *As the objective of the 28-day rat study was to qualify (b) (4), it is unclear why (b) (4) dose groups (G2–G4) were formulated with (b) (4) In addition, (b) (4) was included in these dose groups at greater levels (b) (4) The inclusion of high (b) (4) amounts likely contributed to the animal deaths at the high dose (G4) on days 5 and 6 of treatment (2/6 males and all (6/6) females), which resulted in the decision to terminate the group. Considering G4 mortalities and noted toxicities (e.g., unscheduled deaths and clinical observations including dysentery, piloerection, dehydration, diarrhea, emaciation, epistaxis,*

and hunched back posture) in reference item 2 (G6) that contained the high dose of (b) (4) alone, the inclusion of (b) (4) dose groups (at doses higher than (b) (4) limited the sensitivity of your study and prevented delineation of potential adverse effects from the direct exposure to (b) (4) Provide clarification on the rationale for your selection of dose groups and levels.

2. *Numerous microscopic findings were seen in (b) (4) mid(G3)- and high(G4)-dose groups including decreased cellularity in the femur and bone marrow of all males and females. Limited findings (multifocal tingle body macrophages in the thymus of 1/6 males and 3/6 females) were reported for the low-dose group (G2). Thus, the low dose is considered the NOAEL for this study. According to the Study Report Amendment for Study No. (b) (4)/0419/G/T043, the amount of (b) (4) in the test item was recalculated using a corrected RRF value after additional characterization of the impurity following the 28-day rat study. This changed the low dose from (b) (4) mg/kg/day, and the corresponding human equivalent dose (HED) from (b) (4). This is slightly higher than the maximum daily dose of (b) (4) at the (b) (4) specification limit. Provide justification that the HED based on the NOAEL established in your study would not be considered of toxicological concern. In addition, an updated study report reflecting corrected values for all (b) (4) dose groups should be provided.*

3. *It is unclear why histopathological evaluations for reference item 2 (G6) were only conducted in animals found dead (1/6 males and 4/6 females). For the finding of decreased cellularity in bone marrow smears, your report states "Decreased cellularity in bone marrow smear (cytology) evaluation was attributed to pharmacological effect of Mycophenolate Mofetil and (b) (4) and these lesions were comparable between mid (G3) and high (G4 and G6) dose group animals in both the sex" (page 38). It is unclear how this conclusion was reached considering that only animals found dead, likely to present increased microscopic findings compared to rats that survived to end of study, in G6 were evaluated. Moreover, the assessment of the one male found dead in G6 is inadequate to draw sex-related conclusions. In addition, your histopathology data do not distinguish which G4 animals were found dead versus sacrificed early after the decision to terminate the group. These should be separated as animals found dead may present increased findings compared to those that were terminated. Provide clarification on your rationale to only evaluate animals found dead for reference item 2 (G6) and details on which animals were found dead versus terminated in G4. In addition, provide a detailed interpretation of study findings and additional justification to support your conclusions.*

4. *While you indicated that the 28-day rat study was in compliance with OECD principles of GLP, a number of deficiencies were identified, including a lack of concentration/homogeneity testing or acceptance criteria for all test articles (stated that ready-to-use solutions were issued by Test Item Control Office without further details), and an inadequate number of study animals (generally, 10/sex/group would be considered adequate for rodents). In addition, it is unclear what vehicle was used in your study. For*

justification of vehicle selection, your report states "Placebo was used as vehicle, as suggested by sponsor" (page 24). Provide information on the vehicle formulation for the study, and justification for adequacy of this study to support safety of the impurity, given the aforementioned deficiencies. Also, provide justification for the length of the study (28 days), as a 90-day study length is typically expected for drug products with chronic indications (see Guidance for Industry: Q3A Impurities in New Drug Substances, 2008).

On October 3, 2022, the Applicant provided a response to the Nonclinical IR (SD 14).

Evaluation of the Applicant's Response to Nonclinical Comment No. 1

In the 28-day rat study the (b) (4) dose groups (G2–G4) were formulated with high levels of (b) (4) preventing delineation of potential toxicities from direct exposure (b) (4) To address this issue the Applicant indicates that, (b) (4) (Figure 2).

Figure 2. Applicant-Proposed (b) (4)

(b) (4)

The Applicant also calculates the total amount of (b) (4) dosed (accounting for (b) (4) (b) (4) for each treatment group of the 28-day toxicity study (Table 7), and notes that the findings appear to align with what is known toxicologically in rats for (b) (4) (Table 8).

Table 7. Applicant-Calculated Doses of (b) (4)

	MW (g/mol)	Low (NOAEL) Dose (mg/kg/day)	Mid Dose (mg/kg/day)	High Dose (mg/kg/day)	Ref. #1 Dose (mg/kg/day)	Ref. #2 Dose (mg/kg/day)
(b) (4)						

Table 8. Applicant-Provided Summary of Dose-Response Findings in Rat Studies with (b) (4) (b) (4)

Row	Dose (mg/kg)	Observation	Source
1	(b) (4)	**4-week oral rat study** Mortality Inflammatory lesions in caecum, Splenic and thymic atrophy ↓ bone marrow cellularity	(b) (4) Study: (b) (4) 0419/G/T043
2		(b) (4)	
3		**4-week oral rat study** Mortality Body weight loss; Inflammatory lesions in caecum; Splenic and thymic atrophy. ↓ bone marrow cellularity; ↓ RBC, ↓HGB, ↓ HCT, ↓ LYM, ↓BAS	(b) (4) Study: (b) (4) 0419/G/T043
4		**4-week oral rat study** Inflammatory lesions in caecum Splenic and thymic atrophy. ↓ bone marrow cellularity; ↓ RBC, ↓HGB, ↓ HCT	(b) (4) Study: (b) (4) 0419/G/T043
5		(b) (4)	
6			
7			
8		**NOAEL 4-week oral rat study**	(b) (4) Study: (b) (4) 0419/G/T043
9		(b) (4)	
10		**4-week oral rat study** Inflammatory lesions in caecum	(b) (4) Study: (b) (4) 0419/G/T043

The information provided by the Applicant supports their position that results from the 28-day rat study appear to align with previously reported data for (b) (4) (b) (4) a timeline was not specified by the Applicant for when this assay will be completed/results provided). While the results from the (b) (4) are pending, the reviewer finds the Applicant's response adequate.

Evaluation of the Applicant's Response to Nonclinical Comment No. 2

The NOAEL for (b) (4) in the 28-day rat study is (b) (4) mg/kg/day, which corresponds to a HED of (b) (4) This is slightly higher than the maximum daily dose of (b) (4) at the (b) (4) specification limit. To address this issue the Applicant states the following:

> *Therefore, considering maximum daily dose of (b) (4) is (b) (4), we would like to tighten the specification limit up to (b) (4) [HED (b) (4) /MDD (Maximum daily dose; Product) (b) (4) and provided updated drug product's Sections (3.2.P.5.1; Specification and 3.2.P.5.5.2; Method of Analysis) which will rule out the possibility of any adverse effect or toxicological concern.*

While the Applicant's response does not provide adequate justification that the (b) (4) HED based on the NOAEL in the 28-day study would not be considered of toxicological concern, the difference between the HED (b) (4)) and the maximum daily dose of (b) (4) at the (b) (4) specification limit is minimal (b) (4) It is unlikely that exposure to an additional (b) (4) (b) (4) would result in toxicity, especially if (b) (4) (see previous discussion under section 2.5.2.3.a, above). Therefore, the reviewer does not consider the difference between the HED based on the study NOAEL and the maximum daily dose (b) (4) at the (b) (4) specification limit to be of toxicological concern.

In addition, the Applicant states that an updated study report reflecting corrected values for all (b) (4) dose groups will be provided on or before December 20, 2022.

Evaluation of the Applicant's Response to Nonclinical Comment No. 3

Histopathological evaluations for reference item 2 (group G6) were only conducted in animals found dead (1/6 males and 4/6 females), and histopathology data for the (b) (4) high-dose (group G4) did not distinguish animals were found dead versus sacrificed early after the decision to terminate the group. The Applicant states the following regarding the evaluation of reference item 2 (G6) animals:

(b) (4)

(b) (4)

(b) (4)

While the Applicant's rationale for only evaluating animals found dead for reference item 2 (G6) is inadequate, the Applicant indicates that additional tissues from G6 are planned to process. The Applicant also indicates that histopathology data will be presented separately for found dead and terminally sacrificed animals for better clarity, and that an updated report with detailed interpretation of study findings and additional justification considering histopathology data will be provided on or before December 20, 2022. While this data will be informative and provide a clearer representation of results, the data is not expected to impact the reviewer's conclusions. This is considering that meaningful comparisons of reference item 2 (G6; (b) (4) mg/kg (b) (4) and the (b) (4) high-dose with a matching amount of (b) (4) (G4) were limited given the high mortality levels and decision to terminate G4.

Evaluation of the Applicant's Response to Nonclinical Comment No. 4

Several deficiencies were identified for the 28-day rat study, including a lack of concentration/homogeneity testing or acceptance criteria for all test articles, an inadequate number of study animals, and lack of clarity on the vehicle that was used. The Applicant's responses for each issue identified is discussed below.

Test articles: The Applicant submitted the study protocol for the 28-day rat study and indicates that the protocol provides complete details of test articles. However, the protocol does not provide concentration/homogeneity testing or acceptance criteria for any of the test articles. Rather, only a brief dose formulation section is included, that matches that in the final study report. The section states, "*Ready to use test item, reference item-1 (Mycophenolate mofetil), reference item-2* (b) (4) *impurity) and placebo will be used for the study. The required volume of test/reference items and placebo will be issued by TICO [Test Item Control Office].*"

Vehicle: The Applicant states page 11 of the study protocol for the 28-day rat study has placebo details and indicates that placebo (vehicle) was prepared considering the actual composition of proposed product without API. However, the study protocol contains the same limited information on the placebo/vehicle as the final study report (Table 9). The specific composition of the placebo/vehicle remains unclear (e.g., it is unknown whether the placebo matches the inactive ingredients in the clinical formulation).

Table 9. Placebo Details Given on Page 11 of the Study Protocol

The placebo and its identity in form of (b) (4) was provided by the sponsor. Relevant information is summarized below:

Name	Placebo Mycophenolate Mofetil Oral Suspension 200 mg/mL
Sponsor's Name and Address	(b) (4)
Batch Number	MYCL1056
Manufacturing Date	07/01/2019
Physical Appearance	Liquid
Storage Conditions	2 – 8 °C

Study length: The Applicant indicates that the 28-day study length was designed considering ICH Q3A, which states that a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate for general toxicity studies. The Applicant also asserts that no new safety issues in animals were raised during the 28-day study period and based on the study results, they concluded the NOAEL of (b) (4) is (b) (4) mg/kg/day and "*Therefore, no further studies beyond 28 days is required*."

However, the reviewer notes that ICH Q3A also states "*The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of an impurity.*" Given that the proposed drug product has chronic indications, a 90-day study would have been most appropriate.

Number of study animals: The Applicant indicates that 12 rats (6 males and 6 females) were included per group based on OECD (2008), Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents, which specifies that at least 10 animals (five female and five male) should be used at each dose level. Thus, the number of animals included in the study complies with OECD guidelines for 28-day oral studies in rodents, although the reviewer notes that a 90-day study length would have been most appropriate (OECD Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents specifies that at least 20 animals [ten females and ten males] should be used at each dose level). The initial considerations and limitations in TG 407 states "*The results from the TG 407 should be used for hazard identification and risk assessment. The results obtained by the endocrine related parameters should be seen in the context of the "OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupting Chemicals" (11). The method comprises the basic repeated dose toxicity study that may be used for chemicals on which a 90-day study is not warranted (e.g. when the production volume does not exceed certain limits) or as a preliminary to a long-term study.*"

Overall assessment: While the 28-day rat study has several limitations, outlined above, the information is sufficient to indicate that the specification limit (b) (4) is not of toxicological concern.

5.3.3. (b) (4)

(b) (4) EPA has developed a provisional peer-reviewed toxicity value (PPRTV) for (b) (4) EPA's assessment (b) (4) used the benchmark dose method to estimate an oral chronic reference dose (RfD) of (b) (4) mg/kg/day for (b) (4). An RfD is the estimate of a daily oral exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime. As the RfD is much higher than the potential maximum exposure to the (b) (4) impurity, it is not of toxicological concern.

(b) (4) ." Based on the EPA analysis, (b) (4) can be considered (b) (4) (low toxic potential) per ICH Q3C(R8), for which no health-based exposure limit is needed. As (b) (4) have permitted daily exposures (PDEs) of (b) (4) mg or more per day, the potential maximum exposure to the (b) (4) impurity is not of toxicological concern.

5.4. Studies Submitted

5.4.1. Studies Reviewed

1) **Study No. (b) (4) /0920/G/T105:** Bacterial Reverse Mutation Test of (b) (4) (b) (4) Using *Salmonella Typhimurium* and *Escherichia Coli* Tester Strains

2) **Study No. (b) (4) /1020/G/T111**: *In Vitro* Mammalian Chromosome Aberration Test of (b) (4) in Cultured Human Peripheral Blood Lymphocytes

[15] (b) (4)

3) **Study No. (b) (4) /0419/G/T043:** Repeated Dose (28 Days) Oral Toxicity Study of Mycophenolate Mofetil Oral Suspension with Unknown Impurity A (b) (4) in Wistar Rats

5.5. Integrated Summary and Safety Evaluation

This review provides a nonclinical safety evaluation of excipients, impurities/degradants, (b) (4) identified in the MMF Oral Suspension product, based on data submitted by the Applicant and other available information. The Applicant is seeking approval for the drug product at daily doses up 3 g MMF, to be delivered in a ready-to-use liquid formulation (200 mg/mL). Overall, there appear to be no nonclinical safety concerns with regards to excipients, impurities/degradants, (b) (4)

6. Clinical Pharmacology

6.1. Executive Summary

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid (MPA), a small molecule inhibitor of inosine monophosphate dehydrogenase (IMPDH), an important enzyme in the *de novo* guanosine biosynthesis pathway. Because lymphocytes cannot generate guanosine via salvage pathways and therefore rely on the *de novo* pathway, MPA inhibition of IMPDH can induce cytostatic effects on lymphocytes and inhibit proliferative responses.

The Applicant submitted this 505(b)(2) NDA for a ready-to-use MMF oral suspension, which is distinguished from the currently available MMF for oral suspension, supplied as a powder for reconstitution. The listed drug is CellCept powder for oral suspension, which was approved in 1998 under NDA 50759. The proposed ready-to-use oral suspension is formulated at a concentration of 200 mg/mL, which is identical to the concentration of the listed drug after reconstitution.

The Applicant is seeking approval of the proposed ready-to-use MMF oral suspension for the same populations and indications as the listed drug, including adult and pediatric recipients of kidney, heart, or liver transplants aged 3 months and older. The proposed dosing for each population is identical to that approved for the listed drug, including 1 g BID for adult kidney transplant patients, 1.5 g BID for adult heart transplant and adult liver transplant patients, 600 mg/m^2 for pediatric kidney transplant patients aged 3 months and older, and 600 to 900 mg/m^2 for pediatric heart transplant and pediatric liver transplant patients aged 3 months and older.

To rely on FDA's findings of safety and efficacy for CellCept for oral suspension, the Applicant conducted two open-label relative bioavailability (BA) studies in healthy male adults: CL-155-18 and CL-156-18, conducted under fasting and fed conditions, respectively. Based on the results of studies CL-155-18 and CL-156-18, bioequivalence (BE) based on the C_{max}, AUC_{0-t}, and AUC_{0-inf} of active metabolite mycophenolic acid (MPA) has been established between the proposed ready-to-use MMF oral suspension and the listed drug powder for oral suspension after reconstitution.

Recommendation: From a clinical pharmacology perspective, the data provided in this NDA support approval of MMF ready-to-use oral suspension for use in adult and pediatric recipients of kidney, heart, or liver transplants aged 3 months and older.

Post-marketing requirement/Post-marketing commitment: None.

6.2. Summary of Clinical Pharmacology Assessment

The clinical pharmacology assessment was based on review of studies CL-155-18 and CL-156-18, conducted under fasting and fed conditions, respectively. Both studies were open-label, randomized, four-period, two-treatment, two-sequence, single-dose crossover studies evaluating a 1000 mg oral dose (5 mL x 200 mg/mL) of the test product relative to the listed drug.

6.2.1. Pharmacology and Clinical Pharmacokinetics

A brief summary of the pharmacokinetics of MMF and MPA is given below. Refer to the approved labeling for CellCept for a more detailed description of the pharmacology and clinical pharmacokinetics of MMF and MPA.

Per the approved labeling for CellCept, after oral administration, MMF undergoes complete conversion to MPA, the active metabolite. The mean absolute bioavailability of oral MMF relative to IV MMF was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in kidney transplant patients receiving multiple oral doses of MMF up to a daily dose of 3 g (1.5 g twice daily).

In the early post-transplant period (less than 40 days post-transplant), kidney, heart, and liver transplant patients had mean AUCs approximately 20% to 41% lower and mean C_{max} approximately 32% to 44% lower compared to the late post-transplant period (i.e., 3 to 6 months post-transplant). This is referred to as non-stationarity in MPA pharmacokinetics.

MPA is metabolized principally by glucuronyl transferase to form MPA glucuronide (MPAG), which is not pharmacologically active. *In vivo*, MPAG is converted to MPA during enterohepatic recirculation. Due to the enterohepatic recirculation of MPAG/MPA, secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours post-dose.

At clinically relevant concentrations, MPA is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable kidney transplant patients; however, at higher MPAG concentrations, the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding.

The following are the major clinical pharmacology findings from the current review:

<u>1). Results from studies CL-155-18 and CL-156-18 establish BE between the proposed product and the listed drug under both fasting and fed conditions.</u>

The primary analyses conducted in studies CL-155-18 and CL-156-18 were based on the PK of MPA, the pharmacologically active metabolite of MMF. Both studies were designed as four-

period crossover studies. Therefore, analyses used by the Applicant to determine BE were dependent on calculations of intra-subject variability for the listed drug as follows:

- PK parameters determined to have low intra-subject variability (s_{WR} < 29.4%), BE was determined using a typical unscaled average approach based on geometric mean ratios and associated 90% confidence intervals
- PK parameters determined to have high intra-subject variability (s_{WR} ≥ 29.4%), BE was determined using a reference-scaled approach.
    - Notably, the reference-scaled approach was only applied to C_{max} in fasted study CL-155-18.

This reviewer verified the Applicant's analyses and evaluated all PK parameters, including C_{max}, AUC_{0-t}, and AUC_{0-inf}, using a conservative unscaled BE approach. Results from the reviewer's analysis are shown below in **Table 10**.

Table 10. Bioequivalence analysis based on MPA Cmax, AUC0-t, and AUC0-inf in studies CL-155-18 (fasted) and CL-156-18 (fed).

	GMR (Test/Reference) [90% CI]	
	CL-155-18	**CL-156-18**
C_{max}	1.12 [1.03, 1.21]	0.99 [0.92, 1.05]
AUC_{0-t}	1.08 [1.06, 1.10]	1.04 [1.02, 1.07]
AUC_{0-inf}	1.07 [1.04, 1.10]	1.03 [1.00. 1.06]

Abbreviations: AUC_{0-t}: area under the concentration-time curve from time 0 to the time of last measurable concentration; AUC_{0-inf}: area under the concentration-time curve from time 0 to infinity; C_{max}: maximum concentration; CI: confidence interval; GMR: geometric mean ratio
Source: Reviewer's analysis

The geometric mean ratios and associated 90% confidence intervals for C_{max}, AUC_{0-t}, and AUC_{0-inf} for the test product relative to the listed drug are all completely contained within the 80-125% range. Therefore, the Applicant can rely on the Agency's previous findings of safety and effectiveness of MMF for the listed drug, CellCept powder for oral suspension (NDA 50759). In addition, the Applicant can also rely on the approved U.S. labeling for CellCept (NDA 50759) for relevant information for MMF, including pharmacokinetics (PK), drug interaction, renal and hepatic impairment, etc.

2) As BE was established between the proposed product and the listed drug under both fasting and fed conditions, the recommendations for administration of the MMF oral suspension with regard to food should be the same as the listed drug (CellCept).

3) The relative BA assessment was conducted at a single 1000 mg oral dose. MMF has linear PK up to 3 g. Therefore, the relative BA findings at the 1000 mg dose were

deemed representative of the relative BA of MMF at the proposed doses for all proposed indications.

4) The review team requested an inspection of the clinical and analytical sites for studies CL-155-18 and CL-156-18 from the Office of Study Integrity and Surveillance (OSIS). The inspection request was denied as the clinical and analytical sites had been inspected within the surveillance interval. The inspections were classified as "No Action Indicated" and it was determined that the data from the reviewed studies were reliable.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen for the MMF ready-to-use oral suspension is identical to that approved for CellCept for oral suspension, including a dosage of 1 g BID for adult kidney transplant recipients, 1.5 g BID for adult heart transplant and adult liver transplant recipients, 600 mg/m^2 for pediatric kidney transplant recipients aged 3 months and older, and a dose range of 600 to 900 mg/m^2 for pediatric liver transplant and heart transplant recipients aged 3 months and older. BE has been established between the proposed product and the listed drug based on MPA PK.

The proposed ready-to-use oral suspension has been studied at a single dose level of 1000 mg (5 mL x 200 mg/mL) across studies CL-155-18 and CL-156-18. However, doses of 1.5 g or 600 to 900 mg/m^2 may also be administered. The proposed product will be available at a single strength of 200 mg/mL. Thus, administration of different doses of MMF oral suspension will be based on the volume of administration. Per the approved labeling for the listed drug, MPA AUC appears to increase in a dose-proportional fashion in kidney transplant patients receiving multiple oral doses of MMF up to a daily dose of 3 g (1.5 g twice daily).

Based on the established BE between the proposed product and the listed drug, and dose-proportionality over the dose range, the proposed dosing is acceptable from a clinical pharmacology perspective.

Therapeutic Individualization

No new therapeutic individualization has been proposed

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant submitted data from studies CL-155-18 and CL-156-18 to determine whether MPA exposure after administration of the proposed ready-to-use oral suspension was BE to MPA exposure after administration of the listed drug for oral suspension (requiring reconstitution prior to dosing) under fasted and fed conditions, respectively. Studies CL-155-18 and CL-156-18 were both open-label, laboratory-blind, randomized, four-period, two-treatment, two-sequence crossover studies that evaluated a single 1000 mg oral dose of each product (5 mL x 200 mg/mL).

Both studies enrolled approximately 48 healthy adult males aged 18 to 45 with body mass index (BMI) between 18.5 and 29.9 kg/m^2. The order of receiving the listed and test products for each subject during each period was determined based on a randomization schedule. After dosing, PK samples in each study period were collected up to 72 hours post-dose. Per the approved labeling for CellCept, the mean apparent half-life of MPA following oral administration is approximately 17.9 hours. Thus, the sampling schemes would collect data through approximately 4 half-lives post-dose. Across both studies, a washout period of 10 to 13 days separated each dosing period, which appears sufficient for complete drug clearance based on the mean apparent half-life of MPA.

In study CL-155-18, doses were administered after an overnight fast of at least 10 hours. In study CL-156-18, doses were administered 30 minutes after serving a high-fat, high-calorie breakfast. The standardized meal derived approximately 150, 250, and 500-600 calories from protein, carbohydrates, and fat, respectively.

In both studies, PK data for MPA, the pharmacologically active metabolite, and MMF, the parent drug were collected. In studies CL-155-18 and CL-156-18, BE determinations were made based on MPA data only from 40/48 (83.3%) and 42/48 (87.5%) subjects that completed all dosing periods, respectively. **Table 11** and **Table 12** below compare the PK parameters of MPA and MMF, respectively, following administration of the test product and listed drug across studies CL-155-18 and CL-156-18.

Table 11. MPA PK parameters following administration of the test product (ready-to-use MMF oral suspension) and listed drug (CellCept powder for oral suspension) in studies CL-155-18 and CL-156-18.

	CL-155-18 (Fasting) (n = 40)		CL-156-18 (Fed) (n = 42)	
	Test Product	**Listed Drug**	**Test Product**	**Listed Drug**
C_{max} (ng/mL)	31090 (31)	27969 (37)	9246 (36)	9376 (32)
AUC_{0-t} (ng*h/mL)	59765 (23)	55392 (24)	45139 (29)	43221 (30)
AUC_{0-inf} (ng*h/mL)	63512 (25)	59420 (24)	48400 (30)	46938 (32)
T_{max} (h)	0.50 (0.25, 1.50)	0.50 (0.33, 1.75)	1.00 (0.25, 4.00)	1.00 (0.33, 4.00)
$t_{1/2}$ (h)	11.9 (74)	13.2 (104)	11.4 (47)	11.5 (50)

All values are reported as geometric mean (CV%) except for T_{max}, which is reported as median (range), and $t_{1/2}$ which is reported as arithmetic mean (CV%)
Abbreviations: AUC_{0-t}: area under the concentration-time curve from time 0 to the time of last measurable concentration; AUC_{0-inf}: area under the concentration-time curve from time 0 to infinity; C_{max}: maximum concentration; T_{max}: time to maximum concentration; $t_{1/2}$: half-life
(*Source: Adapted from Table 1A, page 15, Biostatistics Report for Study CL-155-18; and Table 1A, page 15, Biostatistics Report for Study CL-156-18; Module 5.3.1.4, NDA 216482 SDN 1, submitted Mar. 8, 2022*)

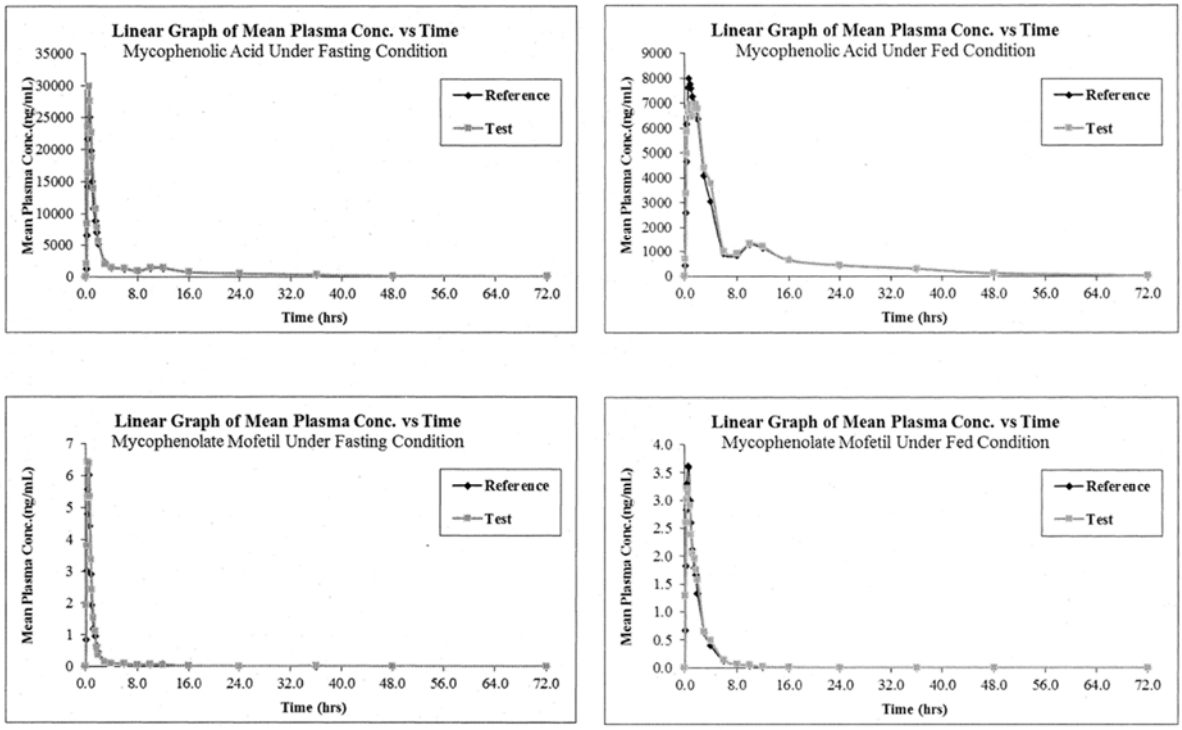
Table 12. MMF PK parameters following administration of the test product (ready-to-use MMF oral suspension) and listed drug (CellCept powder for oral suspension) in studies CL-155-18 and CL-156-18.

	CL-155-18 (Fasting) (n = 40)		CL-156-18 (Fed) (n = 42)	
	Test Product	**Listed Drug**	**Test Product**	**Listed Drug**
C_{max} (ng/mL)	6.16 (87)	5.03 (116)	3.81 (72)	3.80 (67)
AUC_{0-t} (ng*h/mL)	5.16 (76)	4.43 (88)	6.46 (50)	6.23 (51)
AUC_{0-inf} (ng*h/mL)	5.58 (77)	4.98 (220)	6.70 (48)	6.52 (49)
T_{max} (h)	0.42 (0.08, 1.25)	0.50 (0.16, 10.00)	0.50 (0.08, 4.00)	0.67 (0.16, 3.00)
$t_{1/2}$ (h)	3.3 (323)	7.3 (653)	1.9 (56)	1.7 (75)

All values are reported as geometric mean (CV%) except for T_{max}, which is reported as median (range), and $t_{1/2}$ which is reported as arithmetic mean (CV%)
Abbreviations: AUC_{0-t}: area under the concentration-time curve from time 0 to the time of last measurable concentration; AUC_{0-inf}: area under the concentration-time curve from time 0 to infinity; C_{max}: maximum concentration; T_{max}: time to maximum concentration; $t_{1/2}$: half-life
(*Source: Adapted from Table 1B, page 16, Biostatistics Report for Study CL-155-18; and Table 1B, page 16, Biostatistics Report for Study CL-156-18; Module 5.3.1.4, NDA 216482 SDN 1, submitted Mar. 8, 2022*)

Plasma concentration-time profiles for MPA and MMF following administration of the test product and listed drug in studies CL-155-18 and CL-156-18 are shown in **Figure 3**.

Figure 3. Mean plasma concentration-time profiles in the linear scale for MPA (top graphs) and MMF (bottom graphs) following administration of the test product (ready-to-use MMF oral suspension) and listed drug (CellCept powder for oral suspension).



(*Source: Adapted from Figure 1, page 17, Biostatistics Report for Study CL-155-18; and Figure 1, page 17, Biostatistics Report for Study CL-156-18; Module 5.3.1.4, NDA 216482 SDN 1, submitted Mar. 8, 2022*)

PK data from Table 11. MPA PK parameters following administration of the test product (ready-to-use MMF oral suspension) and listed drug (CellCept powder for oral suspension) in studies CL-155-18 and CL-156-18.**Table 11**, **Table 12**, and **Figure 3** indicate that MPA and MMF PK is similar following administration of 1000 mg of the proposed ready-to-use oral suspension and the listed powder for oral suspension in healthy subjects under both fasted and fed conditions.

Notably, MMF PK parameters are not described in the approved labeling for CellCept. The labeling indicates that MMF can be measured systemically during IV infusion, but that after oral administration, MMF concentrations are below the limit of quantitation (0.4 mcg/mL). It is therefore purported that metabolism to MPA occurs pre-systemically after oral dosing. In studies CL-155-18 and CL-156-18, full concentration-time profiles for MMF were measured and PK parameters were estimable. This is likely due to the increased sensitivity of the bioanalytical method used to measure MMF concentrations. The lower limit of quantitation for detection of MMF was 0.050 ng/mL. Refer to the OCP Appendix in **Section 15.4** for additional details on the bioanalytical method used for detection of MMF and MPA.

BE determinations were based on statistical analysis of MPA from both studies. Given the four-period design of the study, the analyses used for BE determinations were dependent on calculations of intra-subject variability for the listed drug.

- For PK parameters determined to have low intra-subject variability ($s_{WR} < 29.4\%$), BE was determined using a typical unscaled average approach based on geometric mean ratios and associated 90% confidence intervals
- PK parameters determined to have high intra-subject variability ($s_{WR} \geq 29.4\%$), BE was determined using a reference-scaled approach.
    - Only applied to C_{max} in fasted study CL-155-18 ($s_{WR} = 0.295$).

This reviewer verified the Applicant's analyses and evaluated all PK parameters, including C_{max}, AUC_{0-t}, and AUC_{0-inf}, using a conservative unscaled BE approach. Results from the reviewer's analysis are shown above in **Table 10** and indicate that BE was met for all PK parameters in both studies CL-155-18 and CL-156-18.

The Applicant analyzed C_{max} using a reference-scaled approach based on a calculation of s_{WR} of 0.295, which is ≥ 0.294. BE criteria was also met for C_{max} using the reference-scaled approach based on a critical bound of $-0.03 < 0$, and a point estimate of the test/reference geometric mean ratio of 1.12, which falls in the 0.80 to 1.25 range.

Overall, data from studies CL-155-18 and CL-156-18 indicate that the proposed ready-to-use oral suspension is BE to the listed drug, CellCept powder for oral suspension, based on analyses of MPA PK.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. This is a 505(b)(2) submission. To rely on FDA's findings of safety and efficacy for the listed drug (CellCept powder for oral suspension, NDA 50759), the Applicant conducted two open-label relative bioavailability studies in healthy male adults: CL-155-18 and CL-156-18, conducted under fasting and fed conditions, respectively. Based on the results of studies CL-155-18 and CL-156-18, bioequivalence (BE) based on the Cmax, AUC0-t, and AUC0-inf of active metabolite mycophenolic acid (MPA) has been established between the proposed ready-to-use MMF oral suspension and the listed drug. Therefore, the Applicant can rely on FDA's previous findings of safety and effectiveness of CellCept.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. BE has been established between the proposed product and the listed drug. In addition, the proposed product will be available at a single strength of 200 mg/mL. Thus, administration

of different doses of MMF oral suspension will be based on the volume of administration. Dose-proportional exposure for MMF has previously been determined over the dose range.

Overall, the proposed dosing regimen, which is identical to that of the listed drug, is appropriate for adult and pediatric recipients of kidney, heart or liver transplants aged 3 months and older.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No new data has been submitted for subpopulations based on intrinsic patient factors. As BE has been established between the proposed product and the listed drug, the dosing recommendations for specific populations can rely on the approved U.S. labeling for CellCept (NDA 50759).

The current approved labeling for CellCept describes the pharmacokinetics of MPA in the context of renal impairment, postoperative delayed renal graft function, hepatic impairment, and sex. For kidney transplant patients with severe chronic impairment of the graft (GFR < 25 mL/min/1.73 m^2), it is recommended not to administer doses greater than 1 g twice daily and to carefully monitor these patients. No other alternative regimens or management strategies are recommended based on intrinsic patient factors.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No new data has been provided regarding drug-drug interactions. The current CellCept labeling also describes information derived from several drug-drug interaction studies, including those with cyclosporine, proton pump inhibitors, and drugs affecting glucuronidation, etc.

Information on food-drug interactions was provided as studies CL-155-18 and CL-156-18 compared the PK of MPA and MMF under fasted and fed conditions, respectively.

A comparison of PK data generated from studies CL-155-18 and CL-156-18 suggest that there is a food effect impacting exposure to MPA and MMF (**Table 11** and **Table 12**). In the fed state, MPA C_{max} is approximately 66 to 70% lower relative to that in the fasted state, while MPA AUC is approximately 21 to 25% lower in the fed state compared to the fasted state. The median T_{max} for MPA was also longer in the fed state (1.00 vs. 0.50 hours), although there is overlap in the observed ranges. For MMF, C_{max} is approximately 24 to 38% lower in the fed state compared to the fasted state, while AUC is approximately 20 to 40% higher in the fed state. MMF T_{max} did not appear to be affected in the presence of food.

Per the approved labeling for CellCept, food had no effect on the extent of absorption of MMF, based on MPA AUC, when administered at doses of 1.5 g twice daily to kidney transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food. The labeling

therefore recommends that MMF be administered on an empty stomach, although it may be administered with food, if necessary, in stable transplant patients. With respect to MPA, although little effects were observed for AUC, the magnitude in decrease of C_{max} appears to be greater than what is reported in the CellCept labeling. Nevertheless, MPA PK of the proposed product was determined to be BE to the listed drug under both fasted and fed conditions, irrespective of the magnitude of the food effect. Therefore, no new management strategy is required for food-drug interactions.

Is the bioanalytical method properly validated to measure MPA concentrations in plasma samples?

Yes. For details, see **Table 16** in the OCP Appendix in **Section 15.4**.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 13: Table of Studies to Demonstrate Bioequivalence

Study Number	Study Design	Objective	Treatment Duration / Follow up	Regimen / schedule / route	No. of patients enrolled
CL-155-18 (FASTING)	Open label, laboratory blind, randomized, four period, two treatment, two sequence, single dose, cross over study after fasting state	To compare rate and extent of absorption of MPA from single dose of TP vs LD To monitor safety and tolerability of single dose of TP in fasting healthy adult males	Single dose of test product or LD in each period Washout period of 10 to 13 days between TP and LD dosing Study Duration: 39 days	Single oral dose after overnight 10 hr fast. Test Product (TP): 1000 mg (5 ml x 200 mg/ml) MMF Oral suspension 200 mg/ml LD: 1000 mg single oral dose (5 ml x 200 mg/ml) CellCept oral suspension 200 mg/ml	48 healthy adult male subjects 20-43 yrs (Mean age: 31.7 yrs)
CL-156-18 (FED)	Open label, laboratory blind, randomized, four period, two treatment, two sequence, single dose, cross over study after fed state (high fat, high calorie breakfast)	To compare rate and extent of absorption of MPA from single oral of TP vs LD To monitor safety and tolerability of single dose TP in fed healthy adult males	Single doses of test product or LD in each period Washout period of 10 to 13 days between TP and LD dosing Study Duration: 36 days	Test Product: 1000 mg single oral dose (5 ml x 200 mg/ml) MMF Oral suspension 200 mg/ml LD: 1000 mg (5 ml x 200 mg/ml) CellCept oral suspension 200 mg/ml	48 healthy adult male subjects 20-42 yrs (Mean age: 31.7 yrs)

APPEARS THIS WAY ON ORIGINAL

7.2. Review Strategy

Section 505(b)(2) of the of the Federal Food, Drug, Cosmetic Act (FDC Act) allows for an NDA to contain " reports of investigations of safety and effectiveness…where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)."[16] This provision under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendment) allows for an expedited pathway for approval of alternate dosage forms, strengths, or formulations, for example, which improves access to additional safe and effective treatment options.

The Agency has formulated several guidances for industry to explain which applications qualify and the information needed to meet requirements for approval under the 505(b)(2) pathway. Essentially, a bridge to the LD needs to be established either through demonstration of comparative bioavailability or bioequivalence (BE).

For this 505(b)(2) MMF oral suspension NDA, the Applicant submitted two studies in healthy adult males under fasting (CL-155-18) and fed (CL-156-18) conditions to demonstrate BE of their product to the identified LD, CellCept for oral suspension 200 mg/ml. The dosage strength of MMF oral suspension is 200 mg/ml, the same as the LD, but the formulation is a ready-to-ingest liquid; whereas the LD is a powder that requires reconstitution by a pharmacist.

The CP reviewer re-analyzed the Applicant's studies and confirmed that the Applicant has met the criteria of BE for the test product (MMF ready-to-ingest oral suspension) to the LD (CellCept for oral suspension). As such, the Applicant can rely on the Agency's findings of safety and effectiveness for the LD. Please **section 6**, Clinical Pharmacology, for details of BE determination.

In regard to safety, a safety concern was identified during the review regarding possible adverse GI effects of this product related to the new combination of inactive ingredients. The theoretical concern arose that this new combination of inactive ingredients with MMF, which is already known to have adverse GI effects, may have a risk for GI intolerance, particularly in pediatric patients. The consequences of not tolerating an essential IS medication were considered serious for the intended pediatric transplant population who could develop allograft rejection and possible allograft failure from inadequate immunosuppression. DRTM consulted DPMH for assistance in reviewing this safety issue. Please see **Section 8.2.3** for an analysis of this safety issue.

Overall, the Applicant demonstrated BE of their proposed product to the LD, and is able to rely on the Agency's finding of safety and effectiveness for CellCept oral suspension. The identified

[16] *Guidance for Industry: Applications Covered by Section 505 (b) 2,* FDA Draft Guidance October 1999.

safety concern was addressed by including cautionary language to subsection 8.4, Pediatric Use, of product labeling. However, as noted in **section 3.1**, mycophenolate NDAs / ANDAs require a REMS with the submission and the Applicant failed to meet this essential REMS requirement for their NDA.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CL-155-18 (Fasting) and Study CL-156-18 (Fed)

The Applicant submitted a 505(b)2 NDA for MMF ready-to-ingest oral suspension 200 mg/ml. As stated in **section 1.2**, the 505(b)(2) pathway permits applicants to rely on the Agency's finding of safety and effectiveness for an approved product if bridging with comparative bioavailability or bioequivalence is established between the proposed drug product and LD. Therefore, for this 505(b)(2) NDA, no clinical studies with the new MMF oral suspension, other than the two BE studies, CL-155-18 and CL-156-18, were conducted.

The Applicant submitted two studies, one under fasting conditions and one under fed conditions, CL-155-18 and CL-156-18, to demonstrate bioequivalence of MMF ready-to-ingest oral suspension 200 mg/ml to the LD, CellCept for oral suspension 200 mg/ml.

Trial Design

The two studies submitted under this application are:
1. Study CL-155-18: an open label, laboratory-blind, randomized, four-period, two treatment, two-sequence, single dose crossover study evaluating a single 1000 mg oral dose (200 mg/ml x 5 ml) of MMF Oral suspension 200 mg/ml relative to the LD, CellCept for oral suspension 200 mg/ml, under fasting conditions. The study enrolled 48 healthy adult Indian males aged 18-45 years with a BMI between 18.5-29.9 kg/m^2. The primary objective was to compare the rate and extent of absorption of mycophenolic acid (MPA) from a single dose of MMF ready-to-ingest oral suspension at a dose of 1000 mg (200 mg/ml x 5 ml) under a fasting condition. Single doses were administered after an overnight fast of at least 10 hours. The washout period between periods of drug administration varied between 10 to 13 days, which was acceptable as the half-life of MPA is approximately 18 hours.

In period I, 45 subjects, in period II, 44 subjects, in period III, 42 subjects, and in period IV, 40 subjects, completed the study period. Forty subjects (40) were included in statistical analysis. Two subjects dropped out and six withdrew from the study. Including the washout period, total duration of the study was 39 days. Ninety-percent confidence interval (90% CI) around the geometric least square mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} were evaluated for bioequivalence (BE). Please see section 6, Clinical Pharmacology, for review of PK data and determination of BE.

2. Study CL-156-18: an open label, laboratory-blind, randomized, four-period, two treatment, two-sequence, single dose crossover study evaluating a 1000 mg oral dose (200 mg/mL x 5 ml) of MMF ready-to-ingest oral suspension relative to the LD, CellCept for oral suspension 200 mg/ml, under fed conditions. The study enrolled 48 healthy adult Indian males aged 18-45

years with a BMI between 18.5-29.9 kg/m^2. The primary objective was to compare the rate and extent of absorption of mycophenolic acid (MPA) from a single dose of MMF oral suspension 200 mg/ml at a dose of 1000 mg (200 mg/ml x 5 ml) under a fed condition. After an overnight fast of at least 10 hrs, a high calorie and high fat breakfast was given to the subjects. Subjects were administered a single dose of 1000 mg mycophenolate mofetil oral suspension (200 mg/ml x 5 ml) 30 minutes after the meal. The washout period between periods of drug administration varied between 10 to 13 days, which was acceptable as the half-life of MPA is approximately 18 hours.

In period I, 47 subjects, in period II, 44 subjects, in period III, 42 subjects, and in period IV, 42 subjects, completed the study period. Forty-two (42) subjects were included in the statistical analysis. Five subjects dropped out and one withdrew from the study. Including the washout period, total duration of the study was 36 days. Ninety-percent confidence interval (90% CI) around the geometric least square mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} were evaluated for bioequivalence.

Summary of PK Data

The CP reviewer notes that, "PK data for MPA, the pharmacologically active metabolite, and MMF, the parent drug were collected. In studies CL-155-18 and CL-156-18, BE determinations were made based on MPA data only from 40/48 (83.3%) and 42/48 (87.5%) subjects that completed all dosing periods, respectively." MMF PK parameters are not described in CellCept labeling. CellCept labeling indicates that MMF concentrations are below the level of quantitation and that metabolism to MPA occurs pre-systemically after oral dosing. The LD was approved in 1998, so bioanalytical methods may have been less sensitive at that time compared to the Applicant's methods.

The CP reviewer's analysis also suggests a possible food effect impact on the exposure of MPA and MMF. BE determinations were based on statistical analysis of MPA from both studies, so food effect of MPA PK will be described. The CP reviewer states, "In the fed state, MPA C_{max} is approximately 66 to 70% lower relative to that in the fasted state, while MPA AUC is approximately 21 to 25% lower in the fed state compared to the fasted state." The percentage of MPA C_{max} decrease appears to be greater than the reported food effect in CellCept labeling. Nonetheless, the MPA PK parameters met BE criteria under both fasting and fed conditions. This Clinical reviewer concurs with the CP reviewer that a food-drug interaction strategy is not required.

Please see **section 6**, Clinical Pharmacology, for details of PK data and determination of BE.

Conclusion

The CP reviewer's analysis of the study results and bioanalytical methods replicated the Applicant's results, and he concluded that the studies demonstrated bioequivalence of MMF ready-to-ingest oral suspension 200 mg/ml to CellCept for oral suspension 200 mg/ml. This

reviewer concurs with the CP reviewer's analysis and conclusion.

8.2. Review of Safety

Study CL-155-18 and Study CL-156-18 are the two studies submitted with this 505(b)(2) NDA to demonstrate bioequivalence of MMF ready-to-ingest oral suspension to CellCept oral suspension. These studies were not conducted to demonstrate safety and do not contain significant safety findings. Four adverse events (AEs) were reported during study CL-155-18, which are described **section 8.2.2**. These AEs were not serious and do not alter the safety evaluation for the proposed product. The Applicant refers to the safety findings of CellCept oral suspension identified in the labeling as applicable to its product MMF ready-to-ingest oral suspension. Under the 505(b)(2) pathway, the Applicant can rely on the Agency's previous finding of safety and effectiveness for the LD. CellCept oral suspension was approved October 1, 1998 and the labeling identifies the various risks associated with this product including infections, embryo-fetal toxicity, myelosuppression, and gastrointestinal complications.

However, a safety concern regarding the combination of inactive ingredients in this formulation that differs from the LD was identified and this issue is reviewed in **section 8.2.3**.

8.2.1. Safety Review Approach

Review of the Safety Database

[N/A]

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The four AEs reported for CL-155-18 were not reported according to a version of the MedDRA coding dictionary. If these studies were larger and necessary to determine clinical efficacy or safety, this issue would have been identified as a quality concern and relayed to the Applicant. As the studies were conducted to determine bioequivalence, the Applicant's method of reporting of AEs is accepted.

Categorization of Adverse Events:

Summary of AEs for Study CL-155-18

Total of four (4) adverse events were reported:

- Wound on dorsum of right foot, headache, fever, and itching on whole body.

Patients who experienced each of these AE's were withdrawn from the study.

None of these events were reported as serious and all resolved without sequelae by study

completion. For the AE of "itching on whole body" the event occurred after dosing of test product and was considered as probably related. This AE did not progress to a serious AE and the subject did not experience any oral cavity swelling or respiratory difficulty. This AE fully resolved after 13 days with an oral anti-histamine agent.

No deaths, serious AEs or significant AEs were reported during the study period.

Summary of AE's for CL-156-18:

No AEs reported for this study.

8.2.3. Analysis of Submission-Specific Safety Issues

Inactive Ingredient Safety Issue

(*Note: See **Section 5** of this review for a detailed Pharmacology/Toxicology discussion of the inactive ingredients.*)

Mycophenolate mofetil ready-to-ingest oral suspension and the LD, CellCept for oral suspension, both contain MMF as the active ingredient (AI); however, MMF ready-to-ingest oral suspension contains six inactive ingredients not present in the LD. These six inactive ingredients and their concentrations are shown in **Table 14**.

Table 14 : Inactive ingredients in Mycophenolate Mofetil Oral Suspension Not Present in the LD

Inactive Ingredients Not Present in LD	Concentration (mg/mL)	IIG* limit from FDA Database		Within IIG limits? Yes or No
		Maximum potency per unit dose (Route, dosage form)	Maximum daily exposure (Route, dosage form)	
(b) (4) Simethicone Emulsion	(b) (4)	350 mg (oral suspension)		Yes
Polysorbate 80		126 mg/ml (oral, solution)	150 mg (powder, for suspension)	Yes
Sodium Phosphate, Monobasic, Dihydrate		--	140 mg (oral, suspension)	Yes
Sodium Phosphate, Dibasic, Dihydrate		1030 mg/ 120 ml (oral suspension)	--	Yes
Glycerin		23520 mg (oral, suspension)	31536 mg (oral, solution)	Yes
Propylparaben	0.560	100 mg (oral, solution)	17 mg (oral, solution)	Yes

IIG: Inactive Ingredient Guide or Inactive Ingredient Database (IID): The IID provides information on inactive ingredients in FDA-approved drug products. An inactive ingredient, or excipient, is any component of a drug product other than an active ingredient (21 CFR 210.3(b)(8) and 314.3(b)).Source: Clinical Reviewer formulated Table, adapted from Applicants Table 2- Qualitative and Quantitative Composition, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Module 2.7.1

Although each of these six inactive ingredients are found in the FDA inactive ingredient database (IID) and are within the highest dose amount used in approved products for that

excipient, the safety and tolerability this combination of inactive ingredients with the active ingredient mycophenolate mofetil are not known. The combination of these inactive ingredients along with MMF has the potential to cause adverse gastrointestinal (GI) effects, particularly in pediatric patients, for the following reasons:

- Four of the six inactive ingredients (propylparaben, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, simethicone, and glycerin) can independently cause GI adverse effects
- 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 MMF's GI adverse effects, which is noted in the Pediatrics sub-heading in Section 6.1 of LD labeling:

  "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 of the proposed drug product may lead to poor medication adherence, dosing interruptions and inconsistent immunosuppression, which could affect graft function and survival. GI adverse events such as nausea, vomiting and diarrhea may also potentially interfere with the absorption of other concomitant immunosuppressants, mainly the CNI (tacrolimus in most patients). The mycophenolate mofetil ready-to-ingest oral suspension is a pediatric-friendly dosage form, and the proposed product is likely to be used in the pediatric kidney, heart, or liver transplant populations. The consequences of GI intolerance could be more severe for these subgroups.

DRTM relayed this concern to the Applicant in the Filing Review Issues Identified Letter to the Applicant dated May 25, 2022 (see DARRTS entry May 25, 2022) and requested a justification supporting the GI tolerability of the proposed dosage form, particularly in a pediatric population.

The Applicant submitted their response to DRTM's concern regarding the GI tolerability of the inactive ingredients in the proposed product formulation for a pediatric population on August 23, 2022. The Applicant provided information supporting the safety of each inactive ingredient, noting that each inactive ingredient is "generally recognized as safe (GRAS)" (under 21 CFR 170.35) with levels within exposures listed in the IID for each inactive ingredient. The Applicant did not provide adequate justification that the combination of the inactive ingredients in this drug product would not lead to adverse GI tolerability.

DRTM consulted DPMH for advice on how to address this issue because the GI tolerability of

the proposed formulation was of particular concern in the pediatric subgroup of the kidney, heart and liver transplant populations. The following information is obtained from the DPMH consultation review by Dr. Shamir Tuchman, MD (see DARRTS entry 11/18/22 for final review), which contains a detailed analysis of the potential exposures of the inactive ingredients in pediatric patients 3 months and older at either ends of the growth spectrum:

> **III. Review of Inactive Ingredients**
> ... 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 (listed drug) 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.
>
> 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., 5th percentile) 3-month old patient.
> 2) The highest weight and height (e.g., 95th 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 95th %ile).
> 4) The tallest pediatric patient (e.g., 95th 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 15.**

Table 15: Potential Inactive Ingredient Exposures in the Proposed Pediatric Allogenic Kidney, Heart or 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 g BID) for an adolescent patient at the 95th Percentile for height	BSA daily r Dose patie 95th P for
Simethicone						(b) (4)

Appears this way in original

Polysorbate 80	[redacted] (b) (4)					
Sodium Phosphate, Monobasic, Dihydrate						
Sodium Phosphate, Dibasic, Dihydrate						
Glycerin						
Propylparaben	0.560	8.4 mg (0.14 mg/kg)	1.5 mL (0.84 mg) 0.19 mg/kg	2.1 mL (1.18 mg) 0.17 mg/kg	10 mL (5.6 mg) 0.1 mg/kg	5.4 m 0.15

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 assuming a 60 kg adult weight. Most of the potential excipient exposures 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 [redacted] (b) (4) less than that with approved drug products containing simethicone as an active ingredient and at least [redacted] (b) (4) lower than 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 [redacted] (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 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] …. 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…. 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).

Clinical Reviewer's Summary:

Overall, the safety of this combination of inactive ingredients is not known because a safe pediatric threshold for each inactive ingredient is not known, and this formulation has not been clinically tested in a pediatric population. This theoretical safety concern cannot be addressed with the data included in this 505(b)(2) NDA submission, which contains the required bioequivalence data to bridge the test product to the LD.

However, as described by the DPMH reviewer Dr. Shamir Tuchman, 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 (adjusted for a standard 60 kg adult body weight). 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.[17,18] Lastly, mycophenolate mofetil, as an active ingredient, is also known to have potential GI tolerability adverse effects. Post-approval safety monitoring to assess the GI tolerability of the proposed formulation in the intended population would be difficult to delineate between the active ingredient and the inactive ingredients, given the overlap in adverse GI effects.

Clinical Recommendation:

The theoretical risk persists for possible worse GI tolerance with use of this product compared to the LD. This theoretical safety concern was thoroughly investigated by the Clinical team who consulted OND Policy and DPMH for guidance and advice. Further discussions with DPMH and members of the entire review team, and with the Director of OII, Dr. Julie Beitz, led to the recommendation to provide cautionary language in subsection 8.4 of labeling. The language proposed would caution prescribers about the theoretical possibility that use of this product may be associated with GI intolerance because of the novel inactive ingredient combination. There is precedent for this approach with at least one other recently approved product, THYQUIDITY. This reviewer concurs with the recommendation to address the theoretical concern of adverse GI tolerability of the proposed formulation related to the combination of inactive ingredients through cautionary language in subsection 8.4 of labeling.

The following language was proposed for inclusion in subsection 8.4 of labeling:

> *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."*

8.3. Statistical Issues

N/A

8.4. Conclusions and Recommendations

The Applicant submitted a 505 (b)(2) NDA for MMF ready-to-ingest oral suspension 200 mg/ml, which qualifies as a new dosage form of mycophenolate mofetil. The approved product, CellCept for oral suspension, is a powder that requires reconstitution to a liquid by the pharmacist. The 505(b)(2) pathway permits applicants to rely on the Agency's finding of safety

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

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

and effectiveness for an approved product if bridging with comparative bioavailability or bioequivalence is established between the proposed drug product and the approved product (e.g., the LD). The Applicant submitted two studies to demonstrate bioequivalence, one under fasting (Study CL-155-18) and one under fed conditions (Study CL-156-18). The studies demonstrated BE of the proposed product to the LD, allowing the Applicant to rely on the Agency's finding of safety and effectiveness for the LD (see **section 6**, Clinical Pharmacology, for details of BE analysis).

In addition to BE determination, this NDA requires a risk evaluation and mitigation strategy (REMS). A required component of all mycophenolate applications since 2008 is a REMS to mitigate the risk of embryo-fetal toxicity, first trimester pregnancy loss, and congenital malformations associated with the use of mycophenolate products. In 2012, the Agency approved a shared system REMS (SS REMS) for sponsors of mycophenolate products. Applicants of mycophenolate product NDAs or ANDAs are required to submit an acceptable REMS prior to approval. At this time, the Applicant has not fulfilled this requirement despite clear communication from the Agency regarding this requirement. See **section 12 REMS** for details on the Mycophenolate REMS program and interactions with the Applicant. Consequently, the Applicant will receive a CR letter for this NDA. A CR letter indicates that the review cycle for an application is complete and that the application is not ready for approval.[19]

In addition, a unique safety concern was identified for MMF ready-to-ingest oral suspension. The theoretical concern arose that this formulation contains six inactive ingredients which may contribute to adverse GI effects, and MMF, the active ingredient, is already known to have adverse GI effects. GI intolerance of this product, an immunosuppressant that is an essential component of the IS regimen, particularly in pediatric transplant patients, the intended target population, may result in inconsistent immunosuppressant exposure. Inconsistent immunosuppression may result in serious consequences including allograft rejection or possible allograft failure. DPMH assisted in the review of this safety concern and details are discussed in **section 8.2.3**. Though this theoretical risk for possible worse GI tolerance with use of this product is not addressed by the two bioequivalence studies, the safety concern was not considered critical to the approvability of this 505(b)(2) NDA.

The team deliberated on the best way to address this concern. A post-marketing study was considered. However, the team decided a post marketing safety study would be difficult to interpret because the etiology of the adverse GI tolerability would be difficult to decipher between the active ingredient versus the inactive ingredients.

After discussions with DPMH, members of the entire review team, and with the Director of OII, Dr. Julie Beitz, this reviewer agrees with DPMH's recommendation to provide cautionary language in subsection 8.4 of labeling. The proposed language would caution prescribers about

[19] https://www.fda.gov/drugs/laws-acts-and-rules/complete-response-letter-final-rule

the theoretical possibility that use of this product may be associated with GI intolerance because of the novel inactive ingredient combination. DPMH noted that a similar safety issue for another recently approved product was also addressed through labeling.

The following language is proposed for inclusion in subsection 8.4 of labeling:

> *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."*

In summary, this reviewer agrees that the two studies submitted with this 505(b)(2) NDA establish BE between the proposed drug product, MMF ready-to-ingest oral suspension, and the LD. Thus, the Applicant can rely on the Agency's finding for safety and effectiveness of CellCept oral suspension for their NDA. However, a required component of this NDA, which is for a mycophenolate product, is a REMS. The Applicant did not submit a letter of authorization to cross-reference the drug master file for the established mycophenolate SS REMS or alternatively, submit a REMS proposal to the current NDA for FDA's review, which is an approvability issue. The safety concern of possible adverse GI tolerability of this product related to the novel combination of inactive ingredients is addressed by adding the proposed cautionary language in subsection 8.4 of labeling.

Ultimately, a CR letter will be issued for this NDA because the Applicant failed to meet the mycophenolate REMS requirement.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not necessary for this application.

10. Pediatrics

The Applicant aims to seek approval for the same indications as the LD for this 505(b)(2) NDA, which includes pediatric kidney, heart and liver transplant recipients 3 months and older. According to the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of safety and effectiveness of the product in pediatric patients unless this requirement is waived, deferred or inapplicable. In prior meetings with the Applicant, the Agency confirmed that the Applicant's 'ready-to-ingest' oral suspension qualifies as a 'new dosage form' because prior approved oral suspensions are manufactured as powders that require reconstitution to oral suspension by a pharmacist. Therefore, this NDA triggers PREA. The Applicant submitted their iPSP prior to NDA submission, which was finalized on March 8, 2021. The agreed upon iPSP included a partial waiver for pediatric kidney transplant recipients less than 3 months old and a deferral for studies in pediatric heart and liver transplant recipients because the LD was not approved in these populations at that time.

CellCept was approved for use in pediatric heart and liver transplant recipients 3 months and older on June 6, 2022. The Agency verified that the Applicant intended to seek approval for all of the same indications as the LD, including pediatric heart and liver transplant recipients 3 months and older. Therefore, the agreed upon iPSP was no longer current with the most recent LD labeling. DRTM presented the application to PeRC on November 29, 2022 to update the pediatric study plan. DRTM proposed the Applicant be granted a partial waiver for studies in pediatric kidney, heart, and liver transplant recipients less than 3 months old because small numbers of patients in these populations make such studies impractical or impossible. PeRC accepted DRTM's proposal. The Applicant will be granted a partial waiver for pediatric kidney, heart, and liver transplant recipients less than 3 months old and with approval for pediatric kidney, heart, liver transplant recipients 3 months and older, once REMS requirement is fulfilled.

This 505(b)(2) NDA for MMF ready-to-ingest oral suspension requires a REMS because of the embryo-fetal risk, first trimester pregnancy loss, and risk of congenital malformations associated with the use of mycophenolate mofetil. A SS REMS for mycophenolate products was established on September 25, 2012. See **section 12 REMS** for details on the Mycophenolate REMS program and interactions with the Applicant. The Applicant has not fulfilled the REMS requirement at the time of this review.

During the review a safety concern was also identified regarding the adverse GI tolerability of MMF ready-to-ingest oral suspension due to the combination of inactive ingredients that differs from the LD. Because MMF ready-to-ingest oral suspension is a pediatric friendly dosage form, the Clinical team considered pediatric populations at particular risk for possible GI intolerance of this formulation. DRTM consulted DPMH to assist in reviewing and addressing this concern. See **section 8.2.3** for details on this safety issue and excerpts from DPMH's review.

Overall, the safety of this combination of inactive ingredients is not known because a safe pediatric threshold for each inactive ingredient is not known, and this formulation has not been clinically tested in a pediatric population. This theoretical safety concern cannot be addressed with the data included in this 505(b)(2) NDA submission, which contains the required bioequivalence data to bridge the test product to the LD. This safety concern was not considered an approvability issue but was considered important to inform prescribers.

Interdisciplinary deliberations, which included DPMH members, determined that adding cautionary language to subsection 8.4, Pediatric Use, of labeling was an acceptable resolution. The proposed language would caution prescribers about the theoretical possibility that use of this product may be associated with GI intolerance because of the novel inactive ingredient combination. DPMH noted that a similar safety issue for another recently approved product was also addressed through labeling.

The following language is proposed for inclusion in subsection 8.4 of labeling:

> *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. Labeling Recommendations

11.1. Carton/Container Labeling

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) reviewed the Applicant's proposed carton and container labeling and noted statements that were not acceptable from a medication error perspective. Specifically, DMEPA 1 suggested that the statements, (b) (4) [redacted]" be removed as they are redundant. DMEPA 1 also suggested the name on the carton and container be replaced with the acceptable proprietary name, (b) (4) These revisions were relayed to the Applicant on December 14, 2022 and agreed upon by the Applicant on December 20, 2022.

Office of Prescription Drug Promotion (OPDP) also reviewed the carton/container labeling and had no comments.

11.2. Prescription Drug Labeling

Prescribing information

11.2.1. Proprietary Name

Liqmeds previously submitted the proposed proprietary name, [(b) (4)]*** on March 29, 2022. However, under NDA 216482 on June 23, 2022, Division of Medication Error Prevention and Analysis (DMEPA found the name, [(b) (4)]*** unacceptable due to orthographic similarities and shared product characteristics with the proprietary name, [(b) (4)].[20]

Thus, Liqmeds submitted the name [(b) (4)] for review on September 7, 2022. Intended pronunciation: [(b) (4)] The Applicant's proposed proprietary name MMF ready-to-ingest oral suspension, [(b) (4)] has been conditionally approved. This name was reviewed by the DMEPA), who concluded that the name is acceptable (DMEPA review dated November 17, 2022).

11.2.2. Proposed changes to CellCept Oral Suspension USPI Pertaining to the Clinical Discipline

Clinical Reviewer' Note: For this 505(b)(2) NDA, the Applicant can rely on approved labeling for the LD as they demonstrated BE to the LD. The Applicant initially submitted a CellCept USPI that did not include the most recently approved pediatric heart and pediatric liver transplant indications as of June 6, 2022. The Agency verified with the Applicant their intent to seek approval for all of the same indications as CellCept oral suspension, and the Applicant resubmitted the most updated CellCept oral suspension USPI on October 11, 2022.

The Agency proposed an addition to subsection 8.4, Pediatric Use. The Agency deleted several sections not relevant to the proposed product including 'Recent Major Changes' and 'Dosage and Administration' in Highlights, subsection 2.6, and subsection 12.3. These specific revisions are highlighted below. The Office of Product Quality (OPQ) submitted product specific labeling suggestions to the Applicant, and this reviewer refers the reader to the OPQ review for details regarding their labeling suggestions (see DARRTS entry 11/23/22 for OPQ Review).

The OPDP and Division of Medical Policy Programs (DMPP) were also consulted to review the PI and no significant changes were suggested for the PI. Please see the OPDP/DMPP combined review in DARRTS entry 11/28/22.

High level labeling recommendations related to the Clinical sections of the PI are discussed below. These recommendations were accepted by the Applicant in their response to our labeling suggestions on November 21, 2022.

[20] McMillan, T. Proprietary Name Review for [(b) (4)] (NDA 216482). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JUN 23. PNR ID No. 2022-1044724514

The following proposed amendments have not been finalized at the time of the review. The labeling will not be made public as the NDA will receive a complete response. Once the application receives an approval determination, labeling will be finalized.

11.2.2.1. Subsection 8.4 Pediatric Use

The following cautionary language highlighting the possible adverse GI tolerability of the novel combination of inactive ingredients for this product is suggested under subsection 8.4, Pediatric Use, to address the safety concern of possible adverse GI tolerability of MMF oral suspension discussed in section 8.2.4 of this review. Subsection 8.4 was considered the appropriate section for this language as this population was considered at higher risk for experiencing this adverse effect. Because the concern is theoretical and is not supported by post-marketing or clinical data at this time, the Agency did not consider it warranted to add this information to section 5, Warnings & Precautions.

The following language was proposed to be included below the Heart Transplant and Liver Transplant paragraph in subsection 8.4 Pediatric Use:

> *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.*

The Applicant accepted this addition in their response to our labeling revisions on November 21, 2022.

11.2.2.2. Highlights: Recent Major Changes

This section was deleted because this is an NDA and the information is carried over from the LD labeling but is not relevant for this application:

(b) (4)

11.2.2.3. Highlights: Dosage and Administration

This section was edited for clarity and for consistency with presentation in the full prescribing information (FPI). The phrase (b) (4) so both were deleted. ~~Maximum~~

~~daily dose~~ was added to the pediatric section of the table for consistency with the FPI.

(b) (4)

----------DOSAGE AND ADMINISTRATION----------

(b) (4)

11.2.2.4. Subsection (b) (4)

(b) (4)

Information regarding storage of the suspension is in subsection 16 (b) (4)

(b) (4)

11.2.2.5. Subsection 12.3 Pharmacokinetics, Metabolism

The Applicant proposed adding the following language to subsection 12.3, *Metabolism*:

(b) (4)

(b) (4)

11.2.3. Medication Guide (MG)

The OPDP and Division of Medical Policy Programs (DMPP) also reviewed the MG and suggested revisions to simplify wording, clarify concepts, remove unnecessary information, and to ensure it was free of promotional language. They ensured the MG met Regulations as specified in 21 CFR 208.20 and the criteria in the July 2006 FDA Guidance, *Useful Written Consumer Information*[21]. Please see the OPDP/DMPP combined review entered in DARRTS 11/29/2022. The Applicant accepted these revisions in their response to FDA's labeling recommendations submitted on December 20, 2022.

12. Risk Evaluation and Mitigation Strategies (REMS)

12.1. Regulatory History of REMS for Mycophenolate Products

Section 505-1 of the FDC Act[22] was created under the Food and Drug Administration Amendments Act (FDAAA) of 2007.[23] It authorizes the Agency to require a REMS, if the Agency becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. In September 2008, the Agency issued REMS notification letters to Roche (CellCept) and Novartis (Myfortic, mycophenolic acid) requiring a REMS for their products because post-marketing reports showed exposure to mycophenolate during pregnancy was associated with increased risks of first trimester pregnancy loss and congenital malformations. Roche and Novartis each submitted a proposed REMS in December 2008. Between 2009 to 2011, the Agency arranged meetings with mycophenolate sponsors to develop a single shared REMS (SS REMS) for all mycophenolate products. On September 25, 2012, the Agency approved the SS Mycophenolate REMS program. The Mycophenolate REMS is a shared system that includes CellCept, Myfortic and generic mycophenolate products.

The Mycophenolate SS REMS was "designed to focus on educating prescribers and patients about the importance of making informed decisions based on the… individualized potential maternal benefits/risks and fetal risks…"[24] The current goal of the Mycophenolate REMS is to

[21] FDA Guidance, *Useful Written Consumer Information,* July 2006: https://www.fda.gov/media/72574/download.
[22] Section 505-1(a) of the FD&C Act.
[23] Public Law 110-85.
[24] Division of Risk Management. Final REMS review for NDA 50-722(CellCept), NDA 50-791 (Myfortic), all generic Mycophenolate products. Date: July 23, 2012.

mitigate the risk of embryofetal toxicity associated with the use of mycophenolate during pregnancy by[25]:

1. Educating healthcare providers on the following:

- The increased risks of miscarriage and birth defects associated with exposure to mycophenolate during pregnancy.
- The need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate.
- The need to report pregnancies to the Mycophenolate Pregnancy Registry.

2. Informing females of reproductive potential who are prescribed mycophenolate about:

- The increased risks of pregnancy loss (miscarriage) and birth defects.
- The importance of pregnancy prevention and planning when taking mycophenolate.

The specific REMS elements of the original REMS included a medication guide (MG), elements to assure safe use (ETASU) and a timetable for submission of assessments. The ETASU consist of:

- Healthcare provider training for those who prescribe mycophenolate
- A centralized pregnancy registry of females who become pregnant and consent to participate maintained by mycophenolate sponsors

The timetable for submission of assessments to determine if the REMS is meeting its objectives was set at every 6 months for the first year of approval and annually thereafter.

The SS REMS underwent a major modification on November 13, 2015 and the medication guide was removed as an element. The modified REMS elements currently include ETASU and a timetable for submission of assessments. Another modification was approved by the Agency in August 2019 after the 5-year (2017) and 6-year (2018) assessment data indicated the goals of the REMS were not being met. Components of ETASU related to prescriber outreach, promoting REMS awareness, streamlining content of REMS materials, and expanding provider training options were amended and approved in August 2019.

12.2. Regulatory Correspondence with Applicant During Review Cycle

The Applicant has failed to meet the REMS requirement for this 505(b)(2) NDA for MMF ready-to-ingest oral suspension by the time of this review.

The following key communications to the Applicant providing them an opportunity to comply are highlighted below:

- On September 14, 2022, the Agency reissued an information request, regarding a

[25] "Welcome to Mycophenolate REMS" http://www.mycophenolaterems.com. Date accessed: 18 Nov 22

REMS requirement for your NDA submission.

- On September 28, 2022, the Applicant submitted a request for an extension to respond to the information request.
- On October 5, 2022, the Agency encouraged the Applicant to submit a letter of authorization to cross-reference drug master file for Mycophenolate SS REMS, or alternatively, submit a REMS proposal to their NDA as soon as feasible.
- On October 7, 2022, the Applicant emailed questions for clarification.
- On October 17, 2022, the Agency responded to the Applicant's questions. Key aspects of this correspondence are included here:
    - "We will grant an extension for you to submit a proposed REMS; however, in order to have sufficient time to review your proposal by the PDUFA goal date, we would need your submission by November 4, 2022. Submission after that date may have implications on the review and PDUFA goal date. The adequacy of the information in your future submission will be a review issue
    - "…all REMS submissions must be submitted in section 1.16 of the eCTD. We reiterate that an acceptable REMS is required for your product, and your NDA as submitted is lacking a required component for a mycophenolate mofetil application.

The Applicant did not submit any further correspondence regarding the REMS by the stated deadline or by the completion this review. The application is not approvable without an acceptable REMS.

13. Postmarketing Requirements and Commitment

There are no postmarketing requirements and commitments for this sNDA.

APPEARS THIS WAY ON ORIGINAL

14. Division Director (Clinical)/Signatory Comments

This Deputy Division agrees that the two studies submitted with this 505(b)(2) NDA, CL-155-18 and CL-156-18, establish BE between the proposed drug product, MMF ready-to-ingest oral suspension, and the LD and the Applicant can rely on the Agency's finding for safety and effectiveness of CellCept oral suspension for their NDA. The safety concern of possible adverse GI tolerability of this product related to the novel combination of inactive ingredients is adequately addressed by adding the proposed cautionary language in subsection 8.4 of labeling.

The Applicant did not submit a letter of authorization to cross-reference the drug master file for the established mycophenolate SS REMS or, alternatively, submit a REMS proposal to the current NDA for FDA's review, which is a required component of this NDA. Therefore, a CR letter will be issued for this NDA because the Applicant failed to meet the mycophenolate REMS requirement.

15. Appendices

15.1. References

1. Center for Drug Evaluation and Research. (2022, January 26). Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions. U.S. Food And Drug Administration: https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-approved-drug-products-search-frequently-asked-questions#purpose
2. Environmental Protection Agency (June 2006): https://www.epa.gov/sites/default/files/2015-04/documents/glycolethers.pdf
3. FDA Draft Guidance, October 1999. *Guidance for Industry: Applications Covered by Section 505 (b) 2.*
4. FDA Guidance, January 2001. *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence.*
5. FDA Guidance, July 2006. *Useful Written Consumer Information*: https://www.fda.gov/media/72574/download.
6. Medicines Complete (14 Oct 2022): https://www-medicinescomplete-com.fda.idm.oclc.org/#/content/excipients/1001941909
7. Mylicon, Phazyme (simethicone) dosing, indications, interactions, adverse effects, and more. (2019, September 28): https://reference.medscape.com/drug/mylicon-phazyme-simethicone-342005#0
8. OSMOPREP USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021892s014lbl.pdf
9. OTC labeling for Simethicone found under Mylicon, Gas X at https://dailymed.nlm.nih.gov
10. Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use. (22 Oct 2015). *Committee for Medicinal Products for Human Use (CHMP):* https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-methyl-propylparaben-excipients-human-medicinal-products-oral-useen.pdf
11. Mycophenolate Shared REMS: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-fda-approves-single-shared-risk-evaluation-and-mitigation-strategy-rems

15.2. Financial Disclosure

Form 3454 was submitted on March 8, 2022, and states that Amit Singh Chouhan, Regulatory Affairs Manager of Liqmeds Worldwide Limited has not entered into any financial agreement with the listed clinical investigators, (b) (6) and (b) (6), and neither investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

Covered Clinical Study (Name and/or Number): CL-155-18 and CL-156-18

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

Studies CL-155-18 and CL-156-18

The Applicant submitted results from studies CL-155-18 and CL-156-18 conducted under fasting and fed conditions, respectively. Both studies were open-label, randomized, four-period, two-treatment, two-sequence, single-dose crossover studies evaluating a 1000 mg oral dose (5 mL x

200 mg/mL) of the test product (MMF ready-to-use oral suspension) relative to the listed drug (CellCept powder for oral suspension).

Primary Objective

The primary objective of both studies was to compare the rate and extent of absorption of MPA following single-dose administration of 1000 mg of MMF ready-to use oral suspension or MMF powder for oral suspension (5 mL x 200 mg/mL) under fasting (CL-155-18) or fed (CL-156-18) conditions.

Study Design

Studies CL-155-18 and CL-156-18 were both open-label, laboratory-blind, randomized, four-period, two-treatment, two-sequence crossover studies that evaluated a single 1000 mg oral dose of each product (5 mL x 200 mg/mL). The order of receiving the listed and test products for each subject during each period was determined based on a randomization schedule. In study CL-155-18, doses were administered after an overnight fast of at least 10 hours. In study CL-156-18, doses were administered 30 minutes after serving a high-fat, high-calorie breakfast. The standardized meal derived approximately 150, 250, and 500-600 calories from protein, carbohydrates, and fat, respectively.

After dosing, PK samples in each study period were collected up to 72 hours post-dose. Per the approved labeling for CellCept, the mean apparent half-life of MPA following oral administration is approximately 17.9 hours. Thus, the sampling schemes would collect data through approximately 4 half-lives post-dose. Across both studies, a washout period of 10 to 13 days separated each dosing period, which appears sufficient for complete drug clearance based on the mean apparent half-life of MPA.

Inclusion and Exclusion Criteria

Both studies aimed to enroll healthy adult males aged 18 to 45 with a body mass index (BMI) between 18.5 and 29.9 kg/m^2.

Subjects were required to abstain from tobacco-containing products, grapefruit and grapefruit-containing products, and xanthine-containing food products. Subjects were also instructed not to take any prescription or OTC medications for at least 14 days prior to study start and during the study.

Patient Disposition and Demographics

Both studies enrolled 48 subjects aged between 20 and 43 years (CL-155-18) or 20 and 42 years (CL-156-18), with BMI between 20.1 and 28.9 kg/m^2 (CL-155-18) or between 19.1 and 29.2 kg/m^2 (CL-156-18). The following table shows the number of subjects dosed in each study period and the number of subjects that completed each study period:

	Number of subjects dosed in each study period			
	Period I	Period II	Period III	Period IV
CL-155-18	47	44	42	41
CL-156-18	47	44	42	42
	Number of subjects that completed each study period			
	Period I	Period II	Period III	Period IV
CL-155-18	45	44	42	40
CL-156-18	47	44	42	42

(*Source: Adapted from the clinical study reports for CL-155-18 and CL-156-18, NDA 216482 SDN 1, submitted Mar. 8, 2022*)

In study CL-155-18, 4 subjects were withdrawn due to AEs, 2 subjects were withdrawn due to positive test for drugs of abuse, and 2 subjects withdrew consent for participation. In study CL-156-18, 5 subjects withdrew consent for participation, and 1 subjects was withdrawn due to positive test for drugs of abuse.

In study CL-155-18, concomitant medications were administered to 4 subjects for treatment of AEs, the same 4 subjects who were withdrawn as noted above. No concomitant medications were taken or administered in study CL-156-18.

PK Sample Collection

PK samples for evaluation of MMF and MPA PK were collected up to 72 hours post-dose at the following time points: pre-dose, and post-dose at hours 0.08, 0.16, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72.

PK Analysis

PK parameters were analyzed using a non-compartmental method. The Applicant's method for determining BE were based on MPA PK and were dependent on calculations of intra-subject variability for the listed drug.

- For PK parameters determined to have low intra-subject variability ($s_{WR} < 29.4\%$), BE was determined using a typical unscaled average approach based on geometric mean ratios and associated 90% confidence intervals
- PK parameters determined to have high intra-subject variability ($s_{WR} \geq 29.4\%$), BE was determined using a reference-scaled approach.
    - Only applied to C_{max} in fasted study CL-155-18 ($s_{WR} = 0.295$).

PK analysis was only conducted in subjects who completed all four period of the study, including 40/48 (83.3%) subjects in study CL-155-18, and 42/48 (87.5%) subjects in study CL-156-18.

The reviewer's analysis followed a similar method as that conducted by the Applicant, including non-compartmental analysis of PK parameters. BE was calculated using a conservative unscaled approach for all PK parameters with BE concluded if the geometric mean ratio and associated 90% confidence interval fell within the 80 to 125% range.

Validation and Bioanalytical Report Review

For studies CL-155-18 and CL-156-18 plasma concentrations of mycophenolate mofetil (MMF) and mycophenolic acid (MPA) were determined with following method:

Table 16. Method Validation Report BL-MVR-227 – Simultaneous Estimation of Mycophenolate Mofetil and Mycophenolic Acid in Humans Plasma Containing K_2EDTA as an Anticoagulant by using LC-MS/MS Method (Alkem Laboratories Ltd.)

Bioanalytical method review summary	Method validation adequate to support results in study CL-155-18 and CL-156-18		
Method description	Sample extraction from K_2EDTA plasma via solid-phase extraction; separation and detection using liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS)		
Materials used for calibration curve, QCs, & concentration	Mycophenolate mofetil, Lot #R090D0, U.S. Pharmacopeia Mycophenolate sodium, Lot #F030Q0, U.S. Pharmacopeia		
Validated assay range	MMF: 0.050 to 25.000 ng/mL in human plasma MPA: 100.000 to 50,000.000 ng/mL in human plasma		
Source & lot of internal standard reagents	MMF internal standard (mycophenolate mofetil-d_4 HCl), Batch #CS-MMD-498, (b) (4) MPA internal standard (^{13}C-mycophenolic acid-d_3), Batch #USM-166-10546, (b) (4)		
Regression model & weighting	Linear regression with $1/x^2$ weighting		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision from accepted validation runs	No of standard calibrators from LLOQ to ULOQ	10	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ MMF MPA	 -2.2 to 1.1% -5.9 to 3.7%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ MMF MPA	 ≤ 5.0% ≤ 4.5%	Yes
QCs performance during accuracy & precision from accepted validation runs	Cumulative accuracy (%bias) in 4 QCs MMF MPA	 1.1 to 5.3% -3.0 to 5.9%	Yes
	Inter-batch %CV MMF MPA	 ≤ 7.6% ≤ 6.0%	Yes

Selectivity & matrix effect	Blank human plasma from six different lots was evaluated. In all cases, no interference was observed at the retention times of MMF, MPA and their internal standards. Post-extracted blank matrix samples spiked with MMF, MPA, or internal standards at the low and high QC were within 20% bias of pure solutions, demonstrating no matrix effects.	Yes
Extraction recovery	Percent recovery was 77.3% for MMF, 87.8% for the MMF internal standard, 85.2% for MPA, and 93.8% for the MPA internal standard.	Yes
Interference & specificity	Quantification of MMF and MPA at the LLOQ was not affected in the presence of possible concomitant medications including ibuprofen, acetaminophen, diclofenac, ranitidine, cetirizine, and domperidone	Yes
Hemolysis effect	Six replicates of low QC and high QC samples were prepared in one lot of hemolyzed plasma. Hemolysis had no effect on the quantitation of MMF (%Bias ≤ 13% and %CV ≤ 4.7%) or MPA (%Bias ≤ 3.4% and %CV ≤ 2.5%)	Yes
Lipemic effect	Six replicates of low QC and high QC samples were prepared in one lot of hyperlipidemic plasma. Hyperlipidemia had no effect on the quantitation of MMF (%Bias ≤ 4.7% and %CV ≤ 2.6%) or MPA (%Bias ≤ 3.4% and %CV ≤ 2.8%)	Yes
Dilution linearity	Accuracy and precision demonstrated for MMF at 40 ng/mL and MPA at 80,000 ng/mL with 4X dilution factor	Yes
Bench-top/process stability	Bench top stability for MMF and MPA established for up to 6 hours and 53 minutes at room temperature and at ice bath temperature. Processed sample stability ("autosampler stability") established for MMF and MPA for up to 189 hours and 11 minutes at 5 °C.	Yes
Freeze-Thaw stability	Established for up to five freeze-thaw cycles at -70 °C	Yes
Long-term storage	Established stability for MMF and MPA in human plasma at -70 °C for 349 days. Stability also established for MPA in human plasma at -20 °C for 349 days. Stability for MMF at -20 °C was not established as acceptance criteria were not met. This is acceptable as all samples were stored at -70 °C prior to analysis.	Yes
Carry over	Carryover was found to be < 20% of LLOQ based on analysis of blank matrix samples immediately following the highest calibration standard	Yes

Method performance in study CL-155-18		
Assay passing rate	• A total of 67 runs were performed in study CL-155-18, including 58 original runs, 5 repeat runs for batch or individual samples, and 4 runs for ISR recreated as new runs • 1 run was reinjected due to instrument failure and passed acceptance criteria • 2 runs were rejected for MMF (but not for MPA) due to significant interference (> 20%) in blank samples observed at the MMF retention time. Both runs were repeated and passed acceptance criteria • 1 run was rejected for MMF (but not for MPA) due to QC's not meeting acceptance criteria. This run was repeated and passed acceptance criteria.	Yes

	• 4 runs (all ISR runs) were recreated as new runs due to improper analysis type selection (samples were not reinjected so values did not change)	
Standard curve performance	MMF • Cumulative accuracy (% bias) range: -2.2 to 2.6% • Cumulative precision (% CV): ≤ 4.0% MPA • Cumulative accuracy (% bias) range: -1.0 to 3.6% • Cumulative precision (% CV): ≤ 2.8%	Yes
QC performance	MMF • Cumulative accuracy (% bias) range: -0.4 to 5.7% • Cumulative precision (% CV): ≤ 5.3% MPA • Cumulative accuracy (% bias) range: -1.5 to 2.3% • Cumulative precision (% CV): ≤ 3.6%	Yes
Method reproducibility	• Incurred sample reanalysis was performed on 320/4122 samples (7.8%) for MMF and 320/4122 (7.8%) for MPA • 268/320 samples (83.8%) for MMF and 320/320 (100%) for MPA met acceptance criteria based on percent difference ≤ 20% of the mean. Total number of samples analyzed (n = 320) is acceptable to account for 10% of first 1000 samples and 5% of the remaining samples (1000*0.1 + 3122*0.05 = 256).	Yes

Repeat analysis	• Repeat analysis was conducted per an existing SOP No. BL/0056-009.
	• 17 (0.41%) individual subject samples were repeated for MMF
	  ○ All samples reassayed either due to concentrations above the limit of quantitation (n = 15) or due to drug concentration greater than LLOQ observed in pre-dose samples (n = 2)
	• 12 (0.29%) individual subject samples were repeated for MPA
	  ○ All samples reassayed either due to concentrations above the limit of quantitation (n = 11) or due to drug concentration greater than LLOQ observed in pre-dose samples (n = 1)
		Yes

Study sample analysis/ stability	Samples were stored at -70 °C until analysis. The first samples were collected Jun. 19, 2020, while the last samples were analyzed Sept. 15, 2020. Per the report, all samples were analyzed within 89 days of collection. Thus, all samples were analyzed within the established stability of 349 days at -70 °C.	

Method performance in study CL-156-18		
Assay passing rate	• A total of 50 runs were performed in study CL-156-18, including 48 original runs and 2 repeat runs for batch or individual samples • 3 runs were reinjected due to instrument failure and passed acceptance criteria • 1 run was rejected for MMF (but not for MPA) due to significant interference (> 20%) in blank samples observed at the MMF	Yes

	retention time. This run was repeated and passed acceptance criteria	
Standard curve performance	MMF • Cumulative accuracy (% bias) range: -2.3 to 2.6% • Cumulative precision (% CV): ≤ 4.0% MPA • Cumulative accuracy (% bias) range: -3.6 to 3.1% • Cumulative precision (% CV): ≤ 3.2%	Yes
QC performance	MMF • Cumulative accuracy (% bias) range: 0.0 to 0.7% • Cumulative precision (% CV): ≤ 5.5% MPA • Cumulative accuracy (% bias) range: -1.3 to 1.4% • Cumulative precision (% CV): ≤ 5.5%	Yes
Method reproducibility	• Incurred sample reanalysis was performed on 336/4156 samples (8.1%) for MMF and 336/4156 (8.1%) for MPA • 299/336 samples (89.0%) for MMF and 335/336 (99.7%) for MPA met acceptance criteria based on percent difference ≤ 20% of the mean. Total number of samples analyzed (n = 336) is acceptable to account for 10% of first 1000 samples and 5% of the remaining samples (1000*0.1 + 3156*0.05 = 258).	Yes
Repeat analysis	• Repeat analysis was conducted per an existing SOP No. BL/0056-009. • 44 (1.1%) individual subject samples were repeated for MMF o All samples reassayed either due to samples with concentrations falling below a truncated LLOQ (n = 37) or due to abnormal, improper, or inconsistent response for internal standard (n = 7) o Of note, all samples reassayed due to truncated LLOQ were from a single subject (S24). The validated LLOQ calibration curve standard of 0.05 ng/mL did not pass acceptance criteria. Thus, in the original run, the LLOQ was set to 0.100 ng/mL. Samples marked as BLQ due to falling below this truncated LLOQ were reanalyzed. All standards met acceptance criteria in the repeated run • 8 (0.19%) individual subject samples were repeated for MPA o All samples reassayed due to abnormal, improper, or inconsistent response for internal standard	Yes
Study sample analysis/ stability	Samples were stored at -70 °C until analysis. The first samples were collected Jul. 31, 2020, while the last samples were analyzed Sept. 29, 2020. Per the report, all samples were analyzed within 61 days of collection. Thus, all samples were analyzed within the established stability of 349 days at -70 °C.	

15.5. Additional Clinical Outcome Assessment Analyses

Method validation and in-study bioanalytical performance in studies CL-155-18 and CL-156-18 were found to be acceptable.

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/

JIANMENG CHEN
01/05/2023 03:39:33 PM

OZLEM A BELEN
01/05/2023 03:47:50 PM