CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210942Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210942
Review #1

Drug Name/Dosage Form	colchicine oral solution
Strength	0.12 mg/mL
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Romeg Therapeutics, LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*30-MAR-2018*	*All*
Amendment	*06-JUN-2018*	*Microbiology*
Amendment	*18-JUN-2018*	*Labeling*
Amendment	*06-SEP-2018*	*Microbiology, drug product*
Amendment	*05-OCT-2018*	*Process*
Amendment	*19-OCT-2018*	*Microbiology*
Amendment	*24-OCT-2018*	*Drug product*
Amendment	*31-OCT-2018*	*Microbiology*
Amendment	*07-DEC-2018*	*Drug Product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sam Bain	Donna Christner
Drug Product	Jizhou Wang	Craig M. Bertha
Process	Steven Fong	Joanne Wang
Microbiology	Andrew Pike	Erika Pfeiler
Facility	Steven Fong	Ruth Moore
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Florence Aisida	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	

ORA Lead	Emily Orban/Robert Barbosa	
Environmental	N/A	

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

. DMFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	NAI - 02-MAY-2018	No new CMC information since last review
	Type III			Not reviewed		Sufficient information provided in NDA
	Type III			Not reviewed		Sufficient information provided in NDA
	Type IV			Adequate	23-JUL-2018	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	129187	oral solution for gout prophylaxis

2. CONSULTS

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

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The CMC team recommends that the application be **approved.**

II. Summary of Quality Assessments

A. Product Overview

The drug product is Colchicine Oral Solution (proposed proprietary name: Gloperba®) and each mL of formulation contains 0.12 mg of colchicine, a narrow therapeutic drug. The drug product is packaged in white high density polyethylene bottles.

The drug substance has the USAN name "colchicine" and a monograph appears in the current edition of the USP. CMC information for the drug substance is mainly provided separately in the drug substance supplier's master file (b) (4) (b) (4) The colchicine that is provided by (b) (4) is confirmed to have the same identity as the Colchicine, USP reference standard by infrared spectroscopy. Colchicine is chiral but also exists as a diastereomeric mixture due to atropisomerism[1] resulting from steric hindrance between the A and C rings. Thus, there are two conformers that can interconvert relatively quickly when the compound is in solution and at ambient temperatures. The ratio of these conformers is approximately 99:1 (i.e., one is highly favored over the other thermodynamically).

The drug product is formulated (b) (4) as an aqueous-based oral solution (b) (4) (b) (4) with citric acid and sodium phosphate (target pH (b) (4)), includes a proprietary artificial cherry flavor and sucralose as a (b) (4), an Agency certified colorant, (b) (4) glycerin and propylene glycol (b) (4), and (b) (4) benzyl alcohol as a (b) (4) The application includes 12 months of long term and 6 months of accelerated stability data for four pilot scale (1/5th planned commercial scale) batches of drug product, one of which (16143A) was used for the clinical pharmacology studies. This batch had the same formulation and was manufactured by the same process proposed for the commercial drug product, but at a smaller scale. Thus, no formulation comparability studies were necessary.

[1] **Atropisomers** are stereoisomers that result from restricted rotation of single bonds due to steric hindrance such that different conformers can be isolated.

The recommended daily dose for the colchicine product is 5 mL (0.6 mg) once or twice daily, with a maximum daily dose of 1.2 mg/day. The marketed drug product will be packaged in HDPE bottles with child resistant closures. Based on the stability data for the registration stability batches, a 24 month expiration dating period is supported.

Proposed Indication(s) including Intended Patient Population	For prophylactic treatment gout flares in adults.
Duration of Treatment	chronic
Maximum Daily Dose	1.2 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

As per the referenced DMF (b) (4) the drug substance, Colchicine USP, is a botanical product obtained (b) (4) Most of the CMC data supporting the colchicine drug substance (active pharmaceutical ingredient or API) is in DMF (b) (4) and this file remains adequate for support of the use of colchicine for oral drug products (see review of 02-MAY-2018). (b) (4) (b) (4) Based upon the current adequacy of the DMF and upon the information provided in the NDA, we find the drug substance manufacturing process, characterization, specification, container closure system, and stability are satisfactory. The proposed retest period of (b) (4) for the drug substance is justified based upon the submitted stability data in the referenced DMF.

The drug product is a non-sterile oral solution dosage form of colchicine, which is an alternative to the three approved solid oral dosage forms already marketed. The applicant has provided sufficient data and information supporting the quality of the formulation components, including a reference to a proprietary DMF for the artificial cherry flavor (DMF (b) (4) found to be adequate). The drug product must comply with a specification that includes all parameters recommended for an oral solution dosage form in ICH Q6A. The applicant has provided sufficient stability data to support an expiration dating period of 24 months. In addition, the applicant has agreed to develop a method for quantifying any racemization of the chiral center at C-7 in colchicine for use in monitoring stability samples, prior to commercialization. The applicant also will provide the results of confirmatory photostability studies of the drug product as per ICH Q1B prior to commercialization.

The DP manufacturing process involves (b) (4)

(b) (4)

(b) (4) The commercial batch formula reflects the proposed composition, the submitted exhibit batch composition, and the commercial scale. The process-related information in the amended application is sufficient to support approval. In addition, from the microbiological perspective, the application was found to be adequate, including the validation of the applicant's test methods to detect contamination with the *Burkholderia cepacia* complex (BCC).

Regarding the facilities inspectional status, the API manufacturer (b) (4) produced low risk sub-scores for facilities, product and process. Although each of the sub-scores was low, the overall risk score was medium based on the occurrence of VAI (voluntary action indicated) decisions in two of the last three inspections. The production load for the past 5 years was consistent (b) (4) (b) (4) Based on compliance history and current approval for manufacture of other U.S. distributed APIs a PAI (pre-approval inspection) of (b) (4) was not deemed necessary. (b) (4) (b) (4) (b) (4) is recommended for approval from the standpoint of facilities assessment.

The initial risk assessment for the drug product manufacturer, Ferndale Laboratories, produced medium risk sub-scores for facilities and process, and a low sub-score for product. The medium facilities and process risk scores were due, respectively, to VAI conclusions for the last three inspections, and low drug content in the final liquid dosage form of the subject drug product. Based on risk analysis, compliance status, and approval for U.S. distribution of multiple oral dose form products, a PAI of Ferndale Laboratories in support of the subject NDA was not deemed necessary. Ferndale Laboratories is currently approved for U.S. distribution of multiple nonsterile, OTC products that have the same profile (LIQ) as the subject Colchicine Oral Solution drug product. In conclusion Ferndale Laboratories is recommended for approval from the standpoint of facilities assessment. The overall manufacturing inspection recommendation is "Approve."

In conclusion, the CMC team recommends that the NDA 210942 be **approved.**

C. Special Product Quality Labeling Recommendations (NDA only)

We discussed with the DPARP, the fact that the application does not propose the inclusion of a dose measuring unit with the drug product, even though colchicine is a narrow therapeutic drug. As a result, the clinical Division is planning on

including wording in the patient instructions that the formulation is to be measured with an accurate dosing device. Because colchicine is known to be light sensitive and the applicant will submit confirmatory photostability studies post-approval, but prior to commercialization, we have added instructions for patients to store the bottle in the carton after use.

D. Final Risk Assessment (see Attachment)

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Primary Quality Review

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

The current availability of colchicine is limited to solid oral dosage forms which contains 0.6 milligrams (mg) of colchicine in each tablet or capsule. Based on the approved solid oral dosage forms and on an accepted dosage of one teaspoon (5 mL), the product is being established at a concentration of 0.6 mg in each 5 mL, or 0.12 mg/mL. The liquid dosage form also provides the added benefit that the physician will have the ability to titrate dosages depending on the patient's needs, which is very important since colchicine is toxic and has a narrow therapeutic index.

2.3.P.1 Description and Composition of the Drug Product

The drug product is an oral solution containing 0.12 mg/mL of colchicine. It is a liquid dosage form alternative for ANDA084279 solid oral dosage forms.

Parameters*	Reference Product	Product under Review
Type	505 (b) (2)	505 (b) (2)
Description	(Probenecid and Colchicine Tablets USP (RS)) for solid oral dosage forms	This NDA for a liquid dosage form alternative for ANDA084279
Target Weight	500 mg probenicid/0.5 mg colchicine	0.6 mg in each 5 mL, or 0.12 mg/mL
Dimensions/Size	See ANDA 84279	N/A
Container/Closure Design	See ANDA 84279	190-cc, Oblong, HDPE Bottles and 38-400 mm (b) (4) CRC with a foil liner
Excipients (not in RLD) which require label warning	See ANDA 84279	N/A

The quantitative composition, grade and functions of the excipients of the oral solution are shown in Table 3.2.P.1-1 below. .

Table 3.2.P.1-1: Colchicine Oral Solution Quantitative Composition

Name of Ingredient	Reference	Function	Quantity	
			mg/mL	% w/v
Colchicine	USP	Active	0.12*	0.012
Benzyl Alcohol	NF	(b) (4)		
FD&C Red No. 40	21 CFR 74.1340			
Artificial Cherry Flavor (b) (4)	DMF			
Citric Acid (Anhydrous)	USP			
Dibasic Sodium Phosphate (b) (4)	USP			
Glycerin	USP			
Propylene Glycol	USP			
Sucralose	NF			
Xanthan Gum	NF			
Purified Water	USP	(b) (4)	q.s.	q.s.

* (b) (4)

A single CCS, a 190 cc HDPE bottle with a child-resistant closure and foil liner for oral liquid dose was proposed as shown below. The extractables/ leachables studies were provided (P.7 below)

Table 3.2.P.1-2: Overview of Container Closure System for Colchicine Oral Solution

Component	Description	Supplier	DMF No.
190-cc Bottles	190-cc, Oblong, HDPE Bottles	(b) (4)	
38-400 mm Closures	38-400 mm (b) (4) CRC with a foil liner		

HDPE: High Density Polyethylene
CRC: Child Resistant Closure

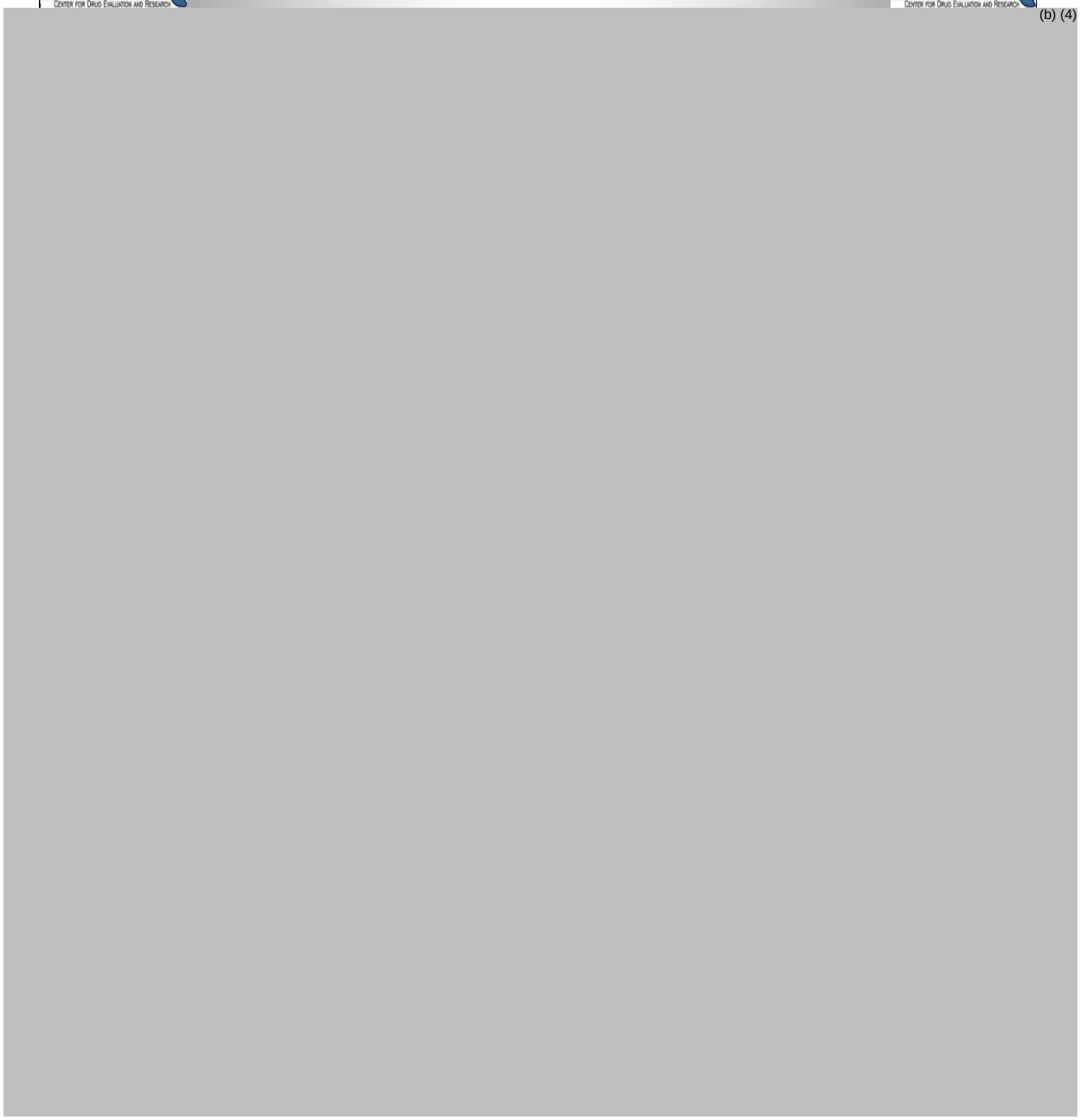
Reviewer's Assessment (review #1): Satisfactory

- It is a liquid dosage form alternative for tablet (N022352, A084279 A040618) and capsules (N204820) solid oral dosage forms.
- Sponsor provide the description of the proposed commercial drug product including the components, function(s) of each excipient, and composition of the final drug product as packaged and administered on both per unit dose and %w/w basis.
- With the exception of the colorant and the flavor, the excipients are all of compendial grade; the colorant is Agency certified and the artificial cherry flavor (b) (4) referenced to an adequate DMF. The level of USP/NF inactive ingredient is within the range of FDA IIG as shown in Table 3.2.P.2-2 below. *It is acceptable from CMC perspective, but we will defer it to Pharma/Tox reviewers to decide.*

2.3.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance



A.2 Adventitious Agents Safety Evaluation

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

Reviewer's Assessment: Satisfactory
This product only has highly purified plant-derived drug substances. No human and animal origin materials has been used in this drug products.

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

Reviewer's Assessment (Review #1):satisfactory
- From a microbiological safety standpoint, we are much more concerned about viruses from animal-derived or cell cultured substances than plant-derived substances. Because this product only has highly purified plant-derived substances, there's no need for Sponsor to provide processing steps assure to microbiological (viral) safety of the component(s) as microbiology reviewer Dr. Andrew Pike recommended.

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

Labeling & Package Insert

1. Package Insert

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

[redacted]

Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Gloperba Established Name: colchicine	Acceptable (established name)
Dosage form, route of administration	Dosage: Solution Route: Oral	Acceptable Acceptable
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	liquid dosage with 0.6 mg in each 5 mL, (b) (4)	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

(b) "Full Prescribing Information" Section

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

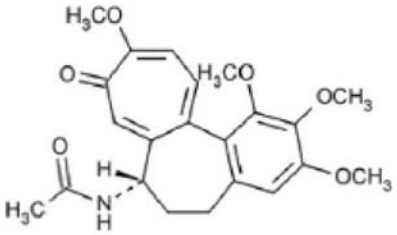
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	oral solution	Acceptable
Strengths: in metric system	(b) (4)	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A slightly hazy, red liquid with a cherry odor (Not provided)	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

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

Colchicine is an alkaloid obtained from various species of *Colchicum*. The chemical name for colchicine is (*S*)-*N*-(5,6,7,9- tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[α]heptalen-7-yl) acetamide with a molecular formula of $C_{22}H_{25}NO_6$ and a molecular weight of 399.4. The structural formula of colchicine is provided in Figure 1.

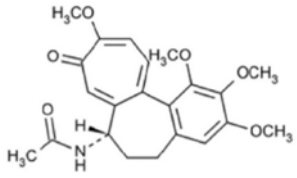
Figure 1: Colchicine Structural Formula



Colchicine consists of pale yellow scales or powder; it darkens on exposure to light. Colchicine is soluble in water, freely soluble in alcohol, and slightly soluble in ether.

GLOPERBA is supplied for oral administration as a slightly hazy, red liquid with a cherry odor, containing (b) (4) of the active ingredient colchicine USP. Inactive ingredients: benzyl alcohol, FD&C Red No. 40, artificial cherry flavor, anhydrous citric acid, dibasic sodium phosphate, glycerin, propylene glycol, sucralose, xanthan gum and purified water.

QUALITY ASSESSMENT
NDA # 210942

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Gloperba; Colchicine USP	Acceptable
Dosage form and route of administration	Oral solution	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	Colchicine (b) (4)	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Benzyl Alcohol, FD&C Red No. 40, Artificial Cherry Flavor (b) (4), Citric Acid (Anhydrous), Dibasic Sodium Phosphate (b) (4), Glycerin, Propylene Glycol, Sucralose, Xanthan Gum and Purified Water.	Acceptable
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	The mode of action of colchicine in gout is unknown. It is not an analgesic, though it relieves pain in acute attacks of gout	
Chemical name, structural formula, molecular weight	 (*S*)-*N*-(5,6,7,9- tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[α]heptalen-7-yl) acetamide Molecular Formula: C22H25NO6 Molecular weight: 399.4	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	/ Photolabile and potential racemization	N/A

Conclusion: Acceptable with the required data elements as summarized above

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
GLOPERBA (colchicine) Oral Solution is a slightly hazy, red liquid with a cherry odor.
150 mL: NDC XXXXX-XXX-XX

16.2 Storage
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. (b) (4)
(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(b) (4)	Acceptable
Available units (e.g., bottles of 100 tablets)	150 mL, 0.6 mg (5 mL) once or twice daily. Maximum dose 1.2 mg/day	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	a slightly hazy, red liquid with a cherry odor, and see reproduced text above	Acceptable
Special handling (e.g., protect from light, do not freeze)	(b) (4)	Acceptable
Storage conditions	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].	Acceptable

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	**Manufactured for:** ROMEG Therapeutics, LLC Woburn, MA 01801 **Manufactured by:** Ferndale Laboratories, Inc. Ferndale, MI 48220	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

2. Labels

1) Immediate Container Label

below.

		Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Gloperba; Colchicine	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4)	Acceptable
Net contents (21 CFR 201.51(a))	150 mL	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage (not required)	Yes	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	not provided	
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Ferndale Laboratories, Inc/℞ OMEG Therapeutics, LLC	Acceptable
Others	N/A	N/A

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Gloperba; Colchicine USP	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4)	Acceptable
Net contents (21 CFR 201.51(a))	150 mL	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not required for oral drugs	Acceptable
Sterility Information (if applicable)	Not applicable for oral drugs	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage Conditions	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. (b) (4) (b) (4)	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Ferndale Laboratories, Inc/℞ OMEG Therapeutics, LLC	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	Yes	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	Not applicable for Rx drugs	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Not applicable for oral drugs	Acceptable

Conclusion:

II. List of Deficiencies To Be Communicated – None; Application is recommended for **approval** from the drug product perspective

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
		H, M, or L		Acceptable or Not Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: Jizhou Wang, PhD/12-DEC-2018
Secondary Reviewer Name/Date: Craig Bertha/12-DEC-2018

Jizhou Wang

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Craig Bertha

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MICROBIOLOGY

Product Background:

NDA: 210942

Drug Product Name / Strength: Colchicine Solution, 0.12 mg/mL

Route of Administration: Oral Solution

Applicant Name: Romeg Therapeutics, LLC

Manufacturing Site:
Ferndale Laboratories, 780 West Eight Mile Road, Ferndale MI 48220

Method of Sterilization: N/A

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

List Submissions Being Reviewed: 3/30/2018, 6/6/2018, 9/6/2018, 10/19/2018, 10/31/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The drug product is a non-sterile oral solution.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug product is non-sterile, so the drug substance is not reviewed.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a red non-sterile oral solution packaged into plastic 190 cc oblong bottles closed with 38 mm locking twist-on caps and sealed with a foil liner.
- **Drug product composition –** The drug product composition is provided in the following table:

Ingredient	Reference	Purpose	mg/mL	% w/v
Colchicine	USP	API	0.12	0.012
Benzyl Alcohol	F	(b) (4)		(b) (4)
FD&C Red No. 40	21 CFR 74.1340			
Artificial Cherry Flavor (b) (4)	DMF			
Citric Acid (Anhydrous)	USP			
Dibasic Sodium Phosphate	USP			
Glycerin	SP			
Propylene Glycol	USP			
Sucralose	F			
Xanthan Gum	NF			
Purified Water	USP		q.s.	q.s.

- **Description of container closure system –** The container closure system consists of a 190 cc oblong HDPE plastic bottle and closed with a 38 mm auto-locking twist on cap and sealed with a foil liner.

Adequate

Reviewer's Assessment: The applicant has provided an adequate description of the drug product and container closure system for a non-sterile oral solution.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Reviewer's Assessment: N/A – the drug product is non-sterile

Antimicrobial Effectiveness Testing

The drug product will be preserved with (b) (4) Antimicrobial effectiveness testing was performed in accordance with USP <51>, category 3 (Section 3.2.P.2 Pharmaceutical Development pgs. 5-7 of 9 and Product Development Report pgs. 7 and 23 of 23). The drug product was inoculated (b) (4) CFU/mL of the five

compendial organisms (*Candida albicans, Aspergillus brasiliensis, Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*) and samples were taken at 14 and 28 days post inoculation. For all five tested organisms, there was (b) (4) reduction in the population at 14 days post inoculation and further reduction by day 28, yielding satisfactory results (Pharmaceutical Development pg. 7 of 9). The test was also conducting using the drug product without (b) (4), yielding similar results. The applicant tested the antimicrobial effectiveness of (b) (4) of the target concentration (Product Development Report pgs. 7 and 23 of 23) with acceptable reductions in the compendial microorganisms, indicating that the preservative is effective at this reduced concentration. Based on this, the applicant created a release specification of (b) (4) (Section 3.2.P.5.1 Specification(s)). AET will be tested on stability samples using the methodology from USP <51>.

Validation data showing the suitability of the antimicrobial effectiveness test methods was not included in the initial submission.

Information Request sent to the applicant on 10 May 2018:
It is important to verify the suitability of the compendial microbiological tests for a given drug product to ensure appropriate microbial control. Verification studies supporting the microbiological tests could not be located in the application. Please describe the verification methods and results for each of the following:

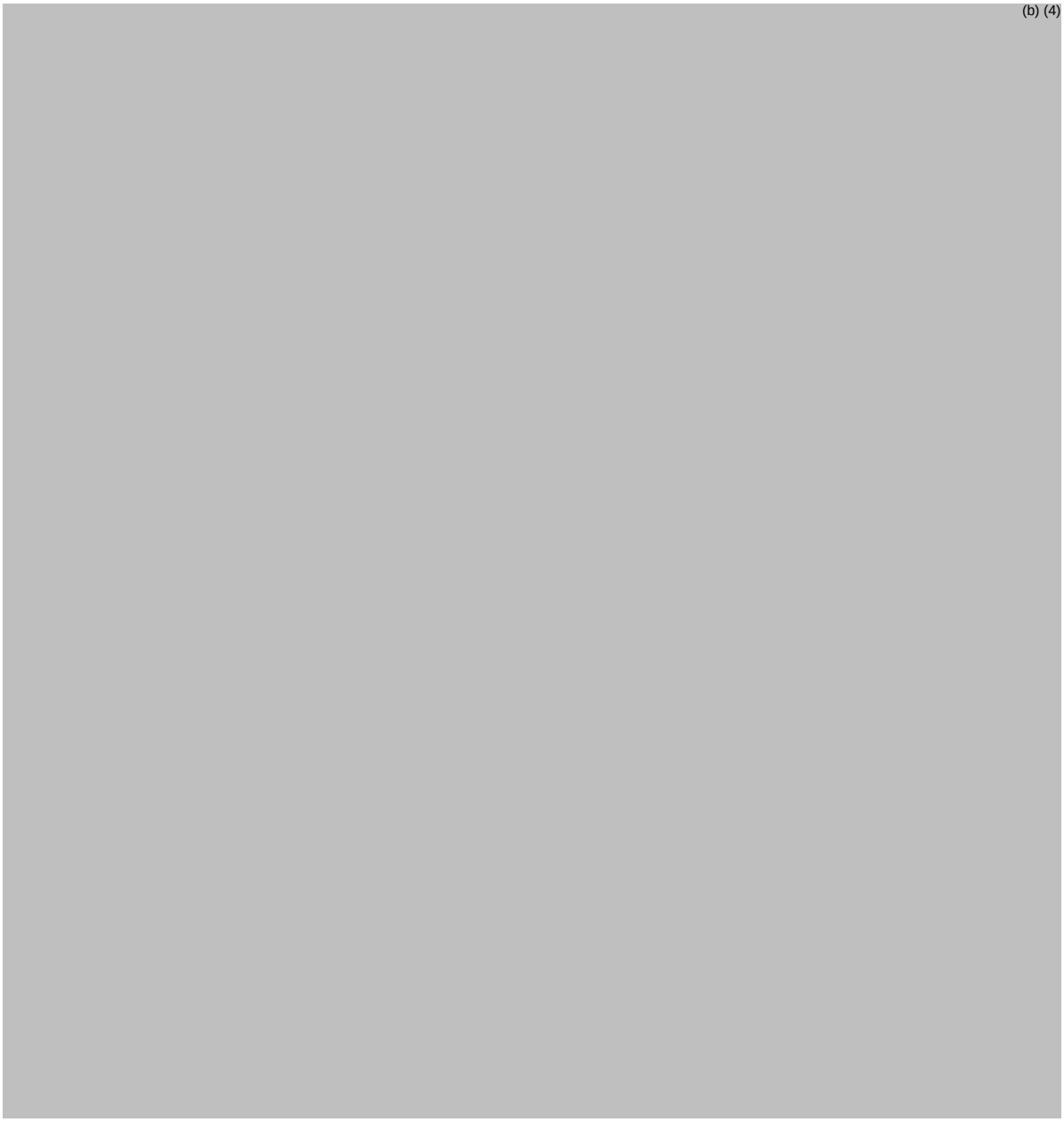
1. *The microbial enumeration tests*
2. *The tests for specified microorganisms*
3. *The antimicrobial effectiveness testing*

Summary of the applicant's response received 6 June 2018:
The applicant updated Section 3.2.P.5.3 to include validation studies for the antimicrobial effectiveness testing. Suitability tests of the five compendial organisms were performed

(b) (4)

(b) (4)

(b) (4)

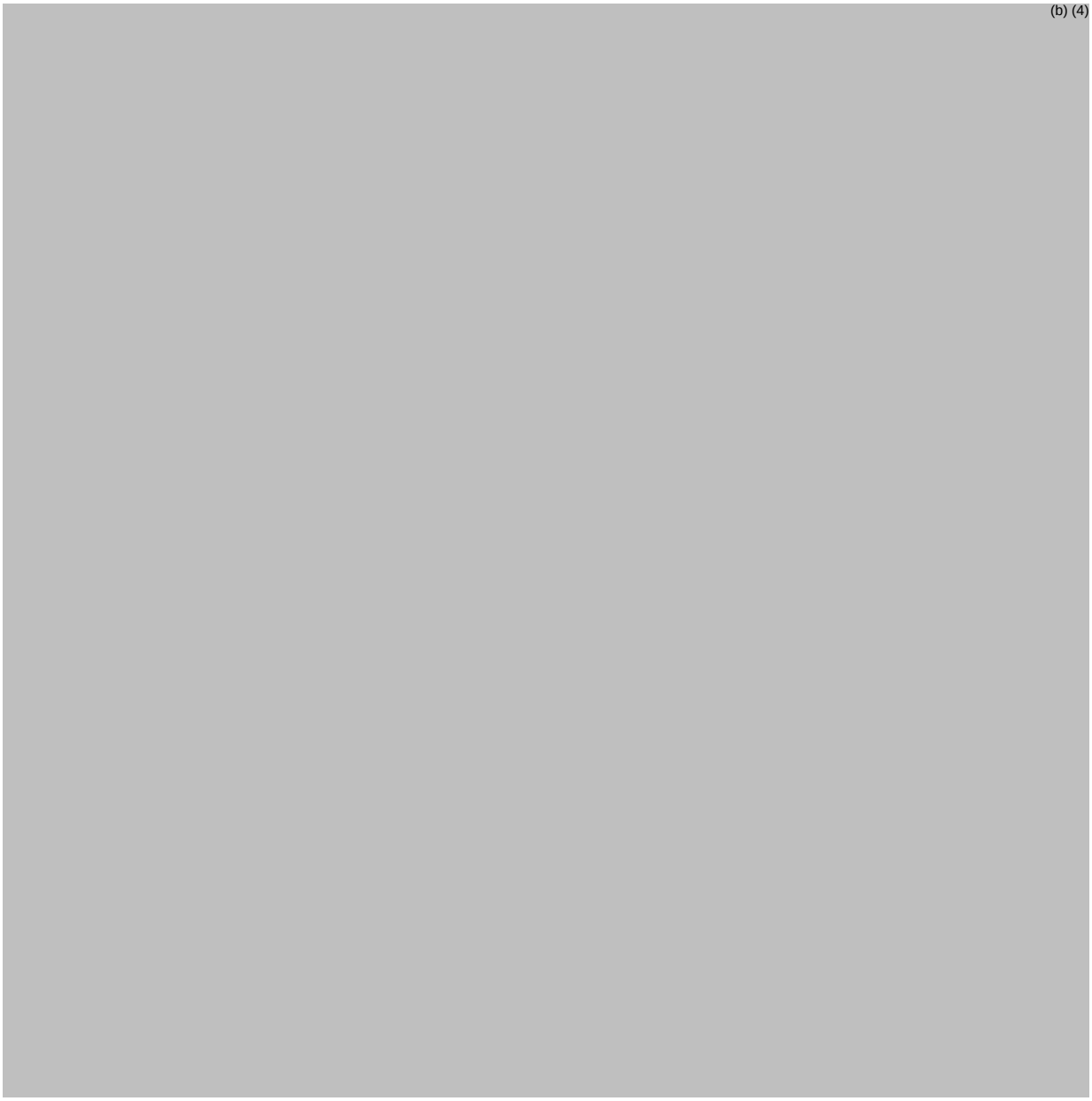


P.3 Manufacture

P.3.1 Manufacturers

Ferndale Laboratories
780 West Eight Mile Road
Ferndale MI 48220

(b) (4)



P.8 Stability

P. 8.1 Stability Summary and Conclusion

Section 3.2.P.8.1 Stability Summary and Conclusion

The drug product is currently being tested under long-term storage conditions (at 25 ± 2° C and 60 ± 5% relative humidity) for 3 years and accelerated storage conditions (40 ± 2° C and 75 ± 5% relative humidity) for 6 months. Samples are also being stored under intermediate conditions (30 ± 2° C and 65 ± 5% relative humidity) for 12 months, though these samples will only be tested if significant changes are observed under accelerated

conditions. Additionally, samples that have been stored under long-term and accelerated (as described above) conditions for up to 36 months are being sampled after use for up to 30 days to simulate in-use stability. Microbial limits will be tested at release and 6, 12, 24 and 36 months under long-term conditions and at release and 6 months under accelerated storage conditions. AET will be tested at release and 12, 24 and 36 months under long-term conditions and at release and 6 months under accelerated conditions.

The applicant proposes a 24 month expiry (Section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment pg. 1 of 2) at controlled room temperature. The drug product (b) (4) (b) (4)

Adequate

Reviewer's Assessment: The applicant's proposed 2 year expiry is acceptable from the standpoint of product quality microbiology.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

The applicant commits to complete the stability studies on the three exhibit batches as described above. Additionally, the first three commercial batches and at least one commercial batch each year of production will be tested for stability using the long-term storage conditions described above. Microbial samples will be tested after 12, 24 and 36 months of storage.

Adequate

Reviewer's Assessment: The applicant provided an acceptable stability program for microbial testing.

P.8.3 Stability Data

Section 3.2.P.8.3 Stability Data

The applicant has provided stability data for four batches stored at 25 ± 2° C and 60 ± 5% relative humidity (long-term batches 16143A, 16154A, 16155A and 16155A) and four batches stored at 40 ± 2° C and 75 ± 5% relative humidity (accelerated batches 16143A, 16154A, 16155A and 16155A) conditions, as well as two batches (16143A and 16154A) under each condition following 0-30 days of use for in-use testing. The dates for which data are available for each batch and condition are summarized in the table below. In all cases, microbial testing results are acceptable.

Storage type	Conditions	Months post release	Batch							
			16143A		16154A		16155A		16156A	
			Micro	AET	Micro	AET	Micro	AET	Micro	AET
Long-term	25 ± 2° C and 60 ±	0	X	X	X	X	X		X	
		6	X							
		12	X	X	X	X	X	X	X	X

	5% relative humidity									
Accelerated	40 ± 2° C and 75 ± 5%	0	X	X	X	X	X		X	
		6	X	X	X	X	X		X	
Long-term in-use	25 ± 2° C and 60 ± 5% relative humidity after 0, 15 or 30 days of use	3	X							
		6	X		X					
		12	X		X					
Accelerated in-use	40 ± 2° C and 75 ± 5% after 0, 15 or 30 days of use	1	X							
		2	X							
		3	X							
		6	X		X					

Adequate

Reviewer's Assessment: The applicant provided acceptable microbiology stability data.

R Regional Information

Executed Batch Records

The applicant states that the clinical supply and NDA registration batches were manufactured using the same process and specifications as will be used for production, and that only one representative batch record is required for this submission. Reference is made to a pre-NDA meeting written response in which the FDA agrees with that plan (Section 1.6.3 pre-NDA Preliminary Responses (Reference ID: 4178618) pg. 6 of 13). The applicant provided bulk and packaging records for batch 16154A (Section 3.2.R). The records for two additional registration batches are included in Section 3.2.P.5.4 Batch Analysis. In total, acceptable microbiological testing results are provided for batches 16143A, 16154A, 16155A and 16156A.

Adequate

Reviewer's Assessment: The applicant provided a single set of executed batch records for Colchicine oral solution 0.12 mg/mL manufactured at Ferndale Laboratories, along with the batch records for two additional registrations batches. Additionally, the applicant is willing to provide additional records at the request of the FDA.

Comparability Protocols

N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

- **Post-dilution/constitution hold time –** N/A

Post-Approval Commitments: – N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Andrew Pike, PhD; 11/6/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): John W. Metcalfe, PhD; I concur with the primary reviewer's assessment. 11/6/2018

Andrew Pike

Digitally signed by Andrew Pike
Date: 11/07/2018 10:52:27AM
GUID: 59c5154001875f37b042284badb3ac00

John Metcalfe

Digitally signed by John Metcalfe
Date: 11/07/2018 12:18:52PM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

ATTACHMENT - NDA 210942 – OPQ Final Risk Assessment

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[4, 2]	D[4]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Comments/Lifecycle considerations
Appearance	• colchicine precipitates	1	3	2	6	(b) (4)		
Identification	• incorrect drug formulated • no API formulated	2	3	4	24			
Assay	• incorrect amount of API formulated • high impurity level of input API • API degradation	1	3	2	6			
Degradation Products	• API degradation	2	3	2	12			
pH	• incorrect amounts of components formulated (e.g., citric acid, sodium phosphate) • pH changes due to leachables (organic or	2	3	3	18			

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

	elemental) or formulation component (API or excipient) degradation					(b) (4)		
Density	• incorrect amounts of components formulated	1	3	1	3			
Deliverable volume	• incorrect fill of bottles during manufacture • leakage of filled containers prior to patient use	2	3	2	12			
Microbial limits	• lower than target amount of (b) (4) formulated	2	3	2	12			
Antimicro-bial preservative content	• lower than target amount of (b) (4) formulated • degradation of (b) (4) (b) (4) (bacteriostatic preservative) • (b) (4)	1	3	2	6			
Leachables	• compounds leached from inner surface of induction seal and bottle	2	3	5	30		15	(b) (4)

ATTACHMENT - NDA

						(b) (4)		(b) (4)
Elemental impurities	• elemental impurities leached from inner surface of induction seal and bottle	1	3	5	15			
Residual solvents	• leached from CCS • sourced from formulation components (API and excipients)	1	3	5	15			

Craig Bertha

Digitally signed by Craig Bertha
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