

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-353

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



URL Pharma, Inc.
URL Distribution
Mutual Pharmaceutical Company, Inc.
AR Scientific, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlpharma.com

PATENT CERTIFICATION
21 CFR 314.50(i)(1)(ii)

In accordance with 21 CFR 314.50(i)(1)(ii), in the opinion and to the best knowledge of Mutual Pharmaceutical Company Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this New Drug Application for Colchicine Tablets USP, 0.6 mg, were conducted or that claim a use of such drug or drugs.

A handwritten signature in black ink, appearing to read 'E. Magrab'.

E. Brendan Magrab
Executive Vice President of
Commercial Operations, General Counsel

11/3/08
Date

EXCLUSIVITY SUMMARY

NDA # 022353

SUPPL #

HFD # 170

Trade Name COLCRYS

Generic Name colchicine

Applicant Name Mutual Pharmaceutical Company, Inc.

Approval Date, If Known October 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?

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

22-351 The following NDAs were recently approved-
22-352 Colchicine (gout flares--approved on July 30, 2009)
Colchicine (prophylaxis of gout flares--approved on July 29, 2009)

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:

In the accompanying cover letter for this NDA, the sponsor stated that the published literature does not contain the necessary data to meet the FDA's current scientific standards to support approval of colchicine for the treatment of chronic gout. However, the Agency has previously approved colchicine as a component of ColBenemid, which

also contains probenecid, for the treatment of all stages of gout and gouty arthritis, including prevention of gout flares. Since the other component, probenecid, does not act to prevent gout flares but actually induces gout flares the approval of ColBenemid reflected the finding of effectiveness of colchicine for preventing gout flares. This earlier finding of efficacy, along with the publicly available data, is sufficient to support approval of the application.

(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:

(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"):

Paulus et al, Arthritis and Rheumatology 1974,17:609-614

Borstad et al, Journal of Rheumatology 2004, 31:2429-2432

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 ☐

! NO ☒

Explain:

! Explain:

Studies are from the literature

Investigation #2

!

!

YES ☐

! NO ☒

Explain:

! 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: Sara Stradley reviewed on 10/16/09

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

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

/s/

SARA E STRADLEY
10/16/2009

RIGOBERTO A ROCA
10/16/2009



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 September 22, 2008.

A handwritten signature in cursive script, appearing to read 'Robert Dettery', written over a horizontal line.

Robert Dettery
Vice-President, Regulatory Affairs

23 Oct 2008

Date

Tossa, Margarita

From: Greeley, George
Sent: Thursday, August 20, 2009 9:17 PM
To: Tossa, Margarita
Cc: Stowe, Ginneh D.
Subject: NDA 22-353 Colcrys

Importance: High

Hi Rita,

The Colcrys (colchicine) full waiver was reviewed by the PeRC PREA Subcommittee on August 19, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children.

The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

 Please consider the environment before printing this e-mail.

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

Application:	NDA 22353/000	Sponsor:	MUTUAL PHARM
Code:	170		1100 ORTHODOX ST
Priority:	7S		PHILADELPHIA, PA 19124
Stamp Date:	25-NOV-2008	Brand Name:	COLCHICINE TABLETS USP 0.6MG
PDUFA Date:	25-SEP-2009	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	27-JUL-2009	Product Number; Dosage Form; Ingredient; Strengths	

FDA Contacts:	M. TOSSA	Project Manager	(HFD-170)	301-796-4053
	C. BERTHA	Review Chemist		301-796-2410
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 28-MAY-2009	by S. FERGUSON	(HFD-322)	301-796-3247
	WITHHOLD	on 17-APR-2009	by C. CRUZ	(HFD-323)	301-796-3254

Establishment: CFN: _____ FEI: _____

b(4)

DMF No: _____ AADA: _____

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER
CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

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: 17-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Establishment: CFN: _____ FEI: _____

b(4)

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: 17-DEC-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

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: 17-DEC-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____

b(4)

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: 17-DEC-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: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2008

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI:

DMF No: AADA: b(4)

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: FEI:

DMF No: AADA: b(4)

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

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: 17-DEC-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

b(4)

Establishment: CFN: _____ FEI: _____

DMF No: _____ AADA: _____
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: PLANT/ANIMAL EXTRACTION CRUDE DRUG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-APR-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

b(4)

Establishment: CFN: _____ FEI: _____

DMF No: _____ AADA: _____
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: PLANT/ANIMAL EXTRACTION CRUDE DRUG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-APR-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

b(4)

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

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: 17-DEC-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

b(4)

Establishment: CFN: _____ FEI: _____

DMF No: _____ AADA: _____
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-DEC-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

b(4)

Establishment: CFN: _____ FEI: _____

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Decision: ACCEPTABLE
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b(4)

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Shment: 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: 17-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

b(4)

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

/s/

JOYCE K DE LEON
10/23/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022353 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
NDA: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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.)		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)): Col-Probenecid Provide a brief explanation of how this product is different from the listed drug. New dose & new formulation ☐ If no listed drug, check here and explain: 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. ☒ No changes ☐ Updated Date of check: 09/23/2009 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. On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.
❖ User Fee Goal Date Action Goal Date (if different)		09/25/2009 10/16/2009
❖ Actions		
• Proposed action		☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☒ None
❖ Promotional Materials (<i>accelerated approvals only</i>) 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 _____		☐ 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: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____ BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies		
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <u>Orphan drug designation</u>	08/19/2009	
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☐ Yes, date	
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No	
❖ Public communications (<i>approvals only</i>)		
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No	
• Press Office notified of action (by OEP)	☐ Yes ☐ No	
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs 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>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
• (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>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• (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>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• (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>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• 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>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire _____
• [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>	☐ N/A (no paragraph IV certification) ☐ 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).

(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? (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). <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> <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>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	
Officer/Employee List	
❖ 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>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action=AP and date= 10/16/09
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	final is attached to action ltr
Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	(attached)
Original applicant-proposed labeling	11/25/2008
Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None

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)	
• Most-recent division proposal for (only if generated after latest applicant submission)	final attached to action ltr
• Most recent applicant-proposed labeling	3/15/2009
❖ Labeling reviews (indicate dates of reviews and meetings)	☐ RPM ☒ DMEPA 08/07/2009 ☐ DRISK ☒ DDMAC 08/31/2009 ☐ CSS ☐ Other reviews
❖ Proprietary Name	
• Review(s) (indicate date(s))	02/26/2009
• Acceptability/non-acceptability letter(s) (indicate date(s))	03/06/2009
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	03/03/2009
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
○ If yes, Center Director's Exception for Review memo (indicate date)	
○ If yes, OC clearance for approval (indicate date of clearance communication)	☐ Not an AP action
❖ Pediatric Page in DARRTS (approvals only, must be reviewed by PERC before finalized)	☒ Included (see DARRTS)
❖ 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)	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications (if located elsewhere in package, state where located)	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ 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	
• PeRC (indicate date; approvals only)	☐ Not applicable 08/20/2009 (PeRC memo)
• Pre-Approval Safety Conference (indicate date; approvals only)	☒ Not applicable

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

• Regulatory Briefing (indicate date)	☒ No mtg
• Pre-NDA/BLA meeting (indicate date)	☐ No mtg 02/04/2008
• EOP2 meeting (indicate date)	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (indicate date for each review)	☐ None
Division Director Summary Review (indicate date for each review)	☐ None 10/16/09
Cross-Discipline Team Leader Review (indicate date for each review)	☐ None 10/15/09
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	
• Clinical review(s) (indicate date for each review)	08/05/2009
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Safety update review(s) (indicate location/date if incorporated into another review)	see clinical review
❖ 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	08/05/2009 (page#14)
❖ Clinical reviews from other clinical areas/divisions/Centers (indicate date of each review)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) • REMS Memo (indicate date) • REMS Document and Supporting Statement (indicate date(s) of submission(s))	☐ None 10/16/09 9/29/09
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ None
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☐ None 08/11/2009
Clinical Pharmacology ☐ 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)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 08/17/2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☒ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 07/30/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☐ None 4/14/2009
• CMC/product quality review(s) (indicate date for each review)	☐ None 02/10/2009, 07/28/2009
• BLAs only: Facility information review(s) (indicate dates)	☐ None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	☒ 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)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	02/10/2009 (page#21)
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	

• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: 05/28/2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: ○ 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: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ 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.

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

/s/

SARA E STRADLEY
10/19/2009

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-353	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Colcrys Established/Proper Name: Colchicine Dosage Form: Tablets Strengths: 0.6 mg		
Applicant: Mutual Pharmaceuticals Company, Inc.		
Date of Receipt: 11/25/2008		
PDUFA Goal Date: 9/25/2009		Action Goal Date (if different): Oct 2009
Proposed Indication(s): Prophylaxis of gout flares (chronic gout)		

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)
Published literature-studies (two published RCTs, and five other clinical studies: supportive) Published literature: recommendations, EULAR and British Rheumatoid Society. FDA's prior approval of Col-Probenecid. Mutual-Sponsored PK Studies (in Healthy Adults)	All sections of labeling and PK data.
NDA 84-279 (Col-Probenecid)	All sections of labeling
Colchicine classified as a pre-DESI drug.	

This is 505(b)(2) application referenced on publicly available information (literature): Borstad (RCT#1); Paulus (RCT#2). Supportive Open-Label studies: Yü TF; Becker MA, Schumacher HR, Wortmann RL, *et al*; Karimzadeh H, Nazari J, Mottaghi P, *et al*

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 ☒ 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?

YES ☒ NO ☐

(Note: None of the literature appeared to refer to ColBenemid, only to "colchicine".)

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 **X** 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 (Watson Laboratories)	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 **X** NO

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

Name of drug(s) approved via the DESI process: colchicine/probenecid products

- c. Described in a monograph?

YES ☐ NO **X**

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

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO ☒

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 ☒

(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 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 ☒

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 ☐

(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 X 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): N/A

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):

- X 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):

5 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

✓ § 552(b)(5) Deliberative Process

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22353

ORIG-1

MUTUAL
PHARMACEUTICA
L CO INC

COLCHICINE TABLETS USP
0.6MG

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/s/

SARA E STRADLEY
10/16/2009

From: Tossa, Margarita
To: "Robert Dettery";
Subject: NDA 22353/REMS
Date: Thursday, September 17, 2009 4:21:47 PM
Attachments: NDA22351-Risk mitigation template 7-28-09.doc

Robert,

You need to submit REMS to NDA 22353 COLCRYS/chronic gout. REMS should be exactly the same with REMS for NDA 22351/acute gout (see attached and make necessary changes).

Please send REMS to me by email asap, and follow up with a submission to the NDA.

Thanks,

Margarita

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22353

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/s/

MARGARITA V TOSSA
09/22/2009

From: Tossa, Margarita
To: "Robert Dettery";
Date: Thursday, September 03, 2009 4:55:46 PM
Attachments: N 22353 COLCRYS combined all indications .doc

Dear Robert,

Please find the attached label for NDA 22353 COLCRYS (chronic gout), revise this label and accept or comment on changes we made, and send the label back to me by next week Friday (9-11-09).

Thanks,

Margarita

Application
Type/Number

NDA-22353

Submission
Type/Number

ORIG-1

Submitter Name

MUTUAL
PHARMACEUTICA
L CO INC

Product Name

COLCHICINE TABLETS USP
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/s/

MARGARITA V TOSSA
09/10/2009

From: Robert Dettery
To: Tossa, Margarita;
cc: Brandi Adoff;
Subject: RE: NDA 22353/label.
Date: Thursday, August 20, 2009 9:46:51 AM

Margarita,

In the process of merging the Colcrys acute gout and chronic gout labeling, we recognized the potential for confusion by the patient in the event they experience a gout flare while taking colchicine for gout prophylaxis. The changes we made to the labeling reflect what, in our opinion, is needed to clarify appropriate safety and dosing directions.

Robert Dettery

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

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]
Sent: Tuesday, August 18, 2009 11:46 AM
To: Robert Dettery
Subject: NDA 22353/label.

Robert,

Clinical reviewer for NDA 22353 asking you to clarify why Mutual made so many changes to the label for the NDA 22353 that do not seem to relate to new information for the chronic gout indication (prophylaxis of gout flares)?

Thank you,

Margarita

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22353	ORIG-1	MUTUAL PHARMACEUTICA L CO INC	COLCHICINE TABLETS USP 0.6MG

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/s/

MARGARITA V TOSSA
09/10/2009

From: Holmes, Loretta
To: Tossa, Margarita;
cc: Arnwine, Kristina;
Subject: RE: NDAs: 22352, 22351 & 22353/container labels.
Date: Monday, August 10, 2009 3:58:32 PM

Hi Rita,
DMEPA finds the company's response acceptable.
Loretta

From: Tossa, Margarita
Sent: Monday, August 10, 2009 10:15 AM
To: Wheeler, Chris; Arnwine, Kristina; Holmes, Loretta
Subject: FW: NDAs: 22352, 22351 & 22353/container labels.
Importance: High

Hi All,

I conveyed the recent DMEPA's comments re: container labels for COLCRYS to the company, and the company's response is below.
Please let me know your opinion.

Thanks,
Rita.

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Monday, August 10, 2009 9:48 AM
To: Tossa, Margarita
Cc: Brandi Adoff
Subject: RE: NDAs: 22352, 22351 & 22353/container labels.

Good Morning Margarita,
I am afraid that DMEPA is incorrect in their assessment of the Colcris container label. After the February 20, 2009 comments was received, we made the exact changes that they are recommending again - the logo and Rx was decreased in size and the established name was increased. The brand name was 16 pt font and the established name was made 8 pt font. I verified this myself by measuring the

height of the letters and the established name letters are exactly ½ the size of the brand name letters. I do not believe we need to make any additional changes to the label.

Robert Dettery

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

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]
Sent: Monday, August 10, 2009 8:34 AM
To: Robert Dettery
Subject: NDAs: 22352, 22351 & 22353/container labels.
Importance: High

Robert,

Please refer to your recently approved NDA 22352/FMF (July 29, 2009), and NDA 22351/gout flares (July 30, 2009).

The Division of Medication Error Prevention and Analysis (DMEPA) completed review of the Final Carton and Container labels, and identified the following deficiencies:

As previously noted in the Agency's February 20, 2009 e-mail containing our label and labeling comments, the established name is not at least ½ the size of the proprietary name. The size of the established name should be increased to at least ½ the size of the proprietary name (taking into account all pertinent factors, including typography, layout, contrast, and other printing features) in order to comply with 21 CFR 201.10(g)(2). We recommend decreasing the size of the manufacturer's logo and the "Rx" symbol, at the bottom of the container label, to allow more space to increase the prominence of the established name.

We recommend you to make necessary changes to the container labels and

submit an amendment to all your NDA's (22352, 22351 & 22353).

Thank you,

Margarita

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22353

ORIG-1

MUTUAL
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/s/

MARGARITA V TOSSA

09/10/2009

From: Tossa, Margarita
To: "Robert Dettery";
Subject: New stability data/letters of cross reference.
Date: Wednesday, February 11, 2009 11:03:14 AM

Good day Robert,

We received your 120-day safety update for the pending NDA 22-351.

This submission includes a new stability data.

If possible, provide us two letters of cross reference (for NDA 22-352 and for NDA 22-353) in order for us to use a new stability data for your other NDAs.

Thank you,

Margarita

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22353

ORIG-1

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/s/

MARGARITA V TOSSA
09/10/2009

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

Margarita,

This email is in follow-up to the telephone conversation between Mutual and the review division a few minutes ago. Upon further review, I have to correct myself from what I stated in that meeting. Mutual's position is that literature alone is insufficient to permit substantive review since it can not demonstrate safety and efficacy of colchicine to treat chronic gout. The literature consists of two published studies testing colchicine for chronic gout – one study used 3 colchicine (with probenecid) tablets per day with no placebo control, while the second study had 1/3 patients using 1 tablet daily and 2/3 patients using 2 tablets daily with the results being combined instead of separated. We do not believe these studies meet the criteria for a well-controlled clinical trial.

Regarding safety, our Agree results demonstrated that colchicine is effective at lower doses than are now commonly used. We believe further dose-ranging clinical studies are necessary in order to establish the optimum therapeutic dose for the prevention of gout flares. In addition, the Agree trial results demonstrated that patients may be overexposed to colchicine, a narrow therapeutic index drug, at the levels now commonly used in medical practice.

In summary, we believe that literature alone and the results of our Agree trial are insufficient to support the safety and efficacy of colchicine tablets for the indication of chronic gout. Instead, we believe that additional clinical studies should be required to determine the proper dose for this chronic indication. Mutual's position, as stated above, is in agreement with our cover letter to NDA 22-353 and our Citizen Petition, Docket Number FDA-2008-P-0442 on August 1, 2008.

Robert Dettery
Vice President, Regulatory Affairs



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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22353

ORIG-1

MUTUAL
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/s/

MARGARITA V TOSSA
09/10/2009

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

Application Information	
NDA # 22-353 BLA#	NDA Supplement #:S- BLA STN #
Efficacy Supplement Type SE-	
Proprietary Name: Colcrys/under review 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: 11/25/2008 Date of Receipt: 11/25/2008 Date clock started after UN:	
PDUFA Goal Date: 9/25/2009	Action Goal Date (if different):
Filing Date: 1/24/2009	
Date of Filing Meeting: 1/23/2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7	
Proposed Indication(s): Prevention/prophylaxis of gout flares	
Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement:	☐ 505(b)(1) ☐ 505(b)(2)
<i>Refer to Appendix A for further information.</i>	
Review Classification:	☒ Standard Priority
<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>	☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐	
Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): 72,586	
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>	☒ YES ☐ 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>	☒ YES ☐ 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>	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status Comments:	☒ Paid Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ 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? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm 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)]?	☐ YES ☒ NO ☐ YES ☐ NO

<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i> Comments:	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? <i>(NDAs/NDA efficacy supplements only)</i> <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> Comments:	☒ YES # years requested: 3 years NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use <i>(NDAs only)</i>: 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)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	☒ Not applicable ☐ YES ☒ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 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)). 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))? <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>	Not applicable ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☒ NO

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>		☐ YES ☒ NO
If yes, please list below:		
Application No.	Drug Name	Exclusivity Code
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.		
Format and Content		
Do not check mixed submission if the only electronic component is the content of labeling (COL). Comments:		☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?		
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)? <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> Comments:		☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)		☒ YES ☐ NO
If not, explain (e.g., waiver granted):		

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

sign the certification. <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) 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> Comments:		
Field Copy Certification (NDAs/NDA efficacy supplements only)		
Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>) <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☒ Not Applicable (<i>electronic submission or no CMC technical section</i>) ☐ YES ☐ NO	
Financial Disclosure		
Financial Disclosure forms included with authorized signature? <i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> Comments:	☒ YES ☐ NO	
Pediatrics		
<u>PREA</u> <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> Are the required pediatric assessment studies or a full waiver of pediatric studies included? If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? <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) Comments:		Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO

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

OTC Labeling	
Check all types of labeling submitted. Comments:	☐ Not Applicable ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? <i>If no, request in 74-day letter.</i> Comments:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> Comments:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> Comments:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? Comments:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	☐ YES Date(s): NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	☒ YES Date(s): February 4, 2008 NO
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i> Comments:	YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1-23-2009

NDA/BLA #: 22-353

PROPRIETARY/ESTABLISHED NAMES: Colcrys/ (colchicine) Tablets USP, 0.6 mg

APPLICANT: Mutual Pharmaceutical Company, Inc.

BACKGROUND: 505(b)(2) referenced on publicly available information, supplemented by nonclinical and clinical pharmacology studies.

The related IND is 72,586:

July 31, 2006: Pre-IND meeting (meeting minutes in DARRTS).

February 4, 2008: Pre-NDA meeting (meeting minutes in DARRTS).

(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	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Jeff Siegel, M.D.		Y
Clinical	Reviewer:	Jane Gilbert, M.D.	Y
	TL:	Jeff Siegel, M.D.	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		

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

OTHER ATTENDEES: Bob Rappaport, Rigoberto Roca, Christopher Wheeler/OSE, Lori Cantin/OSE

505(b)(2) filing issues? If yes, list issues:	☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO

Electronic Submission comments List comments:	☐ Not Applicable
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain: This NDA submission is based on published literature.	YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> - this drug/biologic is not the first in its class - the clinical study design was acceptable - the application did not raise significant safety or efficacy issues - 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	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
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:	☒ Not Applicable ☐ YES NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments: see CMC review in DFS ()	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
- Establishment(s) ready for inspection? - Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☐ YES ☐ NO
Sterile product?	☐ YES ☒ NO

If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)	☐ YES ☐ NO
FACILITY (BLAs only) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob A. Rappaport, MD GRMP Timeline Milestones: Mid-Cycle- 5/24/2009 ; Wrap-Up- 7/23/2009; Action Goal Date- 9/25/2009 Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. X No review issues have been identified for the 74-day letter. Review issues have been identified for the 74-day letter. List (optional): X Standard Review Priority Review
ACTIONS/ITEMS	
☐	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.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	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.
	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	Other

In accordance with pre-submission regulatory meetings with the Agency, where the Agency noted that we concurred with the sponsor's original position that the literature would be sufficient in support of an application of colchicine for the prophylaxis of gout flares, the sponsor submitted NDA 22-353. NDA 22-353 contained the results of the sponsor's extensive literature search for efficacy trials, which includes the two randomized controlled studies previously identified, along with supportive studies, and results of the sponsor's search of global postmarketing safety databases. However, in the cover letter to NDA 22-353, the sponsor re-iterated their current position, which is further detailed in their Citizen Petition (#FDA-2008-0442, submitted August 2008), that the FDA should not approve any colchicine NDA for prophylaxis of gout flares unless the application contains the results of a well-controlled clinical study that determines the lowest effective dose of colchicine, additional drug-drug interaction trials, and studies of pharmacokinetics in the elderly. The fact that the sponsor re-stated these arguments against approval of NDA 22-353 in the cover letter for NDA 22-353 led to further internal discussions as to whether this application was fileable. Ultimately, after discussion with ODEII supervisory staff (Office Director Curtis Rosebraugh and Associate Director for Regulatory Affairs Leah Ripper), it was determined that the sponsor's conclusions as stated in their cover letter were irrelevant to the application's fileability, so long as the application itself contained sufficient data for review. Thus since all disciplines involved had determined the application was fileable from this standpoint, the application was filed.

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.

**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
3/3/2009 03:21:49 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-353

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 November 25, 2008, received November 25, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Colchicine Tablets USP, 0.6 mg.

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 **Standard**. Therefore, the user fee goal date is September 25, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 4, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

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

/s/

Bob Rappaport
2/6/2009 12:15:53 PM

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

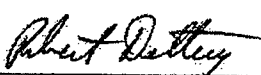
Please mark the applicable checkbox.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Robert Dettery	TITLE Vice President, Regulatory Affairs
FIRM / ORGANIZATION Mutual Pharmaceutical Company, Inc.	
SIGNATURE 	DATE 14 Nov 2008

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

2 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



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

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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 _____
Suman Wason, MD	Executive Director, Branded Products

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?

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.

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)

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?

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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.

IND 72,586
PIND 75,040
PIND _____
Pre-NDA Meeting
Page 6 of 18

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.

b(4)

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.

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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).

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. _____

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

b(4)

_____ 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.

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:

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?

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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/6357fnl.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

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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 SUPPQUAL 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.

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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/6357fn1.htm>
- Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fn1.htm>

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

/s/

MATTHEW W SULLIVAN
02/01/2008
Regulatory Project Manager



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 Detterv	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

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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.

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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.

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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 naïve 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.

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 _____

_____ is provided in Appendix 3.3.1. Is this approach acceptable to the Division? Is the design of the study acceptable?

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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