DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

NDA 022352

NDA APPROVAL

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

Attention: Robert Dettery
Vice President, Regulatory Affairs

Dear Mr. Dettery:

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

We acknowledge receipt of your submissions dated July 7, August 19 and 27, September 17, October 2, 8, and 31, and December 19, 2008, and January 22 and 28, February 2, 10, 12, and 16, March 12 and 17, April 2 and 6, May 5 and 13, and July 23 and 28, 2009.

This new drug application provides for the use of COLCRYS ™ (colchicine, USP) tablets 0.6 mg for the treatment of familial Mediterranean fever (FMF).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022352**."

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your July 23, 2009, submission containing final carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because COLCRYS (colchicine, USP) tablets for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that COLCRYS (colchicine, USP) tablets poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of COLCRYS (colchicine, USP) tablets. FDA has determined that COLCRYS (colchicine, USP) tablets is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, COLCRYS (colchicine, USP) tablets. FDA has also determined that COLCRYS (colchicine, USP) tablets is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed COLCRYS (colchicine, USP) tablets.

Your proposed REMS, submitted on January 22 and February 10, 2009, amended on March 12 and 17, and July 28, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your January 22, February 10, and March 17, 2009, submissions.

Your assessment of the REMS should include an evaluation of:

1. Patients' understanding of the serious risks of COLCRYS (colchicine, USP) tablets (i.e., serious adverse events including misuse, drug-drug interactions, and accidental exposure) associated with use of COLCRYS.

2. A report on periodic assessments of the distribution and dispending of the Medication Guide in accordance with 21 CFR 208.24.

3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual

report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed REMS modifications with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 022352
PROPOSED REMS MODIFICATION
REMS ASSESSMENT
NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 022352
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send five (5) copies of submissions containing REMS assessments or proposed modifications of the REMS.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that it is necessary to assess the carcinogenicity potential of colchicine. The necessity for this evaluation stems from the mechanistic plausibility for the drug to initiate and promote tumor development due to mitotic spindle inhibition and subsequent aneuploidy as well as the observation that familial Mediterranean fever (FMF) affects a younger population and this population may require the drug for prophylaxis treatment for the remainder of their life, which may result in a increased risk for tumor development. The severity of this rare disease, the associated morbidity and mortality, and the substantial history of use of colchicine are factors which allow such a study to be done post-approval.

We have determined that the specifications for (b) (4) (b) (4) which bear a structural alert for mutagenicity, cannot be set to preclude the presence of these compounds above levels considered acceptable for marketed drugs. It is therefore necessary to either improve detection assays for these photo-degradant impurities and set specifications to limit these impurities to no more than (b) (4) day combined total daily intake with maximum daily dosing or conduct genotoxic qualification studies which demonstrate an absence of this hazard.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious

risk of the carcinogenic potential of COLCRYS (colchicine, USP) tablets, the potential for the presence of mutagenic impurities in the formulation, and the unexpected serious risks of cancer or toxicity from exposure to mutagenic impurities.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to identify these unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies.

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

   The timetable you submitted on February 2 and 10, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	July 1, 2010
Study Completion Date:	September 30, 2012
Final Report Submission:	September 30, 2013

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

   The timetable you submitted on February 2 and 10, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	July 1, 2010
Study Completion Date:	September 30, 2012
Final Report Submission:	September 30, 2013

3. Development of improved detection assays to allow reduction of the specifications for (b) (4) to ensure a limit of NMT (b) (4) TDI for the (b) (4)

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

Final Report Submission:	July 1, 2010

4. In vitro genetic toxicology study evaluating the potential mutagenicity of (b) (4) (b) (4). This study will start after PMR #3 is fulfilled.

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

Study Completion Date:	February 1, 2011
Final Report Submission:	May 1, 2011

5. In vitro genetic toxicology study evaluating the potential (b) (4) (b) (4) This study will start after PMR #3 is fulfilled.

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

Study Completion Date:	February 1, 2011
Final Report Submission:	May 1, 2011

Submit the carcinogenicity protocols for Executive Carcinogenicity Assessment Committee concurrence to your PIND 075040, with a cross-reference letter to this NDA 022352. Separate submissions for each carcinogenicity protocol are necessary and should be clearly indicated as a Special Protocol Assessment. Submit all final reports to your NDA 022352. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a form FDA 2253. For instruction on completing form FDA 2253, see page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

EXPIRATION DATING PERIOD

An expiry of 24 months is granted under the recommended storage conditions: Store at 20°-25 °C (68°-77°F) [see USP Controlled Room Temperature].

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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}

Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert
Medication Guide
REMS
Carton and Container