CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-351

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-351 SUPPL # HFD # 170

Trade Name COLCRYS

Generic Name colchicine

Applicant Name Mutual Pharmaceutical Company, Inc.

Approval Date, If Known 7-30-2009

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?

3

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 84-279 Col-Probenecid

NDA# 83-734 Probenecid and Colchicine

NDA# 40-618 Probenecid and Colchicine

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

(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:

Study MCP-004-06-001 was a randomized, placebo-controlled trial conducted by the sponsor of this application in support of the acute gout indication.

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"):

Investigation # 1: Study MCP-004-06-001

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 # 72,586	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(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:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Margarita Tossa
Title: RPM
Date:

Name of Office/Division Director signing form: Rigoberto Roca, MD
Division of Anesthesia, Analgesia and Rheumatilogy Products
Title: Deputy Division Director

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

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

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

/s/

MARGARITA V TOSSA
07/30/2009

RIGOBERTO A ROCA
07/30/2009

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

CERTIFICATION REQUIRED BY GENERIC DRUG ENFORCEMENT ACT OF 1992

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

Robert Dettery
Vice-President, Regulatory Affairs

4 Sept 2008
Date

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-351 | Supplement Number: _____ | NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Anesthesia, Analgesia and Rheumatology Products | PDUFA Goal Date: 7/30/2009 | Stamp Date: 09/30/2008

Proprietary Name: Colcrys ™

Established/Generic Name: Colchicine

Dosage Form: 0.6 mg Tablets

Applicant/Sponsor: Mutual Pharmaceutical Company, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

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

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

Indication: Treatment of gout flares

Q1: Is this application in response to a PREA PMC/PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

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

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

☐ Yes. Please proceed to Section D.

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

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

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

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

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

Q3: Does this indication have orphan designation?

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

☒ No. Please proceed to the next question.

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

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

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

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

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

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

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

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

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

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

☒ Justification attached.

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

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

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

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

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

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

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

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

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

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

☐ Justification attached.

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

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

† *Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)*

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

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

/s/

Margarita Tossa
7/15/2009 02:16:10 PM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22351/000	**Sponsor:**	MUTUAL PHARM
Code:	170		1100 ORTHODOX ST
Priority:	7S		PHILADELPHIA, PA 19124
Stamp Date:	30-SEP-2008	**Brand Name:**	COLCHICINE TABLETS USP 0.6MG
PDUFA Date:	31-JUL-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	01-JUN-2009	**Dosage Form:**	(TABLET)
		Strength:	0.6 MG

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

Overall Recommendation:	ACCEPTABLE	on 01-JUN-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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-OCT-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: 16-OCT-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: 16-OCT-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: 16-OCT-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: 16-OCT-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		
	PHILADEPHIA, PA 19124		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	FINISHED DOSAGE MANUFACTURER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-OCT-2008		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-OCT-2008		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** [redacted] **FEI:** [redacted]		
	[redacted]		
			b(4)
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER		
	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-OCT-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: 16-OCT-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: 16-OCT-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

b(4)

DMF No: **AADA:**

Responsibilities: INTERMEDIATE MANUFACTURER

Profile: PLANT/ANIMAL EXTRACTION CRUDE DRUG **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-APR-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** **FEI:** ———

———————————

b(4)

DMF No: ——————————— **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: PLANT/ANIMAL EXTRACTION CRUDE DRUG **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-APR-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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: 16-OCT-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** ———

———————————

b(4)

———————————

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-OCT-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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-OCT-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-OCT-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

/s/

Srikanth Nallani
6/4/2009 11:01:51 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/5/2009 08:20:28 AM
BIOPHARMACEUTICS

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/s/

NICKEISHA S BURFORD
09/18/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-351 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

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
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.)	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: 07/17/2009 **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)	07/30/2009 07/30/2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain ____	☐ 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 BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: Orphan drug designation	06/24/2009
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• 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)? *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.*	☒ 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)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ 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? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ 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? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ 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)? *(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.)*	☒ 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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ 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). *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*).* *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.*	☐ 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 *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 7-30-2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	7/30/2009 (attached)
• Original applicant-proposed labeling	09/30/2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ 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)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP 02/26/2009 ☐ DRISK ☒ DDMAC 07/06/2009 ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 12/05/2008 12/12/2008 & 02/26/2009
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	02/19/2009
❖ 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 o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ 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 06/24/2009 (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 7/30/2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 07/01/2009
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	07/01/2009
• Clinical review(s) *(indicate date for each review)*	06/26/2009
• 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)*	
❖ 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	06/26/2009 (page#9)
❖ 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
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 06/08/2009
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 06/19/2009
Clinical Pharmacology ☐ None	

[5] Filing reviews should be filed with the discipline reviews.

❖ 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 06/04/09
❖ 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 06/05/2009
❖ 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, 06/01/2009
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ 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) *(date completed must be within 2 years of action date)*	Date completed: 06/01/2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	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.

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/s/

MARGARITA V TOSSA
07/30/2009

From:	Robert Dettery
To:	Tossa, Margarita;
cc:	Andria Werynski; Brandi Adoff;
Subject:	NDA 22351 labeling
Date:	Thursday, July 30, 2009 9:53:07 AM
Attachments:	Combo redline.doc
	Combo clean.doc

Good morning, Margarita,
We accepted the changes that you provided to the combined insert and have made a few editorial changes of our own. They are shown in the attached redlined version. The same insert is also attached as a clean version. Let me know if these editorial changes are OK with you.

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

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

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MARGARITA V TOSSA
07/30/2009

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

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

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

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

Robert,

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

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

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

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

Thank you,

Margarita

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

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/s/

MARGARITA V TOSSA
07/30/2009

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

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

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

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

Robert,

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

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

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

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

Thank you,

Margarita

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

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/s/

MARGARITA V TOSSA
07/30/2009

From: Tossa, Margarita
To: "Robert Dettery";
Subject: RE: COLCRYS Insert for FDA Submission
Date: Wednesday, July 15, 2009 12:05:05 PM

Hi Robert,

We will have a labeling meeting on Monday and I will send you the label on Tuesday. Please do not submit an amendment to the NDA until we reach an agreement.

- The ONDQA is consulting the Office of Compliance regarding your NDC question.

- The ONDQA always recommends the following format for the drug name/label:

  Trade Name (Established Name) Dosage Form

Best regards,
Margarita

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Wednesday, July 15, 2009 11:51 AM
To: Tossa, Margarita; Sullivan, Matthew
Cc: Jennifer W. Phillips; Andria Werynski; Brandi Adoff
Subject: FW: COLCRYS Insert for FDA Submission
Importance: High

Dear Margarita and Matt,

I am including with this email Mutual's comments/revisions to the draft labeling that you provided us for Colcrys, NDA 22-351. Our comments and revisions are the result of our telecon last Thursday, as well as further consideration of that discussion. Please note that in the absence of feedback from the Division's CMC reviewer, we made some assumptions regarding the established name and the NDC

numbers.

Please let me know if our version is acceptable to the Division and I will then submit this labeling as an Amendment to the NDA.

Regards,

Robert Dettery

Vice-President, Regulatory Affairs

Mutual Pharmaeutical Company, Inc.

AR Scientific, Inc.

. <<Colcrys Attachment 1 July 15 2009.doc>> <<Colcrys Attachment 2 July 15 2009.doc>> <<Proposed Colcrys Insert July 15 2009 Tracked Changes Version.doc>>

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/s/

Margarita Tossa
7/16/2009 02:41:31 PM
CSO

From:	Robert Dettery
To:	Tossa, Margarita; Sullivan, Matthew;
cc:	Jennifer W. Phillips; Andria Werynski; Brandi Adoff;
Subject:	FW: COLCRYS Insert for FDA Submission
Date:	Wednesday, July 15, 2009 11:51:51 AM
Attachments:	Colcrys Attachment 1 July 15 2009.doc
	Colcrys Attachment 2 July 15 2009.doc
	Proposed Colcrys Insert July 15 2009 Tracked Changes Version.doc

Dear Margarita and Matt,

I am including with this email Mutual's comments/revisions to the draft labeling that you provided us for Colcrys, NDA 22-351. Our comments and revisions are the result of our telecon last Thursday, as well as further consideration of that discussion. Please note that in the absence of feedback from the Division's CMC reviewer, we made some assumptions regarding the established name and the NDC numbers.

Please let me know if our version is acceptable to the Division and I will then submit this labeling as an Amendment to the NDA.

Regards,

Robert Dettery

Vice-President, Regulatory Affairs

Mutual Pharmaceutical Company, Inc.

AR Scientific, Inc.

. <<Colcrys Attachment 1 July 15 2009.doc>> <<Colcrys Attachment 2 July 15 2009.doc>> <<Proposed Colcrys Insert July 15 2009 Tracked Changes Version.doc>>

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/s/

Margarita Tossa
7/16/2009 02:38:10 PM
CSO

From:	Robert Dettery
To:	Tossa, Margarita;
cc:	Jennifer W. Phillips; Andria Werynski; Brandi Adoff;
Subject:	RE: NDA 22-351 COLCRYS/acute gout/label
Date:	Tuesday, July 07, 2009 4:17:39 PM

Margarita,
Our first review of the division's comments revealed a few questions that we would like clarified. Would it be possible to schedule a quick telecon with the labeling reviewers this week? The points that we would like clarification on are inconsistencies: 1) in the established name of the product between this insert and our FMF insert, and 2) in Tables 1, 5, and 6. We may also have some questions regarding Table 7 and Figure 1, but we are still looking into that data.

Please let me know if we can talk. We would like to resolve our questions as soon as possible.

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

From: Tossa, Margarita [mailto:Margarita.Tossa@fda.hhs.gov]
Sent: Tuesday, July 07, 2009 2:40 PM
To: Robert Dettery
Subject: NDA 22-351 COLCRYS/acute gout/label
Importance: High

Dear Robert,

Please find attached our preliminary comments for the COLCRYS label NDA 22-351/acute gout (please note that we will provide you more comments next week Monday or Tuesday when the DDMAC review of the label will be completed).

1. Remove the reference to the ———— in the HOW SUPPLIED b(4)

section.

2. Replace PI with the MedGuide. The MedGuide should be identical to the MedGide for NDA 22-352/FMF, except you need to revise it accordingly to the acute gout indication.

3. Please revise the label, accept or deny our changes, and do the formatting [change it to the one column throughout the label, except HIGHLIGHTS OF PRESCRIBING INFORMATION]

<<N 22351 Colcrys_ acute gout_proposed lbl.doc>>

Thank you,

Margarita

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/s/

Margarita Tossa
7/16/2009 02:35:28 PM
CSO

14 Page(s) Withheld

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

__√__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Margarita Tossa
7/16/2009 02:36:30 PM
CSO

From: Robert Dettery
To: Tossa, Margarita;
cc: Brandi Adoff;
Subject: RE: NDA 22-351 Colchicine (acute gout).
Date: Thursday, November 20, 2008 10:14:19 AM

Rita,
We will provide the final study reports for ritonavir and azithromycin on Monday, November 24th as an amendment to 22-351 per your email. We will provide the draft study reports for cyclosporin, theophylline, ketoconazole, and diltiazem on December 5th as an amendment to 22-351. Would you also like them submitted to NDA 22-352 for the FMF indication?

I was incorrect when I said we had the draft study reports for grapefruit juice and verapamil. These are not yet available. I will notify you as soon as they are available.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Wednesday, November 19, 2008 6:19 PM
To: Robert Dettery
Subject: RE: NDA 22-351 Colchicine (acute gout).
Importance: High

Hi Robert,

We would prefer to have the Ritonavir and Azithromycin studies as an amendment to NDA 22-351 in addition to the acute gout indication.
You can also submit the Draft study report for Cyclosporin, Theophylline, Ketoconazole, grapefruit juice, Diltiazem, and Verapamil as an amendment to NDA 22-351 also, but of course, the final report should be provided as soon as finalized.

Thank you,
Margarita

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Wednesday, November 19, 2008 2:35 PM
To: Tossa, Margarita
Cc: Brandi Adoff
Subject: RE: NDA 22-351 Colchicine (acute gout).

Greetings Rita,
I'm sorry for the delay in getting back to you with information regarding your request below.

The final study reports for the Ritonavir and Azithromycin studies are due to be received from the CRO by the end of business today. We are planning to include these studies in the NDA that will be filed next week for the chronic treatment of gout, however we could also provide them as an amendment to our NDA 22-351 if you wish.

The final study reports for Cyclosporin, Theophylline, Ketoconazole, grapefruit juice (————), Diltiazem, and Verapamil are due from the CRO around December 19, 2008. We were planning to submit these studies in the 120 day safety update to NDA 22-351. We do, however, currently have the draft study reports and we could provide them now, again as an amendment to 22-351, if that is preferred. b(4)

The study using Seville orange juice is scheduled to begin dosing in February 2009. This is due to the seasonality of the fruit, which do not become available until that time.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Tuesday, November 18, 2008 8:07 AM
To: Robert Dettery
Subject: NDA 22-351 Colchicine (acute gout).

Good morning Robert,

The Clin Pharm reviewer has a question regarding your PK studies for colchicine.

We understand that your company has already finished a drug interaction study with ritonavir, ketoconazole, ——— , cyclosporine, theophylline, and azithromycin could you let us know when you intend to submit the study reports. b(4)

Thanks,

Rita.

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

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/s/

Margarita Tossa
7/16/2009 02:33:44 PM
CSO

From: Robert Dettery
To: Tossa, Margarita;
cc: Brandi Adoff;
Subject: RE: NDA 22-351 Colchicine (acute gout).
Date: Wednesday, November 19, 2008 2:35:38 PM

Greetings Rita,
I'm sorry for the delay in getting back to you with information regarding your request below.

The final study reports for the Ritonavir and Azithromycin studies are due to be received from the CRO by the end of business today. We are planning to include these studies in the NDA that will be filed next week for the chronic treatment of gout, however we could also provide them as an amendment to our NDA 22-351 if you wish.

The final study reports for Cyclosporin, Theophylline, Ketoconazole, grapefruit juice (———————), Diltiazem, and Verapamil are due from the CRO around December 19, 2008. We were planning to submit these studies in the 120 day safety update to NDA 22-351. We do, however, currently have the draft study reports and we could provide them now, again as an amendment to 22-351, if that is preferred. b(4)

The study using Seville orange juice is scheduled to begin dosing in February 2009. This is due to the seasonality of the fruit, which do not become available until that time.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Tuesday, November 18, 2008 8:07 AM
To: Robert Dettery
Subject: NDA 22-351 Colchicine (acute gout).

Good morning Robert,

The Clin Pharm reviewer has a question regarding your PK studies for

colchicine.

We understand that your company has already finished a drug interaction study with ritonavir, ketoconazole, ———— , cyclosporine, theophylline, and azithromycin could you let us know when you intend to submit the study reports. b(4)

Thanks,

Rita.

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/s/

Margarita Tossa
7/16/2009 02:31:28 PM
CSO

From: Robert Dettery
To: Tossa, Margarita;
Subject: RE: NDA 22-351
Date: Tuesday, November 18, 2008 9:07:06 AM

Hello Rita,
Thank you for your prompt reply and I am pleased that the review team will give consideration to our request for a ———— to NDA 22-351. I hope the discussion regarding our request will include the following revelations resulting from Mutual's clinical and DDI studies that have important safety implications: b(4)

- One DDI study has shown colchicine AUC increase 257% when administered with clarithromycin, demonstrating the need to adjust the colchicine dosage when given concurrently with clarithromycin, and
- There is equal effectiveness when colchicine is given in a dosage regime of 1.8mg per attack as compared to the conventional 4.8mg regime, and
- The 1.8 mg. colchicine dosage for this NDA resulted in an incidence of diarrhea that was not significantly different than placebo versus the regimen that is commonly used in medical practice, 4.8 mg., which resulted in a 77% incidence of diarrhea in the AGREE trial.

Thanks again and I am looking forward to the team's decision.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Monday, November 17, 2008 11:32 AM
To: Robert Dettery
Subject: RE: NDA 22-351

Dear Robert,

Thank you for your email.
The review team will discuss your request.

Rita.

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Friday, November 14, 2008 1:01 PM
To: Tossa, Margarita
Cc: Sullivan, Matthew
Subject: NDA 22-351

Greetings Margarita,

As you know, on September 30, 2008 Mutual submitted NDA 22-351 for Colchicine tablets USP, 0.6 mg, indicated for the treatment of acute gout. The application contains data from our AGREE clinical trial, and from drug interaction studies, which revealed significant safety data that would provide improvements for patients, especially for those that are currently being treated with unapproved marketed colchicine products. We would now like to request that priority review status be granted for NDA 22-351.

To support this request, Mutual offers the following supportive rationale:

1. The results of our AGREE trial revealed that patients are currently prescribed marketed unapproved colchicine at doses that are nearly triple the clinically efficacious dose, of this narrow therapeutic index drug, resulting in an unnecessarily high rate of exposure and adverse reactions. Furthermore, our drug-drug interaction studies revealed potentially fatal drug interactions that the vast majority of physicians will not be aware of until our NDA and product labeling are approved. We believe that our product and labeling will provide a major significant improvement in safety and should be available to physicians and patients as quickly as possible.

2. We believe that this application meets the criteria for priority review by providing:

    a. A significant improvement compared to marketed products – this NDA represents an "elimination or substantial reduction of a treatment-limiting drug reaction". The currently marketed

(unapproved) colchicine tablets do not inform physicians of the lower effective dose and favorable safety profile demonstrated in the AGREE trial.

b. A significant improvement compared to marketed products – this NDA includes critical drug-drug interaction discoveries that should result in dosage reductions. Current usage of colchicine has been associated with deaths in the medical literature. The currently marketed unapproved colchicine products, as well as the approved combination products containing colchicine, do not inform physicians of this information.

3. We anticipate that the Office of Compliance will want to take prompt enforcement action against the manufacturers of marketed unapproved colchicine tablets (as they have already done to manufacturers of unapproved colchicine injectables) upon the approval of our NDA 22-352 for FMF. However, this may pose a dilemma for physicians by requiring our product to be used off-label for the treatment of acute gout until NDA 22-351 is approved. By giving NDA 22-351 a priority review, this interim confusion for patients and prescribers may be avoided.

We apologize for this late request for priority review, but we believe that this important dosing information is essential for physicians and important for the safety of patients. Our colchicine gout NDA 22-351 contains much of the same information, including CMC and labeling, as our colchicine FMF NDA 22-352. Therefore, this duplicate information is already undergoing review for NDA 22-352, leaving only the clinical data from our AGREE trial as the primary review focus for NDA 22-351.

Please contact me if you have any questions or comments, or if you would like this correspondence submitted formally to the NDA.

Robert Dettery
Vice President, Regulatory Affairs


please consider the environment before printing this e-mail

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

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/s/

Margarita Tossa
7/16/2009 02:30:13 PM
CSO

From: Tossa, Margarita
To: Tossa, Margarita;
Subject: FW: NDA 22351 Colchicine (gout flares)/information request.
Date: Thursday, July 16, 2009 1:55:53 PM
Attachments: CoA-RD010016-CCU-117153.pdf

From: Robert Dettery [mailto:RDettery@urlpharma.com]
Sent: Monday, October 27, 2008 12:07 PM
To: Tossa, Margarita
Cc: Brandi Adoff
Subject: RE: NDA 22351 Colchicine (gout flares)/information request.

Hello Margarita,
The two lot numbers refer to the same lot of drug substance. The lot number CCU-117153 is from the drug substance manufacturer, ———
Upon receipt of the incoming API from ——— Mutual assigned our own internal lot number RD10016. b(4)
I am attaching a pdf file of our analytical report for this lot of drug substance. As you can see, both our RM lot # and the manufacturer's lot # are referenced.
I hope this answers your questions. If not, please let me know.

Bob

From: Tossa, Margarita [mailto:margarita.tossa@fda.hhs.gov]
Sent: Monday, October 27, 2008 10:20 AM
To: Robert Dettery
Subject: NDA 22351 Colchicine (gout flares)/information request.
Importance: High

Good day Robert,

We need clarification to the following request:

Clarify or explain the discrepancy in the lot or batch number and purity of the colchicine drug substance used in the genetic toxicology studies listed here:

MPC-004-07-0002 Colchicine: Bacterial Mutation Test; Module 4.2.3.3.1

MPC-004-07-0003 Colchicine: Chromosome Aberration Test Module 4.2.3.3.1

In Module 4, section 2.6.7.4 Toxicology, there is a table of the Drug Substance that lists the a batch number as RD10016 with a purity of ——— ———————————. However, the certificate of analysis in Appendix 1 of the study reports lists a batch number of CCU-117153 with a purity of ——————————————————

b(4)

Best regards,

Margarita Tossa, M.S.

Regulatory Project Manager

FDA/CDER/DAARP

phone: (301) 796-4053

fax: (301) 796-9713

Email: margarita.tossa@fda.hhs.gov

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/s/

Margarita Tossa
7/16/2009 02:28:09 PM
CSO

2 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Tossa, Margarita
From: Greeley, George
Sent: Tuesday, July 07, 2009 4:30 PM
To: Tossa, Margarita
Cc: Stowe, Ginneh D.
Subject: NDA 22-351 Colcrys

Importance: High

Hi Margarta,

The Colcrys (colchicine) full waiver was reviewed by the PeRC PREA Subcommittee on June 24, 2009. The Division recommended a full waiver because necessary studies would be impossible or highly impracticable 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

Pediatric Research and Equity Act Waivers

~~IND~~/NDA/~~BLA~~ #: **22-351** Supplement Type: Supplement Number:

Product name and active ingredient/dosage form: Cocrys ™ (colchicine) tablets 0.6 mg

Sponsor: Mutual Pharmaceutical Company, Inc.

Indications(s): Treatment of gout flares
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth through 17 years

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed).

The Division concurs with the Sponsors rationale as provided in their pediatric waiver request and excerpted below:

> Necessary studies with this drug product are highly impracticable because the indication has extremely limited applicability to pediatric patients because the pathophysiology of this disease occurs for the most part in the adult population.
>
> Gout is a rheumatic disorder that usually occurs in hyperuricemic individuals. The prevalence of gout is between 0.13% and 0.37% of the general population in the Western World (Harrison's Principles of Internal Medicine, 9th edition). The peak age of disease onset is between 40 and 60 years for men and after menopause for women. In addition, in a publication by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), it is stated that gout rarely occurs in children or young adults (2006).
> Given the age of disease onset and the rare occurrence in children, it is highly unlikely that pediatric patients would require treatment; in such rare cases, alternative therapy is available. Further, given the potential side effects of colchicine, its use in children is not warranted.

~~b. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. Suggested language includes, "FDA has not required pediatric studies in ages ___ to ___ because (state the safety or effectiveness reason)."~~

~~c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients~~ **and** ~~is unlikely to be used in a substantial number~~

~~of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.~~

d. ~~Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this report submitted by the Sponsor will be publicly posted.~~

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 8, 2009

TO: Margarita Tossa, Regulatory Project Manager
Rosemarie Neuner, M.D., M.P.H., Medical Officer
Jeffrey Siegel, M.D., Medical Team Leader
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-351

APPLICANT: Mutual Pharmaceutical Company

DRUG: Colstat (Colchicine)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of gout flares

CONSULTATION REQUEST DATE: January 19, 2009

DIVISION ACTION GOAL DATE: July 29, 2009
PDUFA DATE: July 30, 2009

b. **General observations/commentary:** The primary endpoint, response to treatment in the target joint based on patient self-assessment of pain at 24 hours following the time of first dose, was verified. A random review of adverse events revealed that all events were included and reported. No regulatory violations were noted.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of all sites did not find regulatory violations. The data from all sites appear acceptable in support of the proposed indication.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Susan Leibenhaut
6/18/2009 05:17:59 PM
MEDICAL OFFICER

Constance Lewin
6/18/2009 05:18:58 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

James E. Greenwald, M.D.
Medex Healthcare Research
1034 South Brentwood Blvd., Suite 1250
St. Louis, MO 63117

Dear Dr. Greenwald:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. Between April 19 and 21, 2009, Ms. Kathleen Swat, representing the FDA, met with you to review your conduct of a clinical investigation (Protocol MPC-004-06-001 entitled, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, 1-Week, Dose-Comparison Study to Evaluate the Efficacy, Safety, and Tolerability of Colchicine in Patients with an Acute Gout Flare") of the investigational drug colchicine (Colstat), performed for Mutual Pharmaceutical Company.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Swat during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

Constance Lewin
6/18/2009 05:01:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Doris Rice, M.D.
3921 Kingman Ave.
Portsmouth, VA 23701-2929

Dear Dr. Rice:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. Between April 14 and 23, 2009, Ms. Sherry Secrist, representing the FDA, met with you to review your conduct of a clinical investigation (Protocol MPC-004-06-001 entitled, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, 1-Week, Dose-Comparison Study to Evaluate the Efficacy, Safety, and Tolerability of Colchicine in Patients with an Acute Gout Flare") of the investigational drug colchicine (Colstat), performed for Mutual Pharmaceutical Company.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Secrist during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

Constance Lewin
6/18/2009 05:01:43 PM

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

DATE: 01-JUN-2009

TO: N22-351 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Update on Establishment Evaluation Request; CMC recommendation on amended application (07-APR-2009; 27-MAY-2009)

SUMMARY:

The applicant was asked to identify the bio-batch of drug product used in the clinical trial and the packaging presentations for the clinical trial drug product. The 07-APR-2009, amendment included this information. It was confirmed that batch BB 374 0215 was the bio-batch. ——— ——— was used for these supplies. Even though the ——— (*vide infra*), the data provided support the stability of the product in these packages for a sufficiently long period of time relative to the short length of the bioequivalence trials. b(4)

The Office of Compliance issued an overall recommendation of WITHHOLD on 29-APR-2009. The only site that was inspected that received a WITHHOLD recommendation was:

——— b(4)
———

This site was responsible for ——— of the drug product ———and was also an alternate site used for ———. The applicant submitted an amendment to the application dated 27-MAY-2009, requesting that the ——— from the application. It was obvious from the information submitted in the application that the ——— ——— had taken place and it had been planned as the ——— to prepare the ———. The 27-MAY-2009, amendment specifically states that ——— b(4)
———." The applicant was asked to identify the test results that were obtained at the ——— since it was unclear if any of these were submitted in support of the application. The amendment of 27-MAY-2009, provides a tabular presentation of the tests that were

performed at the ——————— product of batches BB 374 0215, BB 374 0217, and BB 374 0218. These are the primary stability batches and BB 374 0215 was also used for the bioequivalence studies. The applicant states that all of the tests that were performed by ———were analytical methods that were validated and that were successfully transferred to the ————. These tests, which were performed on the 25°C/60%RH and the 40°C/75%RH stability samples of the above three batches ———— were: physical appearance,—— ——— dissolution, related substances (some time-points). b(4)

As the ———————, the inspection request was removed from the Establishment Evaluation System and the Office of Compliance (OC) was asked (via CDER EESQUESTIONS) to re-evaluate the overall recommendation. On 01-JUN-2009, the OC made an ACCEPTABLE recommendation for N22-351. As there is no longer a ———— for the application, the HOW SUPPLIED section of the labeling should be revised to remove the reference to the —— ———. b(4)

RECOMMENDATION: With reference to first chemistry review dated 10-FEB-2009, the memorandum dated 10-FEB-2009, and considering the ACCEPTABLE recommendation from the Office of Compliance, the application is recommended to be **approved,** from the CMC perspective.

LABELING COMMENT: During the labeling negotiations, the applicant agrees to submit revised labeling that has removed any reference to the ———————— product previously proposed for the ———————. b(4)

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
DAARP/MTossa
ONDQA/DIV 1/CBertha/01-JUN-2009
ONDQA/DIV 1/DChristodoulou
ONDQA/DIV 1/AAl-Hakim

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/s/

Craig Bertha
6/1/2009 11:54:40 AM
CHEMIST

Ali Al-Hakim
6/1/2009 12:07:20 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Adam Karns, M.D.
8920 Wilshire Blvd., Suite 321
Beverly Hills, CA 90211

Dear Dr. Karns:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. Between April 20 and 22, 2009, Mr. Uttaniti Limchumroon, representing the FDA, met with you to review your conduct of a clinical investigation (Protocol MPC-004-06-001 entitled, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, 1-Week, Dose-Comparison Study to Evaluate the Efficacy, Safety, and Tolerability of Colchicine in Patients with an Acute Gout Flare") of the investigational drug colchicine (Colstat), performed for Mutual Pharmaceutical Company.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Limchumroon during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

Constance Lewin
5/29/2009 11:01:38 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-351

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

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

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your NDA dated September 30, 2008, received September 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Colchicine Tablets USP, 0.6 mg.

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

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

If **any** of the proposed product characteristics as stated in your September 30, 2008 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Bob Rappaport
3/6/2009 11:54:49 AM

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-351 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: 9/30/2008 Date of Receipt: 9/30/2008 Date clock started after UN:		
PDUFA Goal Date: 7/20/2009	Action Goal Date (if different):	
Filing Date: 11/29/2008 Date of Filing Meeting: 11/19/2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7		
Proposed Indication(s): Treatment of gout flares		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) X 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	X Standard Priority ☐ 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? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	X YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X 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 X NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES NO
User Fee Status **Comments:**	X Paid Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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).*	
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 X NO ☐ YES ☐ NO

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

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES X NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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) X All electronic ☐ Mixed (paper/electronic) X 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: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***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.* **Comments:**	X YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	X YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments:**	X YES ☐ NO X YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments:**	X 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 X English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	X 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:**	X 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:**	X YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must***	X YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."* **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	**X** Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments:**	**X** YES ☐ NO
Pediatrics	
PREA ***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.* 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? • ***If no, request in 74-day letter.*** • **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 **X** YES ☐ NO ☐ YES ☐ NO **X** YES ☐ NO

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

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? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **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)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☐ YES Date(s): NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	**X** YES Date(s): February 4, 2008 NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	YES Date(s): **X** NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11-19-2008

NDA/BLA #: 22-351

PROPRIETARY/ESTABLISHED NAMES: Colcrys/under review (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/Matthew Sullivan	Y
	CPMS/TL:	Matthew Sullivan (Acting CPMS)	Y
Cross-Discipline Team Leader (CDTL)	Jeff Siegel, M.D.		Y
Clinical	Reviewer:	Rosemarie Neuner, 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	N
	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/Craig Bertha, PhD	Y
	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

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

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable **X** FILE ☐ REFUSE TO FILE **X** Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	**X** YES NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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: **X** 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:**	**X** Not Applicable ☐ YES NO
CLINICAL MICROBIOLOGY **Comments:**	**X** Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable **X** 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 X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable X 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 X YES ☐ NO ☐ YES ☐ NO ☐ YES NO
• Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable X YES ☐ NO ☐ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for	☐ YES X NO ☐ YES

validation of sterilization? **(NDAs/NDA supplements only)**	☐ 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- 3/02/2009 ; Wrap-Up- 5/28/2009; Action Goal Date- .7/30/2009

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. X 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

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
2/19/2009 01:16:17 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-351

NDA ACKNOWLEDGMENT

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

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

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

Name of Drug Product: Colchicine Tablets USP, 0.6 mg

Date of Application: September 30, 2008

Date of Receipt: September 30, 2008

Our Reference Number: NDA 22-351

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 29, 2008, in accordance with 21 CFR 314.101(a).

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

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

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

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

If you have any questions, contact me at (301) 796-4053 or at margarita.tossa@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Margarita Tossa, M.S.
Regulatory Project Manager
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/

Margarita Tossa
10/10/2008 03:11:41 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-351

FILING COMMUNICATION

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

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

Please refer to your new drug application (NDA) dated September 30, 2008, received September 30, 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 July 30, 2009.

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

> Submit your analyses of the 234 postmarketing case reports of deaths and adverse events of interest (e.g., deaths, overdose, serious cardiovascular adverse events, renal and hepatic failures, pancreatitis, Stevens-Johnson Syndrome, tendon rupture, skin adverse events and alopecia) that you obtained via the Freedom of Information Act from FDA's Serious Report System (SRS) and the Adverse Event Reporting System (AERS) databases and that were described as pending in Section 2.7.4.6. Postmarketing Data in the Summary of Clinical Safety section of your NDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

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

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients.

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/

Sharon Hertz
12/12/2008 02:30:35 PM
Signing for Bob Rappaport, M.D.

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
Philidelphia, 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 ———

b(4)

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———

b(4)

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

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

b(4)

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

b(4)

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

CHEMISTRY MANUFACTURING AND CONTROLS

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

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

b(4)

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 ethyl acetate limit. b(4)

Question 4. *Is the proposed specification of —— ethyl acetate (lower than the 8.0% in the USP monograph) for colchicine drug substance acceptable? Does the agency agree that the drug product does not require ethyl acetate testing?*

FDA RESPONSE: b(4)
The proposed limit of —— ethyl acetate in the drug substance exceeds the ICH Q3C limit of 5000 ppm. Provide a safety assessment and/or qualification for the proposed ethyl acetate limit. This will be assessed during the NDA review.

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

b(4)

1. adequate justification that the process converts the ———————— to the ——— form;
2. in-process controls that ensure no residual ———— in the product;
3. in-process (e.g., residual ———————— and release batch analysis data that support removal of residual ———— in the drug product. b(4)

b(4)

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

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

b(4)

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

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

b(4)

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

b(4)

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

b(4)

FDA RESPONSE:

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

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

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

b(4)

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

FDA RESPONSE:

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

PHARMACOLOGY / TOXICOLOGY

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

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

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

FDA RESPONSE:
We agree that no additional studies are necessary.

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

b(4)

FDA RESPONSE:
Carcinogenicity studies will not be required for NDA approval.

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

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

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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.

b(4)

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.

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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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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).*

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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

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

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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).

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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:

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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

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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.

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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* ———— b(4)

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

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

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

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

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

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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 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/

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 Dettery	Vice President, Regulatory Affairs
[redacted]	Consultant, Managing Director [redacted]
[redacted]	Consultant [redacted]
[redacted]	Consultant, Toxicology [redacted]
[redacted]	Consultant [redacted]
[redacted]	Consultant, Chief of Rheumatology [redacted]

b(4)

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

Jeff Siegel, M.D.	Team Leader, Clinical
Joel Schiffenbauer, M.D.	Team Leader, Clinical
Sarah Okada, M.D.	Clinical Reviewer
Matthew Sullivan, M.S.	Regulatory Project Manager

Meeting Objective(s): To discuss questions related to the regulatory requirements to bring this marketed drug into compliance.

Opening Discussion: Following introductions, the discussion focused on Mutual Pharmaceuticals questions that were included in the June 30, 2006, and July 7, 2006, meeting packages. The questions are presented in italicized text and Division responses are in bold. Discussion is presented in normal text. The slides containing the Division's responses were sent to the sponsor on July 28, 2006.

Question 1. Is the CMC information to be included in the IND adequate to support the proposed pharmacokinetic studies? Are the plans for the NDA adequate?

Division Response:
The CMC information proposed to be included in the initial IND submission would appear to support the proposed pharmacokinetic studies. However, for any future NDA submission, it is recommended that you follow all FDA and ICH guidelines regarding specifications, impurities, stability testing, etc. As clinical studies progress, additional information regarding identification and quantitation of individual impurities in the drug substance and drug product should be provided. A more specific analytical procedure should be developed for testing———— the drug substance. b(4)

Discussion:
The Sponsor inquired as to whether or not their current CMC information would be adequate for future clinical studies. The Division commented that there will likely be a need for additional CMC information in later phases of development.

Post-Meeting Note:
A typographical error was noted during the meeting. In the last sentence of the Divisions response, the word ———————————————— . The sentence should correctly read: A more specific analytical procedure should be developed for testing———— the drug substance. b(4)

Question 2. Does the Division agree that the cardiovascular safety studies are necessary?

a. *Are the studies adequate by design?*
b. *Is the use of non-naïve male dogs acceptable in the cardiovascular telemetry study (minimum 1 month wash-out period)?*

c. *If the cardiovascular safety studies are deemed necessary, would this requirement be applicable to all New Drug Applications of colchicine?*

d. *If any of the cardiovascular safety studies are positive, would a thorough QT trial in humans be required and would this requirement be applicable to New Drug Applications of colchicine?*

Division Response:
General Comments: For the nonclinical aspects of your drug development program, you need to consider that colchicine was approved as safe and effective as a combination product under DESI ruling in 1972. Since there is no "colchicine-only" product approved in the United States, it will be necessary to support your clinical studies with sufficient nonclinical toxicology to ensure safe use and labeling according to current guidelines (see Guidances at http://www.fda.gov/cder/guidance/). Much of this information may be obtained through the scientific literature and data compilation services. Where data are lacking, it may be necessary to conduct the appropriate studies, as outlined in the Guidances, or provide sufficient justification as to why those studies would be unnecessary or inappropriate for your drug and its proposed indication. All of this information should be submitted with the initial IND.

Since there is little information concerning colchicine's potential cardiovascular toxicity, we recommend that the proposed cardiovascular safety studies be conducted.

a. **The number and magnitude of doses should be selected to provide appropriate characterization of in vitro or in vivo responses. In vivo studies should incorporate a maximum tolerated dose (MTD) and sufficient doses to determine an appropriate no observed adverse effect level (NOAEL).**

b. **A 1-month washout period is usually adequate, but we recommend that this be verified by monitoring other known pharmacodynamic or pharmacokinetic parameters.**

c. **It would depend on many factors. For the same active compound, the labels would need to be consistent.**

d. **If safety tests for a cardiovascular toxicity (e.g., QT prolongation) were positive with your colchicine formulation, then a thorough QT clinical trial would be required.**

Discussion:
With regard to item b, the Sponsor agreed that they would use 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 ——— b(4)
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.

Post-Meeting Note:
Use of Colbenemid in place of previously proposed ——— is acceptable. b(4)

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. b(4)

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?* b(4)

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 × 2, followed by 0.6 mg every hour to a maximum of 8 tablets total (4.8 mg) versus placebo. Because of the* b(4)

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.* b(4)

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 b(4)

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*

b(4)

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. b(4)

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. b(4)

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