

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-352

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-352

SUPPL #

HFD # 170

Trade Name COLCRYS

Generic Name colchicine

Applicant Name Mutual Pharmaceutical Company, Inc.

Approval Date, If Known 7-29-2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7/Orphan drug designation

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 84-279	Col-Probenecid
NDA# 83-734	Probenecid and Colchicine
NDA# 40-618	Probenecid and Colchicine

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

There are three randomized controlled trials in the published literature supporting the safety and effectiveness of colchicine for the treatment of familial Mediterranean fever (FMF): Dinarello et al., New England Journal of Medicine 1974, 291:934-937, Goldstein and Schwabe, Annals of Internal Medicine 1974, 81:792-794, and Zemer et al., New England Journal of Medicine 1974, 291:932-934. These studies formed the evidentiary basis for NDA 22-352, and were not conducted by the applicant, nor did the applicant have right of reference to the information in these studies.

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

There were no new investigations in the application that were conducted by the applicant that were essential to the approval.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:
Studies were not conducted under IND

Investigation #2 !
IND # YES ! NO
! Explain:
Studies were not conducted under IND

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Studies are from the literature

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

Studies are from the literature

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Margarita Tossa

Title: RPM

Date:

Name of Office/Division Director signing form: Rigoberto Roca, MD

Division of Anesthesia, Analgesia and Rheumatology Products

Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22352	ORIG 1	MUTUAL PHARMACEUTICA L CO INC	COLCRYS TABLETS,6MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARGARITA V TOSSA
07/29/2009

RIGOBERTO A ROCA
07/29/2009



United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500
www.urlmutual.com

CERTIFICATION REQUIRED BY GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Mutual Pharmaceutical Company, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA. This certification is based upon the list of debarred individuals available on the FDA website (http://www.fda.gov/ora/compliance_ref/debar/default.htm), last updated on November 7, 2007.

A handwritten signature in cursive script, appearing to read "Robert Dettery".

Robert Dettery
Vice-President, Regulatory Affairs

4 Sept 2008

Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-352 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Anesthesia, Analgesia and Rheumatology Products PDUFA Goal Date: 12/20/2008 Stamp Date: 6/20/2008

Proprietary Name: Colstat™ (proposed)

Established/Generic Name: Colchicine

Dosage Form: 0.6 mg Tablets

Applicant/Sponsor: Mutual Pharmaceutical Company, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of Familial Mediterranean Fever (FMF)

Q1: Is this application in response to a PREA PMC/PMR? Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMC/PMR #: _____

Does the division agree that this is a complete response to the PMC/PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

NDA # **Error! Reference source not found.****Error! Reference source not found.****Error! Reference source not found.** **Error! Reference source not found.** **Error! Reference source not found.**

Page 6

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Margarita Tossa
11/21/2008 09:14:01 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-352 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: COLCRYS Established/Proper Name: Colchicine, USP Dosage Form: 0.6 mg tablets		Applicant: Mutual Pharmaceutical Company, Inc. Agent for Applicant (if applicable):
RPM: Margarita Tossa		Division: 170
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Col-Probenecid</p> <p>Provide a brief explanation of how this product is different from the listed drug. New dose & new formulation</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 07/14/2009</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		12/20/2008 7/29/2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain:	<u>Orphan drug designation</u>
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other /HCP page

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist³</p>	
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) 7-30-2009</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	<p>07/27/2009</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>06/20/2008</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.

❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	7/23/2009 (attached)
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	7/27/2009 (attached)
❖ Labeling reviews (indicate dates of reviews and meetings)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 02/17/2009 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 12/02/2008, 12/10/2008 & 03/03/2009 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
❖ Proprietary Name	
<ul style="list-style-type: none"> • Review(s) (indicate date(s)) • Acceptability/non-acceptability letter(s) (indicate date(s)) 	12/05/2008 12/12/2008 & 02/26/2009
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	09/20/2008
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (if located elsewhere in package, state where located) 	AP letter
<ul style="list-style-type: none"> • Incoming submissions/communications 	
❖ Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located) • Incoming submission documenting commitment 	
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • PeRC (indicate date; approvals only) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (indicate date; approvals only) 	<input checked="" type="checkbox"/> Not applicable

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg 02/04/2008
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/29/2009
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/01/2008
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	12/01/2008
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	11/30/2008
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	11/30/2008
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 11/03/2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input type="checkbox"/> None 02/19/2009 02/03/2009
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/15/2008
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/15/2008
Clinical Pharmacology <input type="checkbox"/> None	

⁵ Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 11/26/2008
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 11/24/2008 & 12/29/2008
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 11/21/2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 11/20/2008
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 08/25, 10/21 & 11/05/2008
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	08/25/2008 (page #78)
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	

<ul style="list-style-type: none">• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: 05/07/2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none">• BLAs:<ul style="list-style-type: none">○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

From: Robert Dettery
To: Tossa, Margarita;
cc: Jennifer W. Phillips; Andria Werynski;
Subject: RE: NDA 22352 and NDA 22351.
Date: Tuesday, July 28, 2009 1:37:17 PM
Attachments: [NDA22352-Risk mitigation template 7-28-09.doc](#)
[NDA22351-REMS item 7-28-09 .doc](#)
[NDA22351-Risk mitigation template 7-28-09.doc](#)
[NDA22352-REMS item 7-28-09 .doc](#)
[cover-letter SN0021.doc](#)

Margarita,
Attached are information copies for you of what we will be submitting this afternoon.

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.
AR Scientific, Inc.

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]
Sent: Tuesday, July 28, 2009 11:52 AM
To: Robert Dettery
Subject: NDA 22352 and NDA 22351.
Importance: High

Robert,

We are trying to Wrap-Up our documents and we made some minor/editorial changes to the REMS and a PI/MedGuide.

Please look at the changes and let me know if you concur with changes a.s.a.p.

<<REMS item 7-27-09 (3).doc>> <<Risk mitigation template 7-27-09 (2).doc>> <<NDA 22352 COLCRYS FMF final 7-28-09.doc>>

Please make changes to the REMS for NDA 22351 and send it back to me,

Thank you,

Margarita

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22351	ORIG 1	MUTUAL PHARMACEUTICA L CO INC	COLCHICINE TABLETS USP 0.6MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARGARITA V TOSSA
07/30/2009

From: Robert Dettery
To: Tossa, Margarita;
cc: Jennifer W. Phillips; Andria Werynski;
Kim Thorson;
Subject: FW: NDA 22352 and NDA 22351.
Date: Tuesday, July 28, 2009 12:23:32 PM
Attachments: REMS item 7-27-09 (3).doc
Risk mitigation template 7-27-09 (2).doc
NDA 22352 COLCRYS FMF final 7-28-09.doc

We accept the changes to the REMS and the Risk mitigation template. We also accept most of the changes in the FMF insert with the exception of two. See our comments on page 31 of 40. We will make the same changes to the REMS for 22351 and send back.

Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.
AR Scientific, Inc.

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]
Sent: Tuesday, July 28, 2009 11:52 AM
To: Robert Dettery
Subject: NDA 22352 and NDA 22351.
Importance: High

Robert,

We are trying to Wrap-Up our documents and we made some minor/editorial changes to the REMS and a PI/MedGuide.

Please look at the changes and let me know if you concur with changes a.s.a.p.

<<REMS item 7-27-09 (3).doc>> <<Risk mitigation template 7-27-09 (2).doc>> <<NDA 22352 COLCRYS FMF final 7-28-09.doc>>

Please make changes to the REMS for NDA 22351 and send it back to me,

Thank you,

Margarita

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22352	ORIG 1	MUTUAL PHARMACEUTICA L CO INC	COLCRYS TABLETS,6MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARGARITA V TOSSA
07/30/2009

From: Robert Dettery
To: Tossa, Margarita;
cc: Jennifer W. Phillips; Andria Werynski;
Brandi Adoff;
Subject: Re: NDA 22352 COLCRYS (FMF)/final label.
Date: Tuesday, July 21, 2009 12:37:13 PM

The FMF labeling should be no problem for Friday. We are still working on combined acute gout labeling and will submit ASAP.

R. Dettery

sent from Blackberry

From: Tossa, Margarita <Margarita.Tossa@fda.hhs.gov>
To: Robert Dettery
Sent: Tue Jul 21 12:23:08 2009
Subject: FW: NDA 22352 COLCRYS (FMF)/final label.

Hi Robert,

We would like to receive the final version of the label and carton & containers for NDA 22-352/FMF no later than Friday (7-24-09). Please let me know if it is doable.

You may want to submit the final version of carton & containers to the NDA 22-351 as well.

Thanks,

Margarita

From: Tossa, Margarita
Sent: Monday, July 20, 2009 11:27 AM
To: 'Robert Dettery'
Subject: NDA 22352 COLCRYS (FMF)/final label.
Importance: High

Dear Robert,

Here is the final version of the label for NDA 22-352 COLCRYS (colchicine)/FMF with minor editorial changes. Please submit an amendment to the

NDA 22-352 with final version of the label and carton & containers.

<<NDA 22352 final-colcrys-labeling-text.doc>>

Heads up, by the end of this week I will ask you to send me a draft of the "joined" label for acute gout and FMF indications.

Thanks,

Margarita

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/s/

Margarita Tossa
7/23/2009 08:30:40 AM
CSO

From: Tossa, Margarita
To: "Robert Dettery";
Subject: FW: NDA 22352 COLCRYS (FMF)/final label.
Date: Tuesday, July 21, 2009 12:23:09 PM
Attachments: [NDA 22352 final-colcrys-labeling-text.doc](#)

Hi Robert,

We would like to receive the final version of the label and carton & containers for NDA 22-352/FMF no later than Friday (7-24-09). Please let me know if it is doable.

You may want to submit the final version of carton & containers to the NDA 22-351 as well.

Thanks,

Margarita

From: Tossa, Margarita
Sent: Monday, July 20, 2009 11:27 AM
To: 'Robert Dettery'
Subject: NDA 22352 COLCRYS (FMF)/final label.
Importance: High

Dear Robert,

Here is the final version of the label for NDA 22-352 COLCRYS (colchicine)/FMF with minor editorial changes. Please submit an amendment to the NDA 22-352 with final version of the label and carton & containers.

Heads up, by the end of this week I will ask you to send me a draft of the "joined" label for acute gout and FMF indications.

Thanks,

Margarita

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/s/

Margarita Tossa
7/23/2009 08:29:26 AM
CSO

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22352/000	Sponsor:	MUTUAL PHARM
Code:	170		1100 ORTHODOX ST
Priority:	7P		PHILADELPHIA, PA 19124
Stamp Date:	20-JUN-2008	Brand Name:	COLCRYS TABLETS,6MG
PDUFA Date:	20-DEC-2008	Estab. Name:	
Action Goal:		Generic Name:	COLCHICINE TABLETS USP 0.6 MG
District Goal:	19-FEB-2009	Dosage Form:	(TABLET)
		Strength:	0.6 MG

FDA Contacts:	M. SULLIVAN	Project Manager	(HFD-170)	301-796-1245
	C. BERTHA	Review Chemist		301-796-2410
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 07-MAY-2009	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on 29-APR-2009	by M. STOCK	(HFD-320)	301-796-4753

Establishment: **CFN:** _____ **FEI:** _____

DMF No: _____ **AADA:** _____
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

b(4)

Establishment: **CFN:** _____ **FEI:** _____

DMF No: _____ **AADA:** _____
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

b(4)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 2523348 FEI: 2523348
MUTUAL PHARMACEUTICAL COMPANY, INC.
1100 ORTHODOX ST
PHILADELPHIA, PA 19124

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-JUL-2008

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUL-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUL-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: INTERMEDIATE MANUFACTURER
Profile: PLANT/ANIMAL EXTRACTION CRUDE DRUG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-APR-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: PLANT/ANIMAL EXTRACTION CRUDE DRUG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-APR-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: FEI: _____

b(4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JUL-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

From: Tossa, Margarita
To: "Robert Dettery";
Subject: RE: Stability data.
Date: Monday, May 11, 2009 10:07:57 AM

Hi Robert,

Please remove all references to the _____ in the labeling and submit updated label to the NDA 22-352.

b(4)

Thank you,

Margarita.

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Friday, May 08, 2009 9:31 AM
To: Tossa, Margarita
Subject: RE: Stability data.

Hi Margarita,
We submitted an amendment to NDA 22-352 on 2/12/2009 to cross-reference the 24 month stability data. See attached.

Bob

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]
Sent: Friday, May 08, 2009 9:16 AM
To: Robert Dettery
Subject: Stability data.

Hi Robert,

It appears that Mutual provided updated 24 month stability data for the bottled product of both NDA 22-351 and NDA 22-353, but you forgot to cross-reference or update the first NDA 22-352 in the same way.

You need to update NDA 22-352 so that the applications are all consistent.

Thank you,

Margarita

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/s/

Margarita Tossa
5/12/2009 11:49:55 AM
CSO

From: Tossa, Margarita
To: "Robert Dettery";
Subject: NDA 22352 Colcrys (colchicine)/FMF.
Date: Thursday, April 30, 2009 8:34:49 AM

Hi Robert,

I spoke with the reviewer from the Office of Compliance and the CMC reviewer yesterday and they requested the following information:

Clearly specify which testing results were obtained at the _____ and if Mutual used these results to support the application?

b(4)

Thank you,

Margarita

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/s/

Margarita Tossa
5/12/2009 11:48:20 AM
CSO

Date: Saturday, January 01, 4501 12:00:00 AM

Attachments: [Final version REMS.pdf](#)
[OSEs comments REMS.doc](#)
[FINAL INSERT.doc](#)

Margarita,

We have reviewed the Division's comments/changes to the insert and REMS are we accept them all. However, we have also discovered a few inconsistencies and a few editorial changes to the insert that are necessary.

We will incorporate your final comments along with our changes, plus change all the TRADENAMEs to Colcrys™, and submit as an official labeling amendment next week.

Bob

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]

Sent: Friday, March 06, 2009 11:05 AM

To: Robert Dettery

Subject: NDA 22352 colchicine (FMF)/label, MG & REMS.

Importance: High

Dear Robert,

Please find the attachments with the **final** version of the label for colchicine which includes the MedGuide, **final** version of the REMS and the OSEs comments to the REMS.

Please make sure that we did not delete anything from the label without track changes. Please do the following:

1. If you agree with our changes to the label just accept them.
2. If you do not agree make your changes or comments.

<<Final version REMS.pdf>> <<OSEs comments_REMS.doc>> <<FINAL INSERT.doc>>

FYI.

We have completed our review of the proposed proprietary name Colcryx and have concluded that it is acceptable.

I will email you the official letters later today or on Monday.

We encourage you to send your response (label with the MG and REMS) as soon as you can.

Best regards,

Margarita

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/s/

Margarita Tossa
5/12/2009 11:46:47 AM
CSO

From: Tossa, Margarita
To: "Robert Dettery";
Subject: CMC information request for NDAs 22352, 22351 & 22353.
Date: Thursday, March 26, 2009 12:30:37 PM

Dear Robert,

The CMC reviewer requested the following information for NDAs 22-352, 22-351, and 22-353:

1. Confirm the identity of the bio-batch of drug product used in the clinical trial in support of the above NDAs.
2. Identify the exact packaging presentations that were used for the drug product used in the clinical trial.

Thank you,

Margarita

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/s/

Margarita Tossa
3/30/2009 11:33:35 AM
CSO

Date: ~~Saturday, January 01, 2009 12:00:00 AM~~

3/06/2009

Attachments: Final version REMS.pdf

OSEs comments REMS.doc

FINAL INSERT.doc

Margarita,

We have reviewed the Division's comments/changes to the insert and REMS are we accept them all. However, we have also discovered a few inconsistencies and a few editorial changes to the insert that are necessary.

We will incorporate your final comments along with our changes, plus change all the TRADENAMEs to Colcrys™, and submit as an official labeling amendment next week.

Bob

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]

Sent: Friday, March 06, 2009 11:05 AM

To: Robert Dettery

Subject: NDA 22352 colchicine (FMF)/label, MG & REMS.

Importance: High

Dear Robert,

Please find the attachments with the **final** version of the label for colchicine which includes the MedGuide, **final** version of the REMS and the OSEs comments to the REMS.

Please make sure that we did not delete anything from the label without track changes. Please do the following:

1. If you agree with our changes to the label just accept them.
2. If you do not agree make your changes or comments.

<<Final version REMS.pdf>> <<OSEs comments_REMS.doc>> <<FINAL INSERT.doc>>

FYL

We have completed our review of the proposed proprietary name Colcrys and have concluded that it is acceptable.

I will email you the official letters later today or on Monday.

We encourage you to send your response (label with the MG and REMS) as soon as you can.

Best regards,

Margarita

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/s/

Margarita Tossa
3/30/2009 11:31:07 AM
CSO

~~Date: Saturday, January 01, 4501 12:00:00 AM~~

2/20/2009

Margarita,

We will respond ASAP. Should this be an official submission to the NDA?

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]

Sent: Friday, February 20, 2009 8:27 AM

To: Robert Dettery

Subject: NDA 22-352 colchicine (FMF)/Label and labeling review.

Importance: High

Dear Robert:

Please refer to your new drug application (NDA) dated June 20, 2008, received June 20, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Colchicine Tablets USP, 0.6 mg.

Our review of the Label and labeling section of your submission is complete, and we have identified the following deficiencies:

A. General Comments for All Container Labels

1. Submit revised container labels that contain the proposed proprietary name "Colcrys" (please note that the Proprietary Name review is ongoing) for our review and comment.
2. The established name appears less than ½ the size of the proprietary name. Ensure that the established name is at least ½ the size of the proprietary name (taking into consideration the font, type, etc.) as per 21 CFR 201.10(g)(2).
3. The labels lack a Medication Guide statement. Add a Medication Guide statement as per 21 CFR 208.24(d).
4. Provide details on how many medication guides will be included with each container size.

5. Provide details on how the Medication Guide will be provided (e.g., inside bottle, attached to the insert labeling, tear-off sheet, etc.)

B. Container Labels (Trade)

1. Increase the size of the statement of strength (0.6 mg).
2. If the 30-count bottle is a “unit-of-use” bottle to be dispensed on an outpatient basis, ensure that the bottle has a Child Resistant Closure as per the Poison Prevention Act.

C. Container Labels _____

b(4)

1. At the topmost part of the label, the established name and the “each tablet contain” statement
2. (“Tablet contains...”) are printed in _____ that is difficult to read due to the _____ of the background. Revise so that there is sufficient color contrast to improve readability.
3. Increase the prominence of the statement _____

b(4)

D. Insert Labeling

1. In Full Prescribing Information, Section 2, *Dosage and Administration*, there are no directions for means to facilitate administration of the product (e.g., crushing or mixing with food) to those who have difficulty swallowing tablets (e.g., pediatric patients). Include this type of information, if available, in the labeling.
2. The error-prone symbol — is used in the *Dosage and Administration* section of the insert labeling. Delete the symbol and use the appropriate phrase instead.
3. In Full Prescribing Information, Section 3, *Dosage Forms and*

b(4)

Strengths, two units of measure are used to specify the tablet strength [i.e.,
“0.6 mg _____ Delete the _____ strength designation.

b(4)

We encourage you to send us your response as soon as you can.

Thank you,

Margarita Tossa, M.S.

Regulatory Project Manager

FDA/CDER/DAARP

phone: (301) 796-4053

fax: (301) 796-9713

Email: margarita.tossa@fda.hhs.gov

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/s/

Margarita Tossa
3/30/2009 11:28:54 AM
CSO

Date: Saturday, January 01, 4501 12:00:00 AM

2/12/2009

Margarita,

Sorry for the oversight. The completion date for both studies is April 30, 2012.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]

Sent: Thursday, February 12, 2009 3:06 PM

To: Robert Dettery

Subject: NDA 22352 colchicine (FMF)/information request.

Hi Robert,

Please provide the "Study completion date" for both carcinogenicity studies.

An evaluation of the potential carcinogenicity of colchicine in either a 2-year bioassay or 6-month transgenic study in an appropriate mouse model.

The timetable you submitted on February 2, 2009, states that you will conduct this study according to the following timetable:

Final protocol Submission: January 31, 2010

Study Completion Date: XXX

Final Report Submission: April 30, 2013

An evaluation of the potential carcinogenicity of colchicine in a 2-year bioassay in rat.

The timetable you submitted on February 2, 2009, states that you will conduct this study according to the following timetable:

Final protocol Submission: January 31, 2010

Study Completion Date: XXX

Final Report Submission: April 30, 2013

Thank you,

Margarita

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/s/

Margarita Tossa
3/30/2009 11:27:40 AM
CSO

Date: ~~Saturday, January 01, 4501 12:00:00 AM~~

2/09/2009

Attachments: REMS item #1.doc

REMS item 2, 2-9-09.doc

Rita,

Please see the attached REMS program, items #1 and 2. As per your email, we deleted the _____ from our REMS program. This replaces the email I sent to you on Friday afternoon. Our plan is to officially submit this information tomorrow. If you need any additional clarification or help, please let me know.

b(4)

Thanks,

Bob

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/s/

Margarita Tossa
3/30/2009 11:26:19 AM
CSO

From: Tossa, Margarita
To: "Robert Dettery";
Subject: FW: NDA 22-352 cochicine (FMF)/REMS.
Date: Friday, February 06, 2009 12:57:24 PM
Attachments: REMS template.doc

Dear Robert,

Please do not include the _____ in your **REMS communication plan**, because the Division did not requested this letter from you (element not necessary), however, if you wish to use this letter you can use it outside of the REMS.

b(4)

Thanks,

Rita.

From: Tossa, Margarita
Sent: Friday, February 06, 2009 12:27 PM
To: 'Robert Dettery'
Subject: NDA 22-352 cochicine (FMF)/REMS.
Importance: High

Dear Robert,

I just received a call from the OSE and they told me that your REMS submission is incomplete.

The REMS should include two documents:

1. **PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)**
2. **REMS SUPPORTING DOCUMENT**

You sent us **item # 1**, but **item # 2** is missing. Please refer to the attached REMS template.

Item # 2 should include:

Table of Contents:

1. BACKGROUND
2. GOALS
3. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS
 - A. ADDITIONAL POTENTIAL ELEMENTS
 - I. MEDICATION GUIDE
 - II. PATIENT PACKAGE INSERT
 - III. COMMUNICATION PLAN
 - B. ELEMENTS TO ASSURE SAFE USE
 - C. IMPLEMENTATION SYSTEM
 - D. TIMELINE FOR ASSESSMENT OF THE REMS
4. INFORMATION NEEDED FOR ASSESSMENTS
5. OTHER RELEVANT INFORMATION

APPENDICES

ATTACHMENT (MedGuide)

Please note that some elements may not be necessary for your application and you can simply indicate "Element not necessary".

We encourage you to send us a new submission as soon as you can.

Thank you,

Margarita

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/s/

Margarita Tossa
3/30/2009 11:32:12 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-352

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your NDA dated June 20, 2008, received June 20, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Colchicine Tablets USP, 0.6 mg.

We also refer to your December 19, 2008 correspondence, received December 19, 2008 requesting review of your proposed proprietary name, Colcrys. We have completed our review of the proposed proprietary name, Colcrys and have concluded that it is acceptable.

The proposed proprietary name, Colcrys, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 20, 2008 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Chris Wheeler, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0151. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center of Drug Evaluation and Research

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/s/

Bob Rappaport
3/6/2009 11:55:07 AM

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-352	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Colchicine Dosage Form: Tablets Strengths: 0.6 mg		
Applicant: Mutual Pharmaceuticals Company, Inc.		
Date of Receipt: 6/20/2008		
PDUFA Goal Date: 12/20/2008	Action Goal Date (if different): 12/19/2008	
Proposed Indication(s): Treatment of Familial Mediterranean Fever (FMF)		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "YES," proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Literature	All sections of labeling
NDA 84-279 (Col-Probenecid)	PK studies
Fed Register Vol 37, No 146, July 29, 1972, p. 15189 (FR 72-11723)	(DESI 12965 number difficult to read?) DESI review summary for colchicine/probenecid products

The Sponsor summarized the literature as follows:

Three published randomized studies have been identified that demonstrate that colchicine effectively reduces the frequency, intensity, and duration of acute attacks of FMF. Numerous uncontrolled studies and large case series, including in children, provide support. These trials comprise more than 3500 adults and children with FMF. Current practice is that once FMF is diagnosed, colchicine treatment is started and continued for life. Indeed, the diagnosis of FMF is questioned if a patient does not respond to colchicine. The published literature is described in the Integrated Summary of Efficacy included in this NDA.

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA study (Study MPC-004-07-1001) with NDA 84-279 (Col-Probenecid)

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES X NO

If "NO," proceed to question #6.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

(Note: None of the literature appeared to refer to ColBenemid, only to "colchicine".) YES NO X

*If "NO", proceed to question #6
If "YES", list the listed drug(s) identified by name and answer question #5(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)? YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #11.

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Col-Probenecid	84-279	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES NO

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b. Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: Col-Probenecid

- c. Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES NO X

If "YES", please list which drug(s) and answer question d.1.

If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES NO X

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution"). This application provides for a new indication, Familial Mediterranean Fever (FMF), for a new dose, and for a new formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO X

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO X

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES X NO

If "NO", proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES X NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): None

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
- Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Margarita Tossa
2/3/2009 12:39:24 PM
CSO

From: Duvall Miller, Beth A
Sent: Tuesday, February 03, 2009 8:39 AM
To: Tossa, Margarita
Cc: Quaintance, Kim M
Subject: NDA 22-352 - b(2) clearance notice

Good morning Rita,

Your application was discussed at yesterday's clearance meeting. This is official notification that your application is cleared for action from a b(2) perspective.

Beth

Beth Duvall-Miller
Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9858

From: Tossa, Margarita
Sent: Thursday, January 29, 2009 12:05 PM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M
Subject: RE: NDA 22-352 - b(2) assessment needed/action date.

All the disciplines recommended approval, however, the site inspections results are pending.

Rita.

From: Duvall Miller, Beth A
Sent: Thursday, January 29, 2009 11:45 AM
To: Tossa, Margarita
Cc: Quaintance, Kim M
Subject: RE: NDA 22-352 - b(2) assessment needed/action date.

Thanks for the update on your action goal date.

We are discussing your application at Monday's (2/2) clearance meeting – I'll get back to you following that meeting.

Are you planning an approval action?

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9858

From: Tossa, Margarita

Sent: Thursday, January 29, 2009 10:06 AM

To: Duvall Miller, Beth A

Subject: RE: NDA 22-352 - b(2) assessment needed/action date.

Hi Beth,

We are planning to take an action on this application during the week of February 16-20, 2009.

Best,

Rita.

From: Duvall Miller, Beth A

Sent: Wednesday, January 07, 2009 8:32 AM

To: Tossa, Margarita

Cc: Stradley, Sara; Sullivan, Matthew; Colangelo, Kim M

Subject: RE: NDA 22-352 - b(2) assessment needed

Thanks Rita,

We'll be in touch. According to Sara's email, it sounds like you won't be taking an action until February. Once you have a more precise date in mind, please let us know.

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9858

From: Tossa, Margarita
Sent: Wednesday, January 07, 2009 8:21 AM
To: Duvall Miller, Beth A
Cc: Stradley, Sara; Sullivan, Matthew
Subject: RE: NDA 22-352 - b(2) assessment needed
Importance: High

Good morning Beth,

Here is a bit of history re: 505(b)(2) for this NDA.

In the Cover letter (original NDA submission) the sponsor stated that NDA was submitted under Section 505(b)(2) of the Federal Food and Cosmetic Act, however, in Form 356h they checked the _____
The sponsor was notified about the discrepancy and advised to make a necessary change to the NDA.

b(4)

On August 19, 2008, the sponsor submitted an information amendment to the NDA (Cover letter and corrected Form 356h).

The network location is : \\CDSESUB\EVSPROD\NDA022352\022352.ENX

Here is the 505(b) (2) assessment.

<< File: B2 assessment .doc >>

Thank you,

*Margarita Tossa, M.S.
Regulatory Project Manager
FDA/CDER/DAARP
phone: (301) 796-4053
fax: (301) 796-9713
Email: margarita.tossa@fda.hhs.gov*

From: Duvall Miller, Beth A
Sent: Tuesday, January 06, 2009 4:04 PM
To: Tossa, Margarita
Cc: Jani, Parinda; Stradley, Sara
Subject: NDA 22-352 - b(2) assessment needed
Importance: High

Re: NDA 22-352, colchicine tablets

Hi Margarita,

I work with Kim Colangelo to track and clear (with OCC) 505(b)(2) applications.

I stumbled across your application today in my spreadsheet. Your filing letter and RPM filing review indicate that it's a b(2) that received a priority review with a PDUFA due date of 12/20/08. In contrast, the applicant's 356h form indicates it's a _____ . Your filing review indicates it's a b(2) based on published literature – note that the application is considered a b(2) only if you cannot approve the application without reliance on the published literature, not simply that the literature is *supportive* of approval. This is something that you can discuss more with your colleagues in DAARP (and/or us) as you complete the b(2) assessment form.

b(4)

First, can you please confirm if this is in fact a 505(b)(2) application? If so, what is the status of acting on this application – I note that it's past due and do not see a major amendment or letter indicating an extension of the clock but please correct me if I'm wrong.

Finally, if it is in fact a 505(b)(2), we will need you to complete the b(2) assessment form

(<http://inside.fda.gov/CDER/OfficeofNewDrugs/ImmediateOffice/UCMO27499.html>) and return to us ASAP (draft is fine for now) so that we can work with OCC to clear your application for action. You should not take an action on this application until it's been cleared via OCC (assuming this is in fact a b(2)).

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9858

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Margarita Tossa
2/3/2009 02:01:53 PM
CSO

Friday, January 30, 2009

Date: Saturday, January 01, 4561 12:00:00 AM

Margarita,

We are finalizing our official response to the Discipline Review letter and will submit it to the Division on Monday. Meanwhile, here are some preliminary comments regarding the two proposed post-marketing commitments:

1. Conduct an evaluation of the potential carcinogenicity of colchicine in two rodent species.

Response to Item 1.

The post-marketing study commitments, should the product be approved for FMF, are listed below.

1. Description of Commitment – Conduct a 2-year oral (gavage) carcinogenicity study of colchicine in the mouse.

Protocol Submission: by 01/10
Study Start: by 04/10
Final Report Submission: by 04/13

2. Description of Commitment – Conduct a 2-year oral (gavage) carcinogenicity study of colchicine in the rat.

Protocol Submission: by 01/10
Study Start: by 04/10
Final Report Submission: by 04/13

Mutual intends to submit draft protocols to the executive CAC for approval prior to commencing the carcinogenicity studies. Below is the sequence of studies and reviews that would need to occur in order to achieve the proposed commitments, since there are no repeated-dose oral toxicity data currently available, from which to estimate the proper maximum tolerated doses for each species.

Study Type	Initiation	Dose Selection for Subsequent Study	Final Report
14-Day Mouse	Mar 2009	May 2009	May 2009
14-Day Rat	Mar 2009	May 2009	May 2009
28-Day Mouse	May 2009	Jul 2009	Aug 2009
28-Day Rat	May 2009	Jul 2009	Aug 2009
90-Day Mouse	Aug 2009	Jan 2010	Feb 2010
90-Day Rat	Aug 2009	Jan 2010	Feb 2010
CAC Review	Jan 2010	n/a	n/a
2-year Mouse	Apr 2010	n/a	Apr 2013
2-year Rat	Apr 2010	n/a	Apr 2013

2. Improve detection assays to allow reduction of the specifications for the photo-degradant

impurities β - and γ -lumicolchicine or conduct *in vitro* genetic toxicology studies evaluating mutagenicity and clastogenicity.

Response to item 2.

Mutual agrees to a post marketing commitment to supplement the application with newly developed and validated methods and specifications for the finished product to include a specification of NMT 0.06% for the combined impurities of β -lumicolchicine and γ -lumicolchicine. Mutual will also work with the API supplier to add the same specification of NMT 0.06% for the combined impurities to the API specification. At this time, Mutual can not estimate when this method development/validation work will be completed, although we believe that we can begin the project within 6 months post-approval.

I hope this information is helpful until you receive our official response next week.

Have a good weekend.

Bob

From: Robert Dettery
Sent: Wednesday, January 28, 2009 10:22 AM
To: Tossa, Margarita
Cc: Jennifer W. Phillips
Subject: RE: NDA 22-352 colchicine (FMF)/PMR.

Margarita,
We have no objections to the recommended post-marketing commitments and are in the process now of developing carcinogenicity studies. I can respond officially to the DR letter either tomorrow or Friday with proposed timelines.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Wed 1/28/2009 10:05 AM
To: Robert Dettery
Subject: NDA 22-352 colchicine (FMF)/PMR.

Dear Robert,

We would like to know if your company is planning to respond to the attached below Discipline Review letter.

We would appreciate knowing your thoughts on the post-marketing studies if the application is approved and proposed timelines.

Thank you,

Margarita Tossa, M.S.

Regulatory Project Manager

FDA/CDER/D.A.A.R.P

phone: (301) 796-4053

fax: (301) 796-9713

Email: margarita.tossa@fda.hhs.gov

From: Tossa, Margarita
Sent: Thursday, January 08, 2009 4:22 PM
To: 'Robert Dettery'
Subject: NDA 22-352/colchicine/FMF/DR letter.

Dear Robert,

Here is the discipline (Pharm/Tox) review letter for NDA 22-352; you will receive a paper copy in the next few days.

<<PharmTox DR ltr.pdf>>

Best regards,

Margarita

From: Robert Dettery
To: Tossa, Margarita;
cc: Jennifer W. Phillips;
Subject: RE: NDA 22-352 colchicine (FMF)/PMR.
Date: Wednesday, January 28, 2009 10:26:37 AM

Margarita,

We have no objections to the recommended post-marketing commitments and are in the process now of developing carcinogenicity studies. I can respond officially to the DR letter either tomorrow or Friday with proposed timelines.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Wed 1/28/2009 10:05 AM
To: Robert Dettery
Subject: NDA 22-352 colchicine (FMF)/PMR.

Dear Robert,

We would like to know if your company is planning to respond to the attached below Discipline Review letter.

We would appreciate knowing your thoughts on the post-marketing studies if the application is approved and proposed timelines.

Thank you,

Margarita Tossa, M.S.

Regulatory Project Manager

FDA/CDER/DAARP

phone: (301) 796-4053

fax: (301) 796-9713

Email: margarita.tossa@fda.hhs.gov

From: Tossa, Margarita
Sent: Thursday, January 08, 2009 4:22 PM
To: 'Robert Dettery'
Subject: NDA 22-352/colchicine/FMF/DR letter.

Dear Robert,

Here is the discipline (Pharm/Tox) review letter for NDA 22-352; you will receive a paper copy in the next few days.

<<PharmTox DR ltr.pdf>>

Best regards,

Margarita

Confidentiality Notice: This e-mail message, including any attachments, is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is prohibited. If you are not the intended recipient, please contact the sender by reply e-mail and destroy all copies of the original message. Unless expressly stated in this e-mail, nothing in this message or any attachment should be construed as a digital or electronic signature.

Date: Saturday, January 01, 4501 12:00:00 AM
Attachments: [final insert.doc](#)

Margarita,
Attached is the draft colchicine FMF insert with our comments and changes.
The MedGuide is part of the insert in Section 17.6.

We plan to submit our draft REMS program later this week.

Bob

-----Original Message-----

From: Tossa, Margarita [<mailto:margarita.tossa@fda.hhs.gov>]
Sent: Wednesday, January 14, 2009 3:52 PM
To: Robert Dettery
Subject: Emailing: COLSTAT DRAFT INSERT.doc
Importance: High

<<COLSTAT DRAFT INSERT.doc>>

Dear Robert,

Please find the attachment with the draft label for colchicine. Use track changes to make any additions or changes to the label.

Make sure that we did not delete anything from the label without track changes (compare the original draft to this one). Please do the following:

1. If you agree with our changes to the label just accept them.
2. If you do not agree make your changes or comments. If any of your comment(s) is (are) more than one paragraph place your comment(s) in the separate attachment to the label.

We would appreciate if you make available the label and the proposed MedGuide by C.O.B. on Tuesday (01-21-2009).

Thank you,
Margarita

Date: Saturday, January 01, 4501 12:00:00 AM

Margarita,

We will have our comments to the draft insert and MedGuide, plus our proposed REMS program, by Wednesday noon. I will email it to you, but do you also want it as an official amendment to the NDA or should we wait until FDA/Mutual are in agreement before officially submitting?

Robert Dettery

Vice President, Regulatory Affairs



please consider the environment before printing this e-mail

~~Date: Saturday, January 01, 2009 12:00:00 AM~~

01/16/2009

Margarita,

Thank you for the draft label. We are in the process of reviewing and will respond to it and the MedGuide, but I am unclear on the date. You stated Tuesday (01-21-2009) but Tuesday is the 20th? Since Monday is a holiday and Tuesday is Inauguration Day (I assume you have off) I am hoping that you meant Wednesday, 01-21-2009. Can you clarify?

Also, the 120 day safety update for NDA 22-351, acute gout, is 01-31-2009. Due to the time being spent on the FMF labeling and our intention to revise the acute gout labeling to be similar, we may be a few days late on that 120-day update. Would this be a problem?

I'll keep you updated.

Bob

-----Original Message-----

From: Tossa, Margarita [<mailto:margarita.tossa@fda.hhs.gov>]

Sent: Wednesday, January 14, 2009 3:52 PM

To: Robert Dettery

Subject: Emailing: COLSTAT DRAFT INSERT.doc

Importance: High

<<COLSTAT DRAFT INSERT.doc>>

Dear Robert,

Please find the attachment with the draft label for colchicine. Use track changes to make any additions or changes to the label.

Make sure that we did not delete anything from the label without track changes (compare the original draft to this one). Please do the following:

1. If you agree with our changes to the label just accept them.
2. If you do not agree make your changes or comments. If any of your comment(s) is (are) more than one paragraph place your comment(s) in the separate attachment to the label.

We would appreciate if you make available the label and the proposed MedGuide by C.O.B. on Tuesday (01-21-2009).

Thank you,
Margarita

From: Tossa, Margarita
To: "Robert Dettery";
Subject: RE: NDA 22-352, colchicine, FMF
Date: Friday, January 09, 2009 4:05:27 PM

Dear Robert,

I received your email.

I need to discuss all your questions with my team; we will respond by end of next week.

Best regards,
Margarita

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Friday, January 09, 2009 3:53 PM
To: Tossa, Margarita
Cc: Brandi Adoff
Subject: NDA 22-352, colchicine, FMF

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Date: Saturday, January 01, 4501 12:00:00 AM

Margarita,

Thank you for your recent emails regarding our NDA 22-352, colchicine, FMF indication. I wanted to send this email to acknowledge receipt of the various documents and to ask a few questions about the NDA review.

Mutual acknowledges the receipt of the medical Discipline Review letter. We will remove all references to _____ from the FMF labeling.

Questions:

1. Would you like to receive the revised labeling, with _____ at this time or should we wait until labeling discussions begin?
2. When do you think labeling discussions will begin for this application?

b(4)

Regarding the proposed MedGuide and REMS that you sent us, we are in the process of drafting a MedGuide and a REMS template which we believe we can submit within the next two weeks.

Questions:

3. We note the proposed MedGuide from FDA included only the DDI with clarithromycin and colchicine. We have subsequently discovered and submitted in our gout NDAs DDI information regarding colchicine interaction with cyclosporine, diltiazem, erythromycin, ritonavir, verapamil, and ketoconazole. Should we include warnings about the use of colchicine with these drugs in the package insert and MedGuide at this time?
4. When will we know about our proposed brand name for colchicine? We would like to incorporate the brand name into the revised labeling.
5. We proposed a Patient Package Insert in our draft labeling. Now that we agree to include a MedGuide with the product, will the PPI be eliminated?

We acknowledge receipt of the PharmTox Discipline Review letter and we have taken your comments into consideration.

Question:

6. Are there any other DR letters that will be provided to us and, is so,

when can we expect to receive them?

Thanks again and have a good weekend.

Robert Dettery
Vice President, Regulatory Affairs



please consider the environment before printing this e-mail

From: Tossa, Margarita
To: "Robert Dettery";
Subject: NDA 22-352/colchicine/FMF.
Date: Wednesday, January 07, 2009 3:29:52 PM
Attachments: [COLCHICINE MEDICATION GUIDE draft.doc](#)
[REMS template.doc](#)

Dear Robert,

The clinical team has determined that a medication guide may be warranted for your product to alert patients to the potential for serious drug-drug interactions with colchicine and to the increased susceptibility to severe colchicine toxicity in patients with renal or hepatic impairment. A draft medication guide is attached to assist you in developing your medication guide.

As you may be aware, a medication guide is a type of risk evaluation and mitigation strategy (REMS). A template for a REMS submission is also attached for your reference.

If it is determined that a medication guide/REMS is necessary for your product, these items would need to be submitted and reviewed prior to taking an action on your NDA.

Therefore, we recommend you submit these items as soon as possible as an official submission to your NDA.

Best regards,

Margarita Tossa, M.S.

Regulatory Project Manager

FDA/CDER/DAARP

phone: (301) 796-4053

fax: (301) 796-9713

Email: margarita.tossa@fda.hhs.gov

From: Robert Dettery
To: Tossa, Margarita;
cc: Brandi Adoff; Andria Wervnski;
Subject: RE: FYI - _____ for Colchicine API
Date: Thursday, December 11, 2008 3:02:46 PM

b(4)

Dear Margarita,

I want to thank you for your response to my email, which you sent on December 9th.

I understand that the Agency won't approve our NDA for colchicine for FMF by the PDUFA date since our API manufacturer, _____ can't be inspected for cGMP compliance by that date. This resulted from the _____

b(4)

This is one of those occasional cases where the regulatory practices diverge from the science and unique situation. I want to explain what I mean, with the hope that the Agency might reconsider, but I certainly don't want to seem too pushy or offensive.

The unique situation here is that FMF patients must take colchicine so they are currently taking colchicine which is not approved by FDA. This means that the API manufacturers for the unapproved colchicines are not subject to FDA cGMP inspections before these patients take this unapproved product. The unapproved manufacturers can use any API manufacturer that they want, and can change manufacturers whenever they want, so there is no reason to believe that their API manufacturers have passed cGMP inspections. They might even be using our API manufacturer, _____

b(4)

The irony is that our NDA has many API safeguards, that will undergo Agency review and approval, whereas the unapproved manufacturers have undergone no FDA approval at all. For example, our NDA requires that the API be tested for assay, impurities, identity and residual solvents. So the irony is that by the Agency not approving our NDA for FMF by the PDUFA date, since our API manufacturer can't be cGMP inspected by then, the Agency is requiring FMF patients to consume colchicine with less assurances of product quality than if our NDA for FMF was approved by the PDUFA date. This is one of those weird quirks where the regulatory practice diverges with the "facts on the ground".

Regarding the name Colstat™ not being acceptable, we would be willing to market our product without a brand name at first and work diligently with the Agency to determine an acceptable name thereafter. We will be providing alternative trade names for FDA consideration, following the new FDA guidance, in a separate submission to the NDA.

Margarita, again, I don't mean to be a nuisance here. I just wanted the Agency to be able to consider these facts in your decision.

Best regards,
Bob Dettery

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Tuesday, December 09, 2008 11:56 AM
To: Robert Dettery
Subject: RE: FYI - _____ for Colchicine API

b(4)

Dear Robert,

1. _____ therefore, the Division will not be able to meet the PDUFA date. An action will not be taken until the inspections are completed. **b(4)**
2. The Division of Medication Error Prevention and Analysis has concluded that the name COLSTAT is unacceptable because it contains the United States Adopted Names (USAN) Council stem '-stat'. You will receive an official letter with details next week.
3. You should submit an alternative proposed proprietary name for the drug product, Colchicine, for review.

Best regards,
Margarita.

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Tuesday, December 09, 2008 10:26 AM
To: Tossa, Margarita
Cc: Brandi Adoff; Andria Werynski
Subject: FW: FYI - _____ for Colchicine API
Importance: High

Good morning Margarita,
Per the email below, we were just informed that the colchicine API supplier will undergo _____
_____ How does this impact the _____ for NDA 22-352? **b(4)**

Also, have you heard anything about the acceptability of the Colstat trade name?

Bob

From: Dwight Hanshew
Sent: Tuesday, December 09, 2008 10:03 AM
To: Kurt Nielsen; Whitney Stearns; Shawn Watson; Lorraine Betz; Michelle Mohan; Steve Zebovitz; Brendan Magrab; Robert Dettery
Cc: Dwight Hanshew
Subject: FYI - _____ for Colchicine API
Importance: High

FDA notified _____ on Dec 5th of the request for pre-approval inspection relating to Colchicine.
_____ will accept the proposed dates. (Excerpt below and in entirety in the attachment)... **b(4)**

This is to pre-announce a _____
_____ by investigators from the U.S. Food and Drug Administration. The inspection will determine if products are manufactured following the current Good Manufacturing Practice regulations for human pharmaceuticals. Your firm is referenced in the following application:

NDA 22352/000 as the manufacturer of Colchicine Tablets USP 0.6MG. The applicant is Mutual Pharm in Philadelphia, PA

The inspection will be performed at no cost to the company. While it is not necessary that the facility be manufacturing products for the U.S. market at the time of this inspection, we do expect that the facility will be operating and that the investigator can observe production activities. **b(4)**

We are proposing the dates of _____ of the Food and Drug Administration to inspect your facility.

Dwight D. Hanshew, Jr.
Senior Vice President, Operations

URL Pharma

1100 Orthodox Street
Philadelphia, PA 19124

Phone 001.215.288.1309
Fax 001.215.807.1306

dhanshew@urlpharma.com

www.urlpharma.com

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From: [Robert Dettery](#)
To: [Tossa, Margarita](#);
cc: [Brandi Adoff](#);
Subject: RE: Additional information request/NDA 22352/FMF.
Date: Thursday, November 13, 2008 2:54:05 PM

Hi Margarita,

Sorry for the delay in responding to your email from this morning, but we wanted to conduct one final literature search for pediatric PK data. I can now answer your inquiry by stating that Mutual has not generated any pharmacokinetics data, nor does there appear to be any pharmacokinetics data in the literature, for colchicine use in pediatric population.

If you have any other questions, please let me know.
Bob

From: Tossa, Margarita [<mailto:margarita.tossa@fda.hhs.gov>]
Sent: Thursday, November 13, 2008 8:14 AM
To: Robert Dettery
Subject: Additional information request/NDA 22352/FMF.
Importance: High

Good morning Bob,

The Clin Pharm reviewer wants to know if you have any pharmacokinetics data in pediatrics on Colchicine, if you have, please submit this data ASAP as an amendment to your [NDA 22-352/FMF](#).

Thank you,

Margarita

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any attachment should be construed as a digital or electronic signature.

From: Jennifer W. Phillips
To: Tossa, Margarita;
Subject: RE: Colchicine NDA—— Serial S-005 Response to Discipline Review Letter--CMC and Labeling
Date: Thursday, October 09, 2008 3:35:37 PM

b(4)

Margarita—

Just wanted to follow-up with you to let you know that we submitted our letter yesterday for the proprietary name review for COLSTAT. Thanks very much for your help and assistance with this.

With kind regards,
Jennifer

Jennifer W. Phillips, Pharm.D.

Director, Regulatory Affairs

URLPharma

7722 Dungan Road

Philadelphia, PA 19111-3131

215-697-1795

jwphillips@urlpharma.com

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Tuesday, October 07, 2008 11:13 AM
To: Jennifer W. Phillips
Subject: RE: Colchicine NDA —— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

You can do it tomorrow.

Margarita

From: Jennifer W. Phillips [mailto:jwphillips@urlpharma.com]
Sent: Tuesday, October 07, 2008 11:06 AM
To: Tossa, Margarita
Subject: RE: Colchicine NDA —— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Margarita-

Thanks so much for getting back to me. I am out of the office today. Is it acceptable to submit this submission for NDA 22-352 tomorrow or is there an urgency to submit today? Please let me know.

Kind regards,
Jennifer

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Tue 10/7/2008 9:00 AM
To: Jennifer W. Phillips
Cc: Robert Dettery
Subject: RE: Colchicine NDA — Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Good morning Jennifer & Bob,

I have some new information for you:

1. We have a new procedure for handling request for proprietary name review, which was implemented on October 1, 2008.
2. In order for the OSE to review the new proposed proprietary name Colstat™ for **NDA 22-352 (FMF)** you need to send us a separate submission “request for proprietary name review”, because your submission was received by the Agency on October 2, 2008.
3. However, you do not have to send us a separate submission for **NDA 22-351 (acute goat flares)**, because this submission was received by the Agency on September 30, 2008.
4. The Agency will review only one proposed proprietary name at the time, if the Agency concluded that the proposed name is not acceptable than you can submit an additional proposed proprietary name for review.

Here is the minimum amount of information needed for the OSE to begin a proprietary name review:

- Indication
- Dosage forms
- Strength
- Usual dose

- Dosing frequency
- Prescribing population
- Packaging information (if injectable)
- Route of administration
- Any unique product characteristics for the drug
- Major adverse events
- Working model of device for drug delivery (if applicable)
- All labeling: professional and patient

I believe that you have all the information in the labeling section of your submission.

The bottom line:

- You need to send us a separate submission “request for proprietary name review” for NDA 22-352 Colchicine 0.6 mg (FMF) in order for us to review the proposed tradename Colstat™.

Best regards,
Margarita

From: Jennifer W. Phillips [mailto:jwphillips@urlpharma.com]
Sent: Monday, October 06, 2008 12:33 PM
To: Tossa, Margarita
Subject: RE: Colchicine NDA ——— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Thanks so much. I appreciate your help.

Jennifer W. Phillips, Pharm.D.

Director, Regulatory Affairs

URLPharma

7722 Dungan Road

Philadelphia, PA 19111-3131

215-697-1795

jwphillips@urlpharma.com

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Monday, October 06, 2008 12:30 PM
To: Jennifer W. Phillips
Subject: RE: Colchicine NDA ——— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Jennifer,

I have to check on this, I will let you know as soon as I can.

Rita.

From: Jennifer W. Phillips [mailto:jwphillips@urlpharma.com]
Sent: Monday, October 06, 2008 12:20 PM
To: Tossa, Margarita
Subject: RE: Colchicine NDA ——— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

Margarita--One last question—do we need to send in an official letter notifying you of an alternate trade name ——— so it can be reviewed just in case Colstat is not acceptable as a tradename?
Thanks for your help with this.

b(4)

Jennifer W. Phillips, Pharm.D.
Director, Regulatory Affairs
URLPharma
7722 Dungan Road
Philadelphia, PA 19111-3131
215-697-1795
jwphillips@urlpharma.com

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Monday, October 06, 2008 12:02 PM
To: Jennifer W. Phillips
Subject: RE: Colchicine NDA ——— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Hi Jennifer,

Your submission is fine, I can see the PLRdraft label in your submission, and however, for some reasons I can not copy this document to my share drive.

If possible, please send me a word document.

For now I do not need the PLR draft for the alternate name.

*Thanks,
Margarita*

From: Jennifer W. Phillips [mailto:jwphillips@urlpharma.com]
Sent: Monday, October 06, 2008 11:53 AM
To: Tossa, Margarita
Subject: RE: Colchicine NDA ——— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Dear Margarita,
We submitted PLR draft label for Colstat in a word document in S-005. Please let me know if you can't locate in the submission, I can re-send it. Or, do you mean provide PLR draft label for our alternate name ——— as discussed in my Oct 3, 2008 email

b(4)

Thanks!

Jennifer W. Phillips, Pharm.D.
Director, Regulatory Affairs
URLPharma
7722 Dungan Road
Philadelphia, PA 19111-3131
215-697-1795
jwphillips@urlpharma.com

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Monday, October 06, 2008 11:39 AM
To: Jennifer W. Phillips
Subject: RE: Colchicine NDA ——— Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Dear Jennifer & Bob,

If possible, send me the new PLR Draft label for Colchicine 0.6 mg (Colstat™) in a Word document.

Thank you,

Margarita

From: Jennifer W. Phillips [mailto:jwphillips@urlpharma.com]
Sent: Friday, October 03, 2008 10:14 AM
To: Tossa, Margarita; Sullivan, Matthew
Cc: Robert Dettery
Subject: RE: Colchicine NDA ———Serial S-005 Response to Discipline Review Letter--CMC and Labeling

b(4)

Hi Margarita and Matt,
We wanted to let you know that we submitted our response to the Discipline Review letter yesterday for NDA 22-352 Colchicine Tablets USP, 0.6 mg.

We have one question for you concerning the proposed tradename. In our response we included one tradename, COLSTAT, to be reviewed by the Agency. We have an alternate tradename, _____ that was not included in the cover letter. We would like to have both names reviewed just in case COLSTAT is not acceptable. Can you advise us on the best approach for submission of this alternate name? Should we send you a separate letter with both names?

b(4)

Thank you in advance for your guidance and assistance with this issue.

With kind regards,

Jennifer Phillips for *Robert Dettery*
Vice President, Regulatory Affairs

Jennifer Phillips, Pharm.D.
Director, Regulatory Affairs,
URL Pharma
jwphillips@urlpharma.com

From: Robert Dettery
Sent: Monday, August 18, 2008 11:52 AM
To: 'Sullivan, Matthew'
Cc: Brandi Adoff
Subject: Colchicine NDA for gout

Hi Matt,
Given our pending application for colchicine tablets indicated for FMF, should we write the labeling for our NDA, to be submitted next week, for colchicine indicated for Acute Gout independent of FMF or include both

indications (FMF and treatment of acute gout) in the label?

If you need any further explanation regarding this question, please let me know. We would really like to get an answer as soon as possible as this affects how the label will be written.

Thanks much,

Robert Dettery
Vice President, Regulatory Affairs



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From: Jennifer W. Phillips
To: Tossa, Margarita; Sullivan, Matthew;
cc: Robert Dettery;
Subject: RE: Colchicine NDA _____ Serial S-
005 Response to Discipline Review Letter--CMC and Labeling
Date: Friday, October 03, 2008 10:14:12 AM

b(4)

Hi Margarita and Matt,
We wanted to let you know that we submitted our response to the Discipline Review letter yesterday for NDA 22-352 Colchicine Tablets USP, 0.6 mg.

We have one question for you concerning the proposed tradename. In our response we included one tradename, COLSTAT, to be reviewed by the Agency. We have an alternate tradename, _____ that was not included in the cover letter. We would like to have both names reviewed just in case COLSTAT is not acceptable. Can you advise us on the best approach for submission of this alternate name? Should we send you a separate letter with both names?

b(4)

Thank you in advance for your guidance and assistance with this issue.

With kind regards,

Jennifer Phillips for *Robert Dettery*
Vice President, Regulatory Affairs

Jennifer Phillips, Pharm.D.
Director, Regulatory Affairs,
URL Pharma
jwphillips@urlpharma.com

From: Robert Dettery
Sent: Monday, August 18, 2008 11:52 AM
To: 'Sullivan, Matthew'
Cc: Brandi Adoff
Subject: Colchicine NDA for gout

Hi Matt,
Given our pending application for colchicine tablets indicated for FMF, should we write the labeling for our NDA, to be submitted next week, for colchicine indicated for Acute Gout independent of FMF or include both indications (FMF and treatment of acute gout) in the label?

If you need any further explanation regarding this question, please let me

know. We would really like to get an answer as soon as possible as this affects how the label will be written.

Thanks much,

Robert Dettery
Vice President, Regulatory Affairs



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From: Robert Dettery
To: Tossa, Margarita;
cc: Brandi Adoff;
Subject: RE: NDA 22-352 Colchicine (FMF).
Date: Friday, September 19, 2008 2:46:31 PM

Margarita,

The response to the DR letter is almost complete. The last item we are working on is to revise our API method, which is pending information from _____ regarding their specification revisions. Once we have that information, it will take us about 1 day to process our method through change control. We believe it is possible to respond to the deficiency letter no later than Friday, Sept. 26th.

b(4)

I do not know if _____ ever received the official DMF deficiency letter in the mail, but we did fax them the copy that you provided. They are targeting NLT Sept. 30th for their response. _____ responded to their DMF deficiency letter on Sept. 15th.

b(4)

If there is anything else, please let me know.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Friday, September 19, 2008 11:45 AM
To: Robert Dettery
Subject: NDA 22-352 Colchicine (FMF).
Importance: High

Dear Robert,

If possible, please give me an update on your responses to the DR letter and responses to the DMF deficiencies letters.

Did _____ receive the DMF deficiency letter by mail?

b(4)

Thanks,

Margarita

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From: Robert Dettery
To: Tossa, Margarita;
cc: Brandi Adoff;
Subject: RE: NDA 22-352/Regulatory Info.
Date: Wednesday, August 13, 2008 4:31:38 PM

Sorry about that. It was an oversight. We will make the correction and resubmit as you advised.

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Wednesday, August 13, 2008 4:28 PM
To: Robert Dettery
Subject: NDA 22-352/Regulatory Info.

Dear Bob,

I reviewed the regulatory part of your NDA 22-352 (Cover letter, 356h Form) and found some discrepancies in it.

In the Cover letter you stated that your NDA was submitted under Section 505(b)(2) of the Federal Food and Cosmetic Act, however, in Form 356h you checked the _____

b(4)

You must submit the new Form 356h and Cover letter as General Information for your NDA.

Thank you,

Margarita

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From: [Robert Dettery](#)
To: [Sullivan, Matthew](#);
cc: [Andria Werynski](#); [Tossa, Margarita](#);
Subject: RE: N22352 Facilities questions
Date: Wednesday, July 02, 2008 11:24:39 AM

I understand. Most if not all of the domestic places have a current acceptable compliance history and may not need to be inspected. In any event, we will accept the risk that the more facilities we name, the greater the chance of a problem.

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Wednesday, July 02, 2008 11:19 AM
To: Robert Dettery
Cc: Andria Werynski; Tossa, Margarita
Subject: RE: N22352 Facilities questions

Bob –

I heard back from the Chemist. She said that you can submit all the facilities, as you've done, but we're forced to inspect them all. Having more facilities inspected will increase the chance that a violation will be found. If this happens, it may have an impact on the approvability of the application.

Matt

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Wednesday, July 02, 2008 10:47 AM
To: Sullivan, Matthew
Cc: Andria Werynski
Subject: RE: N22352 Facilities questions

Matt,

The "may" simply means that the contract lab will be an option in the event our own lab is over-burdened with work. This is how they have been approved in one other NDA and many ANDAs.

Bob

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Wednesday, July 02, 2008 10:28 AM
To: Andria Werynski; Robert Dettery
Cc: Tossa, Margarita
Subject: RE: N22352 Facilities questions

Thanks, I'll pass this along to the Chemist.

I suspect that they are going to complain that it's inadequate, however. They made specific mention to me that your use of the word "may" (i.e., "may perform"; "may be utilized") wasn't in keeping with a complete submission.

I'll let you know what they say.

Matt

From: Andria Werynski [mailto:awerynski@urlpharma.com]
Sent: Wednesday, July 02, 2008 10:18 AM
To: Sullivan, Matthew; Robert Dettery
Cc: Tossa, Margarita
Subject: RE: N22352 Facilities questions

Matt,

I've attached the requested information regarding the foreign and domestic facilities. We will prepare an amendment to submit this information formally.

Andria

*Andria Werynski
Manager, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124
215-288-6500*

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Tuesday, July 01, 2008 3:37 PM
To: Robert Dettery

Cc: Tossa, Margarita; Andria Werynski
Subject: RE: N22352 Facilities questions

Bob –

Please submit it via email to me when it's available. You should also submit it officially so we have it on record, but that can be done at your first lifecycle update (whenever that occurs).

Remind me what the May 21st submission was for?

Matt

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Tuesday, July 01, 2008 3:35 PM
To: Sullivan, Matthew
Cc: Tossa, Margarita; Andria Werynski
Subject: RE: N22352 Facilities questions

Matt,

I can probably have the information you requested together by tomorrow. How do you want us to submit it? Informally (i.e. email, fax, or other non-eCTD format), I could have it to you by the end of this week. Formally, it will take longer to prepare the eCTD submission and it would be ready sometime next week.

On another colchicine-related topic that I was intending to talk to you about anyway, we filed a General Correspondence to IND 72,586, Serial No. 0034, on May 21, 2008. Do you have any idea when we might hear a response about this?

Bob

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Tuesday, July 01, 2008 3:12 PM
To: Robert Dettery
Cc: Tossa, Margarita
Subject: N22352 Facilities questions

Bob –

We are (unofficially at this point) planning for a priority review for this application. As such, we need to ensure that everything is lined up right from the start since we have no time to loose.

To that end, we need to have some information on facilities as soon as you can provide it.

Specifically:

b(4)

1 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

b(4)

Thanks, and please let me know when you'll be responding to this request.

Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

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/s/

Margarita Tossa
2/3/2009 01:44:21 PM
CSO



DISCIPLINE REVIEW LETTER

NDA 22-352

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your new drug application (NDA) dated June 20, 2008, received June 20, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Colchicine Tablets USP, 0.6 mg.

Our review of the nonclinical section of your submission is complete, and we are considering the following recommendation for post-marketing studies if the application is approved:

1. Conduct an evaluation of the potential carcinogenicity of colchicine in two rodent species. Studies may consist of a 2-year bioassay in rat and a 6-month transgenic study in an appropriate mouse model. You are strongly encouraged to submit protocols for Agency concurrence on study design prior to initiation of studies.

We acknowledge that we previously agreed that carcinogenicity studies would not be required for approval of the FMF or gout indications; however, the recommendation to conduct the carcinogenicity evaluation of colchicine as a post-marketing study stems from the mechanistic plausibility for the drug to initiate and promote tumor development due to mitotic spindle inhibition and subsequent aneuploidy as well as the observation that Familial Mediterranean Fever (FMF) strikes a younger population compared to gout and this population may require the drug for prophylaxis treatment for the remainder of their life. The risk therefore is magnified due to the longer duration of treatment. The severity of this rare disease and associated morbidity and mortality as well as the substantial history of use of colchicine are factors which allow such a study to be done post-approval.

2. Improve detection assays to allow reduction of the specifications for the photo-degradant impurities β - and γ -lumicolchicine to ensure a limit of NMT 1.5 μ g TDI for the combined degradants. Alternatively, you may conduct in vitro genetic toxicology studies evaluating mutagenicity and clastogenicity which, if negative, would support the current proposed specifications.

NDA 22-352

Page 2

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Margarita Tossa, Regulatory Project Manager, at margarita.tossa@fda.hhs.gov or at (301) 796-4053.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
1/8/2009 04:05:04 PM



DISCIPLINE REVIEW LETTER

NDA 22-352

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your new drug application (NDA) dated June 20, 2008, received June 20, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Colchicine Tablets USP, 0.6 mg.

Our review of the clinical section of your submission is completed, and we have the following comments:

1. You have provided insufficient evidence of efficacy for the proposed indications regarding the ability of colchicine to _____ in patients with Familial Mediterranean Fever (FMF):

b(4)

b(4)

b(4)

b(4)

- d. Although publication bias is a concern for any application based primarily on the published literature, the tendency to publish positive results in this case cannot be mitigated by having randomized and controlled data to rely upon.

b(4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

NDA 22-352

Page 3

If you have any questions, contact Margarita Tossa, Regulatory Project Manager, at margarita.tossa@fda.hhs.gov or at (301) 796-4053.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
1/6/2009 02:59:57 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-352

**PROPRIETARY NAME REQUEST
- UNACCEPTABLE**

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your New Drug Application (NDA) dated June 20, 2008, received June 20, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Colchicine Tablets USP, 0.6 mg.

We also refer to your October 8, 2008, correspondence, received October 8, 2008, requesting review of your proposed proprietary name, COLSTAT. We have completed our review of this proposed proprietary name and have concluded that the name COLSTAT is unacceptable because it contains the United States Adopted Names (USAN) Council stem '-stat'. USAN stems are intended to indicate a pharmacological or chemical trait of a drug. The USAN definition of the stem '-stat' is 'enzyme inhibitors'. Since COLSTAT is not an enzyme inhibitor, the use of this stem in the proposed proprietary name is inconsistent with the USAN definition.

The USAN Council (tri-sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA)) works closely with the International Nonproprietary Name (INN) Programme of the World Health Organization (WHO) and various national nomenclature groups to achieve global standardization and unification of drug nomenclature and related rules with the goal of ensuring that drug information is communicated accurately and unambiguously.

Use of these stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names we recommend you screen potential proprietary names against the USAN stem list, and eliminate those that would incorporate USAN stems.

NDA 22-352

Page 2

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/cder/guidance/7935dft.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Chris Wheeler, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0151. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
12/12/2008 12:57:09 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-352

**PROPRIETARY NAME REQUEST
- UNACCEPTABLE**

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

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NDA 22-352

Page 2

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If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Chris Wheeler, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0151. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
12/18/2008 01:04:32 PM

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-352 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Colchicine Dosage Form: Tablets Strengths: 0.6 mg		
Applicant: Mutual Pharmaceuticals Company, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 6/20/2008 Date of Receipt: 6/20/2008 Date clock started after UN:		
PDUFA Goal Date: 12/20/2008	Action Goal Date (if different): 12/19/2008	
Filing Date: 8/19/2008 Date of Filing Meeting: 7/17/2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7P		
Proposed Indication(s): Treatment of Familial Mediterranean Fever (FMF)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>Refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 75,040	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	X YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i>	<input type="checkbox"/> YES X NO
If yes, explain:	
If yes, has OC/DMPQ been notified of the submission?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES NO
User Fee Status	<input type="checkbox"/> Paid X Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i>	<input type="checkbox"/> YES X NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments: However, seven years of orphan exclusivity was requested.</p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p>Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p>Format and Content</p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If not, explain (e.g., waiver granted):</p>			

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must</i></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><i>sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p>PREA</p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <p>Comments: Orphan designation granted, so PREA doesn't</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

apply. Despite this designation, the Sponsor plans to submit a pediatric plan for children ages 4 years or older.	
BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted.	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Comments:	
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
------------------	--

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): X NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): Feb 1, 2008 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 07-17-2008

NDA/BLA #: 22-352

PROPRIETARY/ESTABLISHED NAMES: Colchicine Tablets USP, 0.6 mg

APPLICANT: Mutual Pharmaceutical Company, Inc.

BACKGROUND: 505(b)(2) (referencing published literature), orphan designation, priority review, for the Treatment of Familial Mediterranean Fever (FMF)
 The related IND is 75,040. August 2006: Pre-IND meeting (meeting minutes in DARRTS).
January 2008: Pre-NDA meeting (Division's responses to the meeting questions in DARRTS) the Sponsor was informed that additional clinical trials will not be required for an NDA submission for colchicine for the FMF indication. However, the adequacy of these data in providing the substantial evidence of efficacy required for approval is a review issue and will be determined on review of the NDA.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Margarita Tossa/Matthew Sullivan	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Sarah Okada		Y
Clinical	Reviewer:	Keith Hull	Y
	TL:	Sarah Okada	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:		

	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:		
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Steve Leshin	Y
	TL:	Adam Wasserman	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Danae Christodoulou/Craig Bertha	Y
	TL:	Ali Al Hakim	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Bob Rappaport, Jeffrey Siegel, Rigoberto Roca, Mary Dempsey, Kathleen Coyle, David Petullo

505(b)(2) filing issues? If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable
CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: This NDA submission is based on published literature.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: see CMC review in DFS (8-25-08)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Bob A. Rappaport, MD</p> <p>GRMP Timeline Milestones: Mid-Cycle-9/19/2008; Wrap-Up-11/17/2008; Action Package to DD-11/22/2008; Action Goal Date-12/19/2008.</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<input type="checkbox"/>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>
<input type="checkbox"/>	<p>If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<input checked="" type="checkbox"/>	<p>If BLA or priority review NDA, send 60-day letter.</p>
<input checked="" type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Other</p>

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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this page is the manifestation of the electronic signature.**

/s/

Margarita Tossa
9/25/2008 01:01:40 PM
CSO



NDA 22-352

DISCIPLINE REVIEW LETTER

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your new drug application (NDA) dated June 20, 2008, received June 20, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Colchicine Tablets USP, 0.6 mg.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. The _____ was reviewed and was found to be inadequate. A deficiency letter was forwarded to the holder of the file on August 21, 2008. **b(4)**
2. Drug Master File _____ was reviewed in support of your application and was found to be inadequate. A deficiency letter was forwarded to the holder of the file on August 21, 2008.
3. Revise the drug substance test for physical appearance acceptance criterion from "meets description" to a description of the acceptable appearance.
4. The development report in P.2 indicates that the exposure of the drug substance to _____ leads to the formation of substantial quantities of the _____ Clarify how these data were obtained considering your claim that the current related substances method can not quantify this apparent _____ **b(4)**
5. Continue your efforts towards the development of a quantitative and specific method for the determination of _____ levels in the colchicine drug substance.
6. Provide justification as to why the microbial limits testing was not proposed for the colchicine drug substance (e.g., low water activity), or propose testing with acceptance criteria for this parameter. Although primarily concerned with new chemical drug substances, we recommend you refer to the ICH Q6A guideline. **b(4)**

7. Provide data/information supporting the establishment of the identity of the conformational isomer peak [(+)-(aS, 7S)-colchicine] in the chromatograms obtained from the drug substance and drug product related substances methods (e.g., figures 3 and 4 in the method validation report ARD-2007-159 for the drug substance related substances method).
8. It is stated in S.4.5 that the physical appearance acceptance criterion for colchicine, i.e., _____ is "based on the USP description of colchicine." Provide the USP description referred to in your justification. Refer to comment 3 above. **b(4)**
9. It does not appear that friability of the tablet cores was determined during the production as indicated in the three executed batch records provided in 3.2.R. The master batch record also includes the work-sheet for the determination of tablet core friability (p. 19 of 122) with an acceptance criterion of not more than _____ loss. Provide a justification for the absence of this typical in-process testing. **b(4)**
10. Provide a summary description of the test method used to determine the particle size distribution of the carnauba wax, NF.
11. You have indicated in your Reference Standard Assessment report that you could find no discrepancies during the auditing of the qualification documentation for the Secondary Standard 397. Provide any additional information uncovered in your investigation that might explain the discrepant purity factor and how such problems will be avoided in future qualifications of secondary standards.
12. Your process assessment report included in P.5 indicates that _____ contributed to the observed above target tablet assay results. Describe what will be done in future production to provide assurance that the tablets will be formulated and manufactured such that the assay will be on target. **b(4)**
13. Provide justification as to why the microbial limits testing was not proposed for the drug product, or propose testing with acceptance criteria for this parameter. Justification should include identification of microbial controls for incoming materials and during drug product manufacture (e.g. controls to inhibit microbial growth during _____ . Consideration of _____ may also be appropriate. **b(4)**
14. Revise the drug product method to include the expected retention time for the conformational isomer (+)-(aS, 7S)-colchicine (RRT 0.93).
15. The current method used for determination of related substances in the drug product can not detect _____ a known _____ of colchicine. Indicate how levels of this impurity will be monitored in the drug product at release and during stability studies. Alternatively, provide justification for why this is not necessary. **b(4)**

16. Provide clarification of the significance of the comparative dissolution results from _____ reported in P.5.4.
17. Elaborate on the derivation of the limit of NMT _____ of the drug product, based on the "theoretical amount of _____."
18. Based on the release and stability dissolution data provided for the drug product, the proposed specification acceptance criteria of $Q = \text{_____}$, is too permissive. Increase the value of Q to more realistically reflect the data for your product.
19. Based on the release and stability data for the drug product, the limit of NMT _____ for _____ is broad. Decrease the acceptance criterion to more closely reflect the data.
20. Provide a tabular presentation of the combination of specific container closure components (manufacturer, bottle, cap, cap liner, induction seal) that are to be marketed with the 1000, 500, 250, 100, 60, and 30 tablet counts. Without this information, it is unclear that the stability program sufficiently brackets all of the intermediate presentations.
21. Provide a revised post-approval stability commitment to clarify that stability studies will also include drug product in _____ (i.e., the _____ presentation). Further revisions to the post-approval stability protocol may be necessary depending on your response regarding the packaging details with respect to the bracketing currently in use in the stability program. See comment 20 above.
22. The following preliminary comments pertain to the labels and labeling:
 - a. Revise the "Description" section of the package insert to list the pharmacological or therapeutic class of the drug as per 21 CFR 201.57(c)(12)(E).
 - b. Revise the drug listing data element table such that it is consistent with what is recommended on the following web page <http://www.fda.gov/oc/datacouncil/spl.html>. Specifically, revise the name of the active ingredient by removing the dosage form descriptor (tablet, film coated) and add the descriptor to the "Dosage Form" part of the "Product Information" section.

b(4)

b(4)

b(4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Margarita Tossa, Regulatory Project Manager, at (301) 796-4053 or at margarita.tossa@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Pharmaceutical Assessment Lead for the
Division of Anesthesia, Analgesia and
Rheumatology Products
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Ali Al-Hakim
9/2/2008 09:49:17 AM



NDA 22-352

FILING COMMUNICATION

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your new drug application (NDA) dated June 20, 2008, received June 20, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Colchicine Tablets USP, 0.6 mg.

We also refer to your submission dated July 7, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 20, 2008.

During our filing review of your application, we identified the following potential review issues:

1. The _____ will not be reviewed during this review cycle. The proposed alternate supplier, _____ for the drug substance is not supported by comparability data for the colchicine tablets, or an appropriate comparability protocol in your NDA submission. Withdraw the alternate drug substance manufacturing site from your current submission. You may seek qualification of the alternate site post-approval, by submitting supporting comparability data and comparability protocol.

b(4)

Your proposal to qualify _____ as a primary supplier of the drug substance will be reviewed during the current review cycle of the NDA, consistent with your pre-NDA agreements with the Agency.

b(4)

2. Provide a Letter of Authorization for a supporting DMF for the _____ Purple color.

b(4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), 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 the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because colchicine for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, contact Margarita Tossa, Regulatory Project Manager, at (301) 796-4053 or at margarita.tossa@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
8/18/2008 11:16:13 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-352

NDA ACKNOWLEDGMENT

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Colchicine Tablets USP, 0.6 mg

Date of Application: June 20, 2008

Date of Receipt: June 20, 2008

Our Reference Number: NDA 22-352

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 19, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Matthew Sullivan
6/26/2008 04:08:37 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 72,586
PIND 75,040
PIND _____

b(4)

AR Scientific Company, Inc.
c/o Mutual Pharmaceutical Company
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your Investigational and Pre-Investigational New Drug Applications (IND and PIND) files for Colchicine Tablets.

Attached are the Division's responses to the questions from your December 21, 2007, meeting package for our upcoming meeting, scheduled for February 4, 2008, to discuss plans for your NDA submissions. Your questions are in italics and the Division's responses are in normal text.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

b(4)

SPONSOR MEETING AGENDA

MEETING DATE: February 4, 2008

TIME: 3:00 to 4:00 pm

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: IND 72,586
PIND 75,040
PIND _____

STATUS OF APPLICATION: Active (IND 72,586)
Pre-IND (PIND 75,040 and _____)

PRODUCT: Colchicine Tablets 0.6 mg

INDICATIONS: Treatment and prevention of acute gout flares (IND 72,586)
_____ of Familial Mediterranean Fever
(PIND 75,040)
_____ (PIND _____)

SPONSOR: AR Scientific, Inc

TYPE OF MEETING: Type B, Pre-NDA

MEETING CHAIR: Sarah Okada, M.D., Division of Anesthesia, Analgesia and
Rheumatology Products (DAARP)

MEETING RECORDER: Matthew Sullivan, M.S., DAARP

b(4)

b(4)

FDA Attendees	Title
Bob Rappaport, M.D.	Director, DAARP
Rigoberto Roca, M.D.	Deputy Director, DAARP
Sarah Okada, M.D.	Medical Team Leader, DAARP
Jeff Siegel, M.D.	Medical Team Leader, DAARP
Sarah Cochran, M.D.	Medical Officer, DAARP
Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology, DAARP
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer, DAARP
Dionne Price, Ph.D.	Team Leader, Statistics, DAARP
Yongman Kim, Ph.D.	Statistics Reviewer, DAARP

b(4)

Ali Al Hakim, Ph.D.	Chief, CMC Branch II, Office of New Drug Quality Assessment (ONDQA)
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead, ONDQA Branch II
Adam Wasserman, Ph.D.	Supervisor, Pharmacology/Toxicology, DAARP
L. Steve Leshin, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Janice Weiner, J.D., MPH.	Regulatory Counsel, Office of Regulatory Policy
Shary Jones, Pharm.D.	Safety Evaluator, Office of Surveillance and Epidemiology, Division of Medication Errors and Technical Support (OSE, DMETS)
Darrell Jenkins	Regulatory Project Manager, OSE
Linda Kim-Jung, Pharm.D.	Team Leader, OSE, DMETS
Sally Loewke, M.D.	Associate Director for Guidance and Policy and Unapproved Drugs Coordinator, Office of New Drugs
Matthew Sullivan, M.S.	Regulatory Project Manager, DAARP
AR Scientific / Mutual Pharmaceutical Company, Inc.	Title
Matthew Davis, M.D.	Vice President, Branded Products and Medical Affairs
Robert Dettery	Vice President, Regulatory Affairs
Kurt Nielsen, Ph.D.	Executive Vice President of Pharmaceuticals
Kristin Arnold, Ph.D.	Senior Director of Research and Development
Shawn Watson	Associate Director, R&D Raw Materials
Kimberly Stulir	Senior Manager, Project Management
_____	Consultant, Managing Director _____
_____	Consultant _____
_____	Toxicology Consultant _____
_____	Executive Director, _____

b(4)

Below are the Division's responses to the questions from your December 21, 2007, meeting package for our upcoming meeting, scheduled for February 4, 2008, to discuss plans for your NDA submissions. Your questions are in italics and the Division's responses are in normal text.

CHEMISTRY MANUFACTURING AND CONTROLS

Question 1. Are the types of tests proposed in the drug substance and drug product specifications adequate for purposes of the NDA?

FDA RESPONSE:

Yes. Consult the ICH Q6A Guidance for test methods and specifications in new drug substances and products. Also see our response to Question 5 regarding the _____ specification.

b(4)

b(4)

Question 2. Are the proposed specification limits for the drug substance acceptable, including the specification for the colchicine conformational isomer?

FDA RESPONSE:

As you proposed, the impurity limits should be lowered by the time of NDA submission as per ICH Q3A (R2). Regarding the conformational isomer, provide adequate justification in the NDA, including:

1. Equilibrium data between the conformers in solution
2. Comparative batch analysis data to marketed unapproved products
3. Your supporting safety assessment

The specification for the conformer will be assessed during the NDA review.

Question 3. Are the proposed specifications for the drug product acceptable, including the specification for the colchicine conformational isomer?

FDA RESPONSE:

As you proposed, the impurity limits should be lowered by the time of NDA submission as per ICH Q3B. See our response to Question 2 regarding the specification of the conformer, and Question 4 regarding the residual _____ limit.

b(4)

Question 4. Is the proposed specification of _____ than the _____ in the USP monograph) for colchicine drug substance acceptable? Does the agency agree that the drug product does not require _____ testing?

b(4)

FDA RESPONSE:

The proposed limit of _____ in the drug substance exceeds the ICH Q3C limit of _____. Provide a safety assessment and/or qualification for the proposed _____ limit. This will be assessed during the NDA review.

b(4)

In addition, provide a residual _____ limit in the drug product as per ICH Q3C. Your proposal to omit routine testing for _____ in the drug product will be assessed during the NDA review, based on:

b(4)

1. adequate justification that the process converts the _____ to the _____ form;
2. in-process controls that ensure no residual _____ in the product;
3. in-process (e.g., residual _____ and release batch analysis data that support removal of residual _____ in the drug product.

b(4)

b(4)

b(4)

Provide the supporting data and justification in the Pharmaceutical Development Report (PDR) section of the NDA.

Question 5. Does the Agency agree that routine _____ testing in the drug substance and drug product is not required?

b(4)

FDA RESPONSE:

This proposal will be assessed during the NDA review based on adequate justification and supporting data.

You have proposed the complete conversion of the _____ to the _____ during the _____ process in the manufacture of the drug product. To ensure that no other potential _____ enter the drug product manufacturing process, provide a _____ specification for the drug substance. In addition, monitor the _____ during this process. Provide appropriate data, e.g., dissolution profiles, stability, to support your contention that a _____ purity does not have an impact in the manufacturability, quality or performance of the drug product. This information should be included in the Pharmaceutical Development Report (PDR) section of the NDA.

b(4)

Additionally, consult the ICH Q6A Decision Tree 4 for establishing _____ for the drug substance and product.

b(4)

Question 6. Are the amounts of stability data for bottles _____ to be included in the NDA submission in February sufficient to allow filing?

FDA RESPONSE:

Yes. Consult the ICH Q1 Guidances with respect to your stability protocol, the NDA registration batches and the amount of stability data needed at the time of filing.

Question 7. Is the plan for updating stability data during the course of the review acceptable?

We strongly recommend that any amendments containing stability data be submitted early in the review cycle. While every effort will be made to review an amendment to the NDA, its review will depend on the timeliness of submission, extent of submitted data and available Agency resources. Therefore, in accordance with our Good Review Management Practice (GRMP) timelines, we may not be able to review an amendment submitted during the review cycle.

b(4)

Question 8. Will these data allow for a 24-month expiration dating as proposed in each configuration?

FDA RESPONSE:

Expiration dating will be assessed upon review of all available data at the time of NDA and statistical analysis as per ICH Q1E. Stability configurations should support the proposed commercial packaging presentations.

PHARMACOLOGY / TOXICOLOGY

Question 9. Mutual seeks confirmation that no further nonclinical safety pharmacology studies are warranted.

FDA RESPONSE:

As previously agreed, no further nonclinical safety pharmacology studies will be required, including the proposed neurobehavioral study.

Question 10. Mutual seeks confirmation that the published literature submitted has been reviewed and that the Division agrees that no additional studies are needed for successful NDA filing.

FDA RESPONSE:

We agree that no additional studies are necessary.

Question 11. Although Mutual is continuing to evaluate the potential for performing such a study, Mutual asks that the Division re-confirm that such a study will not be required prior to the approval of an NDA for treatment and prevention of acute gout flares / _____ of FMF / _____

b(4)

FDA RESPONSE:

Carcinogenicity studies will not be required for NDA approval.

Question 12. Is it necessary to perform a repeated dose toxicity study to qualify the conformational isomer? If yes, is the planned study and the timing of submission of the final study report acceptable?

FDA RESPONSE:

The conformational isomer will not require a repeated-dose toxicity study.

Question 13. With respect to genotoxicity studies, is it sufficient to perform only the Ames test? Is the chromosomal aberration study necessary given that results for colchicine have already been shown to be positive?

FDA RESPONSE:

Although we encourage you to perform genetic toxicology studies in the interest of public health, neither genetic toxicology assay will be required.

BIOPHARMACEUTICS / CLINICAL PHARMACOLOGY

Question 14. Does the Division agree that no additional clinical pharmacology studies, including in patients with renal or hepatic impairment, are needed?

FDA RESPONSE:

No additional renal or hepatic impairment clinical pharmacology studies are needed. However, it does not appear that the publications provide comprehensive data that dedicated renal and hepatic impairment studies conducted per Agency guidances would provide. Based on all available data from literature and your own studies, provide your best assessment of dosage adjustment in these sub-groups.

Question 15. Does the Division agree that no additional drug interaction studies are required other than the two studies described?

FDA RESPONSE:

Yes, we agree that no additional drug interaction studies are required.

Question 16. Does the Division agree that, unless clinical significant changes are observed, the potential for prolongation of the QTc interval by colchicine has been adequately evaluated?

FDA RESPONSE:

Yes, we concur.

CLINICAL EFFICACY

Question 17. Three placebo-controlled trials of colchicine in the management of gout have been published, one in acute gout and two in prophylaxis. These will form the basis for the initial NDA submission in February. As noted earlier, enrollment in one additional placebo-controlled trial in patients with acute gout, sponsored by Mutual, has just completed. Available safety data will be included in with the 120-day Safety Update to the NDA and the final study report will be provided as an NDA amendment (projected for June 2008) as soon as it becomes available. It has been previously agreed that this trial is necessary for approval. In addition to demonstrating efficacy, the results of the trial will be used to determine the appropriate dosing regimen to propose for labeling.

We seek confirmation that this approach will be acceptable for successful filing of the NDA, including for both the acute and prophylaxis indications.

FDA Response:

As discussed in the August 31, 2006, Pre-IND meeting minutes, the three placebo-controlled trials of colchicine in the management of gout, along with the AGREE trial, the requested bioavailability and PK studies, and other supportive literature comprise an acceptable package for filing an NDA for colchicine in the treatment of gout, for both the acute and prophylaxis indications. However, the AGREE trial must be submitted in full with the original submission, not as an NDA amendment. Also see our response to Question 20.

Question 18. FMF is a hereditary disease of unknown origin that is characterized by recurrent fever, abdominal and chest pain, arthralgia, and rash. Some affected individuals may also experience amyloidosis, a potentially life-threatening complication that could result in renal failure. As described in the Orphan Drug Designation recently granted for colchicine in this indication, it is estimated that fewer than 5000 people in the United States are diagnosed with FMF. Overall, 14 clinical studies have been identified in the published literature, of which one is a placebo-controlled trial of the treatment of acute attacks and three are double-blind, placebo-controlled studies in the prevention of attacks. Three studies address the effect of oral colchicine in reducing or preventing amyloid nephropathy. As discussed at the Pre-IND meeting, the published literature appears adequate to support an indication for FMF. Therefore, Mutual will submit an NDA for this orphan indication in February 2008 based solely on the published literature.

We seek confirmation that this approach will be acceptable for successful filing of the NDA.

b(4)

FDA Response:

The published literature for colchicine in FMF includes 3 randomized, double-blind, placebo-controlled trials which, while small, were consistent in demonstrating a large treatment-effect in favor of colchicine in reducing the number and severity of FMF attacks. The totality of the evidence that supports the effectiveness of colchicine in FMF includes 9 open-label studies involving approximately 1700 patients with FMF and/or amyloid nephropathy of FMF, which are consistent with the controlled studies' results in demonstrating a salutary effect of colchicine treatment in this disorder. These results, and decades of clinical experience, have resulted in colchicine being widely accepted as the standard of care in the prophylactic treatment of FMF. Therefore, additional clinical trials will not be required for an NDA submission for colchicine for the FMF indication. However, the adequacy of these data in providing the substantial evidence of efficacy required for approval is a review issue and will be determined on review of the NDA.

b(4)

b(4)

b(4)

b(4)

CLINICAL SAFETY

Question 20. The primary safety database will be based upon the published literature, publicly available postmarketing safety reports, together with FDA's prior judgment of the safety of colchicine (ColBenemid), an NDA that was recently transferred to Mutual. At the time of NDA submission in February 2008, it is estimated that safety data will be available for approximately 126 healthy volunteers who will receive single dose (82 subjects) to short-term repeated dose regimens (44 subjects) of colchicine consistent with the doses to be proposed. Safety data (adverse events, vital signs, and clinical laboratory testing) will be submitted with the _____ for approximately 125 patients who are estimated to have been randomized to colchicine in the recently completed Phase 3 trial in the treatment of acute flares of gout. The study recently completed with a total of 186 patients exposed to double-blind study drug and data entry is underway; the blind has not been broken and a final study report is projected for June 2008 (approximately 5 months after submission of the NDA).

b(4)

Mutual seeks confirmation that these data are adequate to allow a safety review.

FDA Response:

An NDA for the acute gout indication will need to have the complete safety and efficacy results of the AGREE trial at the time of NDA submission. _____

b(4)

_____ You may submit NDAs under Section 505(b)(2) for colchicine in the prophylactic treatment of gout and/or one for the

b(4)

_____ of FMF before the AGREE trial is completed and submit interim safety results from the AGREE trial as a 120-day safety update. It is acceptable to combine the acute and chronic gout indications into one 505(b)(2) NDA; however then the AGREE trial results must be submitted in full at the time of NDA submission.

b(4)

The integrated summary of safety for all the NDAs should also include all available information from the published literature and spontaneous reporting systems.

Question 21. Mutual will commit to a Risk Management Plan, the basic elements of which are outlined in Section 3, and views this as a mandatory part of labeling. As this includes patient-directed educational materials and innovative packaging, we wish to engage the Division of Medication Errors and Technical Support (DMETS) and the Division of Drug Risk Evaluation (DDRE) in discussions as soon as possible. Is it possible to have preliminary feedback at the time of the meeting? Mutual also seeks guidance on how to facilitate future discussions.

FDA Response:

We note that you propose routine pharmacovigilance measures along with education (Medication Guide or patient package insert) and _____. This plan is consistent with other approved combination colchicine products; augmented by the proposed _____ and patient-directed labeling. Based on the information provided, the proposal does not constitute a formal risk minimization action plan (RiskMAP).

b(4)

You also states that the _____ DMETS requests that you provide further information regarding how the packaging will _____. In addition, please address these questions in your NDA submission:

b(4)

1. What information do you have on overdose (intentional and unintentional)?
2. What, if any, effect do you expect the packaging will have on medication errors?

We encourage you to submit the product and container labeling along with the patient-directed labeling as soon as possible to facilitate the review process.

If you believe that there are product risks that merit more than conventional professional product labeling (i.e., package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage, then you are encouraged to engage us in further discussions about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP). If you submit a RiskMAP, please remember to submit all

planned materials identified within the RiskMAP that will be necessary to implement your proposal.

Question 22. In CMC documentation, Mutual refers to the potency of colchicine in terms of mcg, i.e., the target tablet strength is 600 mcg. Is this appropriate for labeling and packaging? Do the DMETS or DDRE have advice with respect to this?

FDA Response:

All expressions of strength should be consistent with the manner in which colchicine has previously been expressed (i.e., 0.6 mg). Consistency regarding the expression of strength will help to decrease the potential for dosing errors which may arise as a result of confusion between milligrams and micrograms.

ADMINISTRATIVE

Question 23. The NDA for colchicine will be submitted electronically in CTD format. A proposed table of contents for the CTD application is provided in Section 3.7.

Does the Agency agree with the proposed eCTD organization?

FDA Response:

The proposed table of contents for the eCTD (Table 3:5 of the briefing package) is acceptable.

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 5.3 Exposure-Response Relationships - important exposure-response assessments.
3. Section 7.1.6 - Less common adverse events (between 0.1% and 1%).
4. Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.

7. Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.1.8.3.2 - Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.1.8.3.3 - Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.1.9.3. – Standard analyses and explorations of ECG data.
12. Section 7.1.16 – Overdose experience.
13. Section 7.4.2.1 - Explorations for dose dependency for adverse findings.
14. Section 7.4.2.2 - Explorations for time dependency for adverse findings.
15. Section 7.4.2.3 - Explorations for drug-demographic interactions.
16. Section 7.4.2.4 - Explorations for drug-disease interactions.
17. Section 7.4.2.5 - Explorations for drug-drug interactions.
18. Section 8.2 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

For the AGREE trial, also provide subset analyses for the primary endpoint, including subgroups by:

1. Baseline demographics (age, gender, race, weight),
2. Baseline disease characteristics,
3. Investigational site.

Question 24. We plan to submit data tabulation and data analysis datasets. The tabulation datasets will follow the CDISC SDTM version 3.1 and the data analysis datasets will follow the CDISC ADaM 2.0 models. The appropriate metadata, analysis programs, and supporting documentation will accompany the data. Raw data entry datasets (SAS version 5 transport format) and annotated case report forms will also be included in the submission. A representative example of the datasets being provided for biopharmaceutical studies and the AGREE clinical trial is appended at the end of Section 3. We do not plan on submitting data profile or data listing datasets.

Does the Agency agree with this plan or have any guidance regarding the format and content of the proposed datasets?

FDA Response:

Your plan for the proposed datasets is acceptable. The following are general comments regarding CDISC submissions:

Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

At a minimum the Safety Analysis Plan should address the following components:

1. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fml.pdf>).
2. Safety endpoints for Adverse Events of Special Interest (AERI)
3. Definition of Treatment Emergent Adverse Event (TEAE)
4. Expert adjudication process (Expert Clinical Committee Charter)
5. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
6. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
7. When unanticipated safety issues are identified the QSAP may be amended.

Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed.
 - a. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
 - a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - i. (DV) Protocol deviations
 - ii. (DA) Drug Accountability
 - iii. (PC, PP) Pharmacokinetics

iv. (MB, MS) Microbiology

v. (CF) Clinical Findings

b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.

i. Tumor information

ii. Imaging Data

iii. Complex Inclusion/Exclusion Criteria

3. Variables

a. All required variables are to be included.

b. All expected variables should be included in all SDTM datasets.

c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division prior to the time of submission.

d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division prior to the time of submission.

e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided prior to the time of submission.

f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

4. Specific issues of note:

a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets, unless specified by the SDTM standard.

b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPQUAL dataset or an ADaM dataset.

c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues:

1. Please specify which ADaM datasets you intend to submit.

2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.

3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.

4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.

b(4)

5. Please indicate which core variables will be replicated across the different datasets, if any.

6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

General Items:

1. Controlled terminology issues

- a. Please use a single version of MedDRA for a submission, which does not necessarily have to be the most recent version.
- b. We recommend that the WHO drug dictionary be used for concomitant medications.
- c. Please refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements should be addressed.

Question 25. The plan is to submit three separate NDAs, one each for gout, FMF and

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Can the CMC, toxicology, and clinical pharmacology technical sections be provided in only one of the three NDAs and incorporated by reference in the remaining two or should all three NDAs be complete?

FDA RESPONSE:

It is acceptable to cross-reference this information contained in one NDA to the other two NDAs.

Additional CMC Comments:

Provide a complete list of drug substance and drug product manufacturing facilities (with street addresses) in the NDA. For all foreign manufacturing sites, include contact names and telephone numbers at the site. In addition, provide verification in the NDA that all sites are ready for cGMP inspection.

Additional OSE Comments:

For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

- Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>
- Development and Use of Risk Minimization Action Plans: <http://www.fda.gov/cder/guidance/6358fnl.htm>

- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

If there is any information on product medication errors from the premarketing or clinical experience, OSE requests that this information be submitted with the NDA.

You are encouraged to submit the proprietary name for review as soon as it is available.

Additional Regulatory Comments:

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Linked Applications	Sponsor Name	Drug Name
IND 72586	AR SCIENTIFIC INC	COLCHICINE TABLETS
IND 75040	MUTUAL PHARM	COLCHICINE TABLETS
IND _____	MUTUAL PHARMACEUTICAL CO INC	COLCHICINE

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/s/

MATTHEW W SULLIVAN
02/01/2008
Regulatory Project Manager



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

SEP 25 2007

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, Pennsylvania 19124

Attention: Robert Dettery
Regulatory Agent

Re: Designation request #07-2458

Dear Mr. Dettery:

Reference is made to your request for orphan-drug designation submitted July 10, 2007, of colchicine for "treatment of Familial Mediterranean Fever." Please also refer to our letter of July 13, 2007.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of colchicine is granted for *treatment of Familial Mediterranean Fever*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Kathryn O'Connell, M.D., Ph. D., at 301-827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 72,586
PIND 75,040

Mutual Pharmaceutical Company, Inc.
1100 Orthodox St
Philadelphia, PA 19124

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your Pre-Investigational New Drug Application (PIND) files for colchicine tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 31, 2006. The purpose of the meeting was to discuss the regulatory requirements to bring this marketed drug into compliance.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Meeting Date: July 31, 2006
Location: White Oak Conference Room 1417
Application: PIND 75, 040
PIND 72, 586
Drug Name: Colchicine Tablets
Indication: Treatment of Familial Mediterranean Fever (FMF) [PIND 75, 040]
Treatment of acute goat attack and prophylaxis of gouty flares [PIND 72, 586]
Sponsor: Mutual Pharmaceutical Company, Inc
Type of Meeting: Pre-IND, Type B
Meeting Chair: Rigo Roca, M.D.
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Minutes Recorder: Matthew Sullivan, M.S., Regulatory Project Manager

Mutual Pharmaceutical	Title
Matthew Davis, M.D.	Vice President, Branded Products and Medical Affairs
Kurt Nielsen, Ph.D.	Vice President, Research and Development
Jie Du, Ph.D.	Director of Biopharmaceutics
Robert Dettery	Vice President, Regulatory Affairs
_____	Consultant, Managing Director _____
_____	Consultant _____
_____	Consultant, Toxicology _____
_____	Consultant _____
_____	Consultant, _____
FDA - DAARP	Title
Robert Meyer, M.D.	Director, Office of Drug Evaluation II (ODE II)
Curtis Rosebraugh, M.D.	Deputy Director, ODE II
Bob Rappaport, M.D.	Director
Rigo Roca, M.D.	Deputy Director
Ali Al Hakim, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Sue-Ching Lin, M.S., R.Ph.	Chemistry Reviewer, ONDQA
Adam Wassermann, Ph.D.	Supervisor, Pharmacology/Toxicology
Steve Leshin, Ph.D.	Pharmacology/Toxicology Reviewer
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer
Dionne Price, Ph.D.	Team Leader (acting), Statistics
Yongman Kim, Ph.D.	Statistics Reviewer

b(4)

Jeff Siegel, M.D.	Team Leader, Clinical
Joel Schiffenbauer, M.D.	Team Leader, Clinical
Sarah Okada, M.D.	Clinical Reviewer
Matthew Sullivan, M.S.	Regulatory Project Manager

Meeting Objective(s): To discuss questions related to the regulatory requirements to bring this marketed drug into compliance.

Opening Discussion: Following introductions, the discussion focused on Mutual Pharmaceuticals questions that were included in the June 30, 2006, and July 7, 2006, meeting packages. The questions are presented in italicized text and Division responses are in bold. Discussion is presented in normal text. The slides containing the Division's responses were sent to the sponsor on July 28, 2006.

Question 1. Is the CMC information to be included in the IND adequate to support the proposed pharmacokinetic studies? Are the plans for the NDA adequate?

Division Response:

The CMC information proposed to be included in the initial IND submission would appear to support the proposed pharmacokinetic studies. However, for any future NDA submission, it is recommended that you follow all FDA and ICH guidelines regarding specifications, impurities, stability testing, etc. As clinical studies progress, additional information regarding identification and quantitation of individual impurities in the drug substance and drug product should be provided. A more specific analytical procedure should be developed for testing _____ the drug substance.

b(4)

Discussion:

The Sponsor inquired as to whether or not their current CMC information would be adequate for future clinical studies. The Division commented that there will likely be a need for additional CMC information in later phases of development.

Post-Meeting Note:

A typographical error was noted during the meeting. In the last sentence of the Divisions response, the word _____ . The sentence should correctly read: A more specific analytical procedure should be developed for testing _____ the drug substance.

b(4)

Question 2. Does the Division agree that the cardiovascular safety studies are necessary?

- a. *Are the studies adequate by design?*
- b. *Is the use of non-naïve male dogs acceptable in the cardiovascular telemetry study (minimum 1 month wash-out period)?*

- c. *If the cardiovascular safety studies are deemed necessary, would this requirement be applicable to all New Drug Applications of colchicine?*
- d. *If any of the cardiovascular safety studies are positive, would a thorough QT trial in humans be required and would this requirement be applicable to New Drug Applications of colchicine?*

Division Response:

General Comments: For the nonclinical aspects of your drug development program, you need to consider that colchicine was approved as safe and effective as a combination product under DESI ruling in 1972. Since there is no "colchicine-only" product approved in the United States, it will be necessary to support your clinical studies with sufficient nonclinical toxicology to ensure safe use and labeling according to current guidelines (see Guidances at <http://www.fda.gov/cder/guidance/>). Much of this information may be obtained through the scientific literature and data compilation services. Where data are lacking, it may be necessary to conduct the appropriate studies, as outlined in the Guidances, or provide sufficient justification as to why those studies would be unnecessary or inappropriate for your drug and its proposed indication. All of this information should be submitted with the initial IND.

Since there is little information concerning colchicine's potential cardiovascular toxicity, we recommend that the proposed cardiovascular safety studies be conducted.

- a. The number and magnitude of doses should be selected to provide appropriate characterization of in vitro or in vivo responses. In vivo studies should incorporate a maximum tolerated dose (MTD) and sufficient doses to determine an appropriate no observed adverse effect level (NOAEL).
- b. A 1-month washout period is usually adequate, but we recommend that this be verified by monitoring other known pharmacodynamic or pharmacokinetic parameters.
- c. It would depend on many factors. For the same active compound, the labels would need to be consistent.
- d. If safety tests for a cardiovascular toxicity (e.g., QT prolongation) were positive with your colchicine formulation, then a thorough QT clinical trial would be required.

Discussion:

With regard to item b, the Sponsor agreed that they would use naive dogs. The Division recommended a range of doses be utilized in this evaluation. Should the Sponsor wish to use a single high dose, the Division encouraged the Sponsor to conduct preliminary dose range-finding studies to ensure the dose would be appropriate, or provide an adequate justification for the selected dose based on prior study or published literature.

Question 3. Does the Division agree that no additional toxicology studies are required prior to NDA submission?

Division Response:

Until the IND package is submitted, we cannot determine if for the existing information is sufficient to assess the safety of colchicine in the proposed indications. Please include copies of all cited literature used to support your drug development program.

If unexpected or additional safety concerns develop during manufacturing or during clinical trials, additional toxicological studies may be required.

Discussion:

The Sponsor indicated that they performed a thorough literature search, and have referenced all colchicine studies that were located.

The Division commented that there are studies in the literature with slightly different forms of colchicine, since these were usually isolated compounds of varying purity. Some of the reproductive studies used a form of colchicine that differed in a carbon-group. The Sponsor indicated that they would attempt to note those studies that use their form of colchicine versus those that use another.

The Sponsor inquired if other pre-clinical studies might be required. The Division replied that a carcinogenicity evaluation would be desirable but will not be required. However, the Sponsor is encouraged to summarize the current knowledge concerning the carcinogenic potential of colchicine.

Question 4. From a Biopharmaceutics perspective, is the choice of comparator drug product acceptable?

Division Response:

The approach is acceptable.

To fulfill 505(b)(2) requirement, relative bioavailability of proposed drug product must be evaluated with a product approved in the US. This may be accomplished by the addition of another treatment arm.

Discussion:

The Sponsor requested clarification regarding whether the _____ also need to be used as a comparator (i.e., in their bridging studies to build on the Ahern clinical trial) in addition to the reference listed drug ColBenemid, since ColBenemid also contains 0.5 mg of colchicine (in addition to 500 mg of probenecid). The Division asked the Sponsor to propose the scenario they request, with justification, and a written response will be provided as a post-meeting note in the minutes.

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Post-Meeting Note:

Use of Colbenemid in place of previously proposed _____ is acceptable.

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Question 5. Is the single arm study acceptable by design?

Division Response:

Yes.

Discussion:

The Sponsor wishes to perform formal QT studies in conjunction with the inpatient PK studies, as opposed to with any clinical trials. The Division commented that this would be acceptable, but the formal QT studies should assess not only the maximal therapeutic dose, but also supra-therapeutic doses. If supra-therapeutic doses will not be studied the Sponsor needs to provide a rationale for why this would not be feasible or safe (e.g., known range of toxicity of colchicine). Dr. Nallani recommended ECG monitoring in all of the proposed PK studies.

Question 6. Due to the teratogenic nature of colchicine, a colchicine + oral contraceptives drug-drug interaction study looking at the effects of colchicine on oral contraceptives is being proposed.

a. Are the designs of the proposed studies acceptable?

Division Response:

Yes

b. Would a positive result (interaction with oral contraceptives) require labeling which would be applicable to all New Drug Applications of colchicine?

Division Response:

Yes, safety information will be applicable to other NDAs.

Discussion:

There was no discussion beyond that the Division's initial written response.

Question 7. Mutual has conducted Cytochrome P450 isoenzyme induction and inhibition studies. The results of the induction study indicate that colchicine did not induce activity of P450 (CYP) isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in human hepatocytes, but did decrease substrate metabolism for many of the isoforms. In the inhibition study, colchicine only weakly inhibited activities of CYP2A6 and CYP2C8 in human liver microsomes following in vitro exposure (IC50 > 50 µM).

a. Are the results of these studies required to be in the product labeling?

Division Response:

Yes

If yes, are the results required to be in the labeling for all New Drug Applications of colchicine?

Division Response:

Safety information will be applicable to other NDAs.

- b. *The results suggest down regulation of P450 isoenzymes. While published studies (Dvorak et al., 2003) have shown that colchicine-induced down regulation of CYP2B6, CYP2C8/9, and CYP3A4 [in parallel with that of the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR)] expression occurs, Mutual proposes to study the potential down regulation of CYP 1A2 and AhR expression (dioxin/ Aryl hydrocarbon receptor). If positive, are the results of this study required to be in the product labeling?*

Division Response:

Yes

If yes, are the results required to be in the labeling for all New Drug Applications of colchicine?

Division Response:

Yes, Safety information will be applicable to other NDAs.

Discussion:

With regard to item b, the Division confirmed that positive results would need to be included in the package insert.

Question 8. Mutual requests confirmation that no additional clinical pharmacology studies are required.

Division Response:

It is acceptable to submit good quality publications addressing the clinical pharmacology of colchicine. From a safety perspective, provide dosage adjustment recommendations information in the product label based on available publications or clinical data for patients with:

- a. **Hepatic impairment**
- b. **Renal impairment**

With respect to pharmacokinetic drug-drug interactions, we recommend clinical evaluation of effect of strong CYP3A4 and P-gp inhibition on the PK of colchicine.

Discussion:

The Sponsor requested an example of CYP3A4 and P-gp inhibitors for use in such a study. The Division mentioned a commonly used drug/regimen is ketoconazole 200 mg twice a day for 5-7 days. The Sponsor then asked whether ketoconazole could be used as the P-gp inhibitor as well,

since it affects both pathways and it is difficult to sort out the CYP3A4 effects from the P-gp inhibitory effects. The Division stated they would provide further comment upon review of the Sponsor's proposed studies. While such a study is not required for the IND submission, it will be expected for NDA submission, and the Sponsor was encouraged to seek input either with the IND, or in an End of Phase 2 (EOP2) meeting.

Post-Meeting Note:

Although ketoconazole was mentioned as a model drug in the face-to-face meeting, after internal discussion, Division is now recommending clarithromycin, instead. Clarithromycin is a strong CYP3A4 and P-gp inhibitor, with reported clinically relevant drug interactions with colchicine. It would be clinically relevant to investigate the single dose pharmacokinetics of colchicine and its metabolites before and after treatment with 3-7 days of 250 mg BID clarithromycin.

Question 9. Is the published literature sufficient to allow for filing of an NDA for colchicine for the management of an acute gout flare?

Division Response:

In general, the ability to rely solely on published literature for approval of products, is limited. Please refer to the *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998*.

As stated in this Guidance Document, published reports of studies are the result of judgments by peer reviewers that are based on limited data sets and analyses. Limitations of some published literature reports include the lack of a prospectively defined protocol and statistical analysis plan, the lack of randomization codes, the lack of full accounting of study subjects, the lack of case report forms and paper records of data, to mention a few. However, if the totality of the evidence for the effectiveness of a product supports adequate and well-controlled trial evidence from the published literature, then it is possible that, together, the evidence could be sufficient to allow filing of an NDA.

The published literature that you have submitted for consideration includes a single randomized controlled trial (RCT) in acute gout, 2 RCTs in chronic gout, and 3 RCTs in FMF. In general, these studies are quite small and limited information is available in the reports. As a whole, these do appear to support the efficacy of colchicine for these indications. Nonetheless, some important questions remain unresolved. Given the significant difference between the dosing regimen for acute treatment of gout versus the regimen used for chronic prophylaxis of gout, and the relative lack of controlled safety information on this regimen provided in the published literature, the Division strongly recommends you supplement the published literature reports with at least a single trial in acute gout for safety and efficacy, pre-registration. You should consider incorporating collection of QT data into this trial. See FDA responses to question 10 and 11.

You have proposed 3 studies to further explore PK issues. Additional drug-drug interaction studies may be warranted to further explore the safety of colchicine in situations of typical use. These studies, along with the published literature and a single

clinical trial in acute gout, could provide a package appropriate for filing of an NDA for colchicine for the indications requested.

Discussion:

The Sponsor requested confirmation that the Division would expect any applications for colchicine (i.e., from other sponsors) to contain the evidence enumerated in the above response. The Division clarified that the extent of the evidence (published literature, even if primary data from the Ahern study were obtained by the Sponsor) provided in the briefing package would likely be insufficient to achieve approval. Other sponsors using similar evidence from the literature would also be expected to provide additional evidence.

The Sponsor also asked for clarification regarding what additional drug-drug interactions might be warranted. At the present time, studies with CYP3A4/P-gP inhibitors, as mentioned in the response to question 8, are reasonable. The Division may provide additional suggestions once the Sponsor's proposed studies in this regard are reviewed. Depending on the information provided in the IND, an additional EOP2 meeting may be requested to further discuss issues, including further drug-drug interaction studies, if warranted. The Sponsor also broached the subject of the possibility of filing the NDA with the published literature, and _____ . Dr. Meyer, Director, ODE II, clarified that the clinical trial results would need to be submitted with the NDA.

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Post-Meeting Note:

In the event that this application is successful in achieving approval, it may be possible for another applicant to utilize this product as the reference-listed product.

Question 10. Given the toxicity profile of colchicine and the evolution to the use of lower dose regimens, Mutual proposes to _____

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_____ is provided in Appendix 3.3.1. Is this approach acceptable to the Division? Is the design of the study acceptable?

Division Response:

The Division recommends that you conduct such a study pre-approval, and that the results be submitted with the NDA. See FDA response to question 11 for comments on study design.

Discussion:

There was no discussion beyond that the Division's initial written response.

Question 11. If the Division determines that the published literature with _____ is not sufficient for NDA filing, _____ will not be performed. Instead, Mutual wishes to discuss the possible design of an adequate and well-controlled study, given the anticipated difficulties in including a placebo control. Mutual proposes the following: a placebo-controlled trial comparing colchicine 0.6 mg x 2, followed by 0.6 mg every hour to a maximum of 8 tablets total (4.8 mg) versus placebo. Because of the

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anticipated difficulty in enrolling patients into a placebo-controlled trial, all patients will be offered _____ with pre-defined treatment failure / exit criteria. Otherwise, the trial will be similar in conduct and primary endpoints to the study synopsis provided in Attachment 3.3.

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- a. Does the Division have any recommendations with respect to the study design?
- b. Does the Division agree that one placebo-controlled trial, supported by the published literature, is sufficient for NDA filing?

Division Response:

a. The design of an adequate and well-controlled efficacy study to support the use of colchicine in the acute treatment of gout flares could follow a number of approaches, including:

- 1) Superiority to a placebo control or active comparator with appropriate rescue.
- 2) Non-inferiority to an active comparator (e.g., NSAID). You should be aware that use of a non-inferiority design should follow the recommendations in the Effectiveness Guidance Document. For example, it will be necessary to rigorously establish an effect size for the active comparator based on placebo-controlled trials, and to establish an appropriate non-inferiority margin.
- 3) A placebo phase design, where patients are randomized to receive colchicine initially, or to receive placebo initially followed by colchicine at later time points, then comparing time to response between study groups. [Feldman BM, "Innovative Strategies for Trial Design, J Rheumatol 2000; 27 Suppl 58:4-7]. Such a trial, with a subset of patients evaluated in an inpatient setting (similar to the 1987 Ahern study), could also incorporate a formal QT evaluation. Please refer to the Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005.
- 4) A dose-response trial (e.g., randomization to high versus intermediate versus low dose) with efficacy demonstrated based on superiority of the higher doses to the lower doses. One endpoint to consider would be the proportion of subjects with 50% improvement in pain at a specified timepoint.

The study you propose in question 11 may be problematic in that the use of _____ will make it difficult to assess pain endpoints, which should be one of the primary endpoints in any gout trial. One approach to address the issue of placebo controlled trials in gout would be to define the need for such rescue medication as a treatment failure/drop out, and evaluate time to drop-out as the endpoint. The pre-selection of an appropriate primary endpoint is important and will depend on the study design selected. Therefore, further comments may be provided upon review of the final protocol. You are also referred to the

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discussions at an Arthritis Advisory Committee meeting on this topic, which may be found at: <http://www.fda.gov/ohrms/dockets/ac/cder04.html#arthritis>.

b. See response to question 9.

Discussion:

The Sponsor proposed a hybrid placebo-controlled/dose-response trial, with one treatment arm receiving placebo, another treatment arm receiving low dose colchicine (0.6 mg x 2, followed by another 0.6 mg dose an hour later), and a third treatment arm receiving the standard acute dose regimen (0.6 mg x 2, then 0.6 mg every hour to response or toxicity, maximum of 8 tablets total). The Sponsor proposed an endpoint of average pain from 12 to 36 hours. The Division expressed some concern for an average pain measure as a drug may appear effective early but lose its effect later and still "win" on an endpoint that averages pain scores. It was also commented that during an Arthritis Advisory Committee meeting to discuss endpoints in gout trials, there was a general impression that for acute gout, it would be important to show an effect within the first 24 hours. The Division commented that the clinical trial should assess the minimally clinically important difference (MCID), and the Sponsor should provide justification for how this was determined. Depending on the trial and endpoint, an appropriate imputation technique for missing data will be important as well. As mentioned in the Division's response to question 11, one approach to address concerns regarding the use of a placebo control would be to define the need for rescue medication as treatment failure/drop out, and evaluate time to drop-out as the endpoint. The Division also suggested the possibility of using a continuous responder analysis. In such an analysis, the proportion of responders is calculated using multiple definitions of treatment response ranging from 0% to 100% improvement. The Division referred the Sponsor to the labels for Lyrica[®] and Cymbalta[®], which contain examples of this.

Post-Meeting Note:

Although a minimally-clinically difference should be addressed in the application, the approvability of the application will be determined by evaluation of the efficacy and safety profile demonstrated.

Question 12. Does the Division agree that the two published studies are sufficient to allow for approval of colchicine as prophylaxis of acute gout flare?

Division Response:

See response to question 9.

Discussion:

There was no discussion beyond that the Division's initial written response.

Question 13. If no, Mutual proposes to perform one _____ in patients initiating treatment with _____ along with a Risk Management Plan that focuses on educating physicians and pharmacists on the safe use of

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colchicine and an educational brochure for patients. A synopsis for the study is included in Appendix 3.3.2.

- a. *Is the design of the study acceptable?*
- b. *If a phase IV comitant [sic] is not acceptable to the FDA, is one single trial Appendix 3.3.2), supported by the published literature, without the Risk Management Plan commitment, adequate?*

Division Response:

See response to question 9.

As you have noted, colchicine has the potential for significant toxicity, and a relatively narrow therapeutic window, making it a good candidate for a Risk Minimization Action Plan.

Discussion:

The Sponsor provided general descriptions of possible Risk Minimization activities, to include a _____ with a _____

along with clear labeling on the packaging to warn against exceeding the maximum dose or using the pills as general analgesics. The Sponsor also plans to incorporate physician and patient information sheets into the packaging. The Sponsor commented that a _____ would likely require stability testing/data. The Division commented that in general these ideas sounded reasonable, but more specific input may be requested after the plan is submitted and reviewed; for example, with the IND submission or an EOP2 meeting.

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Question 14. Is the published literature sufficient to allow for filing of an NDA for colchicine for the _____ treatment in adults of FMF attacks? If no, given the rarity of the condition in the United States, Mutual seeks advice on the studies required.

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Division Response:

See response to question 9.

Discussion:

There was no discussion beyond that the Division's initial written response.

Question 15. As an Orphan indication, Mutual requests confirmation that the requirements for pediatric studies will be waived.

Division Response:

Submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time.

Discussion:

There was no discussion beyond that the Division's initial written response.

Action Items:

1. The Sponsor will review the need for carcinogenicity studies, and provide a rationale for performing or not performing them.
2. The Sponsor will perform formal QT studies using supra-therapeutic doses. Justification will be provided if they elect not to use a supra-therapeutic dose.
3. The Sponsor will ensure that any clinical trial is powered to assess a minimally clinically important difference (MCID), and the Sponsor will provide justification for how this was determined.

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/s/

Sara Stradley
8/31/2006 10:58:54 AM
for Matthew Sullivan, MS