

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

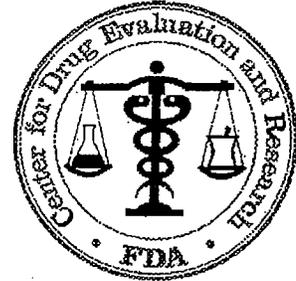
*APPLICATION NUMBER:*

**22-352**

**CHEMISTRY REVIEW(S)**

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

**DATE:** 11-MAY-2009  
**TO:** N22-352 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 (28-JAN-2009; 02-FEB-2009; 12-FEB-2009; 02-APR-2009; 05-MAY-2009)

**SUMMARY:** The applicant submitted an amendment dated 28-JAN-2009, which withdrew the \_\_\_\_\_ site as a \_\_\_\_\_ for the drug product. The request for inspection was canceled in the EES on 02-FEB-2009.

**b(4)**

A discipline review letter from the pharmacology/toxicology team included the following comment:

“Improve detection assays to allow reduction of the specifications for the photo-degradant impurities  $\beta$ - and  $\gamma$ -lumicolchicine to ensure a limit of NMT 1.5  $\mu\text{g}$  TDI for the combined degradants. Alternatively, you may conduct in vitro genetic toxicology studies evaluating mutagenicity and clastogenicity which, if negative, would support the current proposed specifications.”

The 02-FEB-2009, amendment from Mutual agrees to a “post marketing commitment to supplement the application with newly developed and validated methods and specifications for the finished product to include a specification of NMT 0.06% for the combined impurities of  $\beta$ -lumicolchicine and  $\gamma$ -lumicolchicine. Mutual will also work with the drug substance supplier to add the same specification of NMT 0.06% for the combined impurities to the drug substance specification.” Completion of the method development and validation will be done within a year of the approval of the application. This time-line was considered to be acceptable to both the CMC and the pharmacology/toxicology teams.

The 12-FEB-2009, amendment cross-references NDA 22-351 for updated stability data for the drug product. As a result, a 24 month expiry period is acceptable for the bottled product (see related memorandum dated 10-FEB-2009).

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 02-APR-2009, amendment included this information. It was confirmed that batch BB 374 0215 was the bio-batch. \_\_\_\_\_ packaging was used for these supplies. \_\_\_\_\_

\_\_\_\_\_, 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 packaging of the drug product in \_\_\_\_\_ and was also an alternate site used for stability testing of the drug product. The applicant submitted an amendment to the application dated 05-MAY-2009, requesting that the \_\_\_\_\_ site be withdrawn from the application. It was obvious from the information submitted in the application that the \_\_\_\_\_ facility was the site where the \_\_\_\_\_ had taken place and it had been planned as the site for \_\_\_\_\_ to prepare the \_\_\_\_\_. The 05-MAY-2009, amendment specifically states that "Mutual will not distribute \_\_\_\_\_ unless [they] obtain FDA approval in the application of an acceptable facility to perform that function." The applicant was asked to identify the test results that were obtained at the \_\_\_\_\_ site since it was unclear if any of these were submitted in support of the application. The amendment of 05-MAY-2009, provides a tabular presentation of the tests that were

**b(4)**

\_\_\_\_\_ 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, loss on drying, dissolution, related substances (some time-points).

**b(4)**

As the \_\_\_\_\_ site was withdrawn, 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 07-MAY-2009, the OC made an ACCEPTABLE recommendation for N22-352. 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 the third chemistry review dated 05-NOV-2008, 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.

**ACTION ITEM:** The PM is asked to send the following comment to the sponsor with regard to the labeling:

*Comment:* Remove all reference to the \_\_\_\_\_ in the labeling.

**b(4)**

---

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

cc:

DAARP/MTossa

ONDQA/DIV 1/CBertha/11-MAY-2009

ONDQA/DIV 1/DChristodoulou

ONDQA/DIV 1/AAI-Hakim\_\_\_\_\_

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/s/

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Craig Bertha  
5/11/2009 06:54:04 AM  
CHEMIST

Ali Al-Hakim  
5/11/2009 10:03:57 AM  
CHEMIST

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

DATE: 10-FEB-2009  
TO: N22-352 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 to Chemistry Review #3 regarding stability data

The third review of N22-352 had included a comment to be included in the action letter indicating that the applicant's proposal for a \_\_\_\_\_ expiration dating period for the \_\_\_\_\_ product was not acceptable, but that an \_\_\_\_\_ expiry could be given. This comment is reproduced below:

b(4)

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

The drug product stability batches for N22-352 are the same as those presented in the related applications from the applicant for treatment and prevention of gout (N22-351 and N22-353). The applicant provided updated stability data in the 03-FEB-2009, amendment to N22-351, which supported their proposal for a \_\_\_\_\_ expiration dating period for \_\_\_\_\_ product. Thus, it is no longer necessary to include the comment to the applicant in the forthcoming action letter for N22-352 regarding the expiry period for the \_\_\_\_\_ product.

b(4)

ACTION ITEM: NAI

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

cc:

DAARP/MTossa

ONDQA/DIV 1/CBertha

ONDQA/DIV 1/DChristodoulou

ONDQA/DIV 1/AAI-Hakim \_\_\_\_\_

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/s/  
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Craig Bertha  
2/10/2009 09:03:14 AM  
CHEMIST

Ali Al-Hakim  
2/10/2009 12:59:14 PM  
CHEMIST

**COLSTAT® (COLCHICINE) TABLETS**  
**NDA 22-352**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

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

**Indication:** Colstat® is a beta-tubulin interactor that is indicated for the treatment of Familial Mediterranean Fever (FMF) and gout (see NDA 22-351).

**Presentation:** A single strength of 0.6 mg/tablet is proposed for marketing. There are six presentations in HDPE bottles proposed for marketing: 30, 60, and 100 ct in 75 cc; 250 ct in 100 cc; 500 ct in 120 cc; 1000 ct in 180 cc. There is a \_\_\_\_\_

b(4)

**EER Status:** Pending.

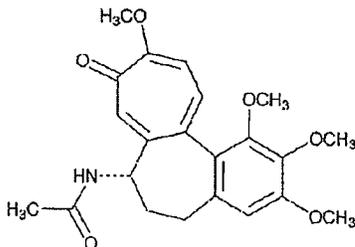
**Consults:** EA – categorical exclusion provided  
Statistics – N/A  
Methods Validation – Deemed not necessary to be forwarded to Agency laboratory.  
Microbiology – N/A  
Pharmacology/toxicology – completed; additional phase 4 impurities qualification studies to be requested

**Original Submission:** 20-JUN-2008

**Re-submissions:** N/A

**Post-Approval CMC Agreements:** None beyond the typical stability commitment.

**Drug Substance:** The drug substance has the USAN name “colchicine” and a monograph appears in the official edition of the USP. The chemical name of Colchicine is N-[5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy 9-oxobenzo[*a*]heptalen-7-yl], (S)-Acetamide and the structure (reproduced from application), molecular formula, and molecular weight are shown below.



Molecular formula: C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>; Molecular weight: 399.44 g/mole

Information about the retest date for the drug substance is provided separately in the drug substance supplier's master file \_\_\_\_\_ . Colchicine that is provided by \_\_\_\_\_ . It was shown by the data included in the report from \_\_\_\_\_ that the \_\_\_\_\_ that occurs when the \_\_\_\_\_

\_\_\_\_\_ is part of the manufacturing process; therefore the \_\_\_\_\_ in the final drug product. It is further noted that \_\_\_\_\_ of colchicine that were revealed in the \_\_\_\_\_ were \_\_\_\_\_. Because of the unique structure of colchicine, it exists as a mixture of conformers that can interconvert relatively quickly when the compound is in solution and at ambient temperatures. The ratio of these conformers is approximately 99:1.

b(4)

**Conclusion:** Drug substance is acceptable.

**Drug Product:** The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and is coated with a proprietary coating from \_\_\_\_\_. The manufacturing process is summarized as follows. Colchicine drug substance is \_\_\_\_\_

b(4)

\_\_\_\_\_ It is important to note that the primary stability/registration batch BB 374 0215 of the drug product was that used in the clinical pharmacology studies supporting the application. This batch has the same formulation and is manufactured by the same process proposed for the commercial tablets. Thus, no formulation comparability studies were necessary.

The recommended daily dose for the colchicine product for FMF is to be \_\_\_\_\_ with a maximum daily dose of 2.4 mg (i.e., four tablets). Doses are given once a day or can be divided. The marketed drug product will be packaged in HDPE bottles with internal desiccants and with the following tablet counts: 30, 60, 100, 250, 500, and 1000. The current proposed expiration dating period for the bottled product of 24 months is supported by the data provided. Whereas the applicant proposes that the \_\_\_\_\_ expiration dating period, the data provided only support and \_\_\_\_\_ expiry.

b(4)

**Conclusion:** Drug product is satisfactory. However, the following comment should be included in the action letter regarding the expiry for the \_\_\_\_\_ drug product:

b(4)

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**b(4)**

**Additional Items:** All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

**Overall Conclusion:** From a CMC perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance regarding GMPs. Currently, the recommendation is PENDING.

Ali Al-Hakim, Ph.D.  
Branch Chief, Branch II  
DPA I/ONDQA

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/s/

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Ali Al-Hakim  
11/20/2008 06:17:59 PM  
CHEMIST



**CHEMISTRY REVIEW**



**NDA 22-352**

**Colchicine Tablets USP**

**Mutual Pharmaceutical Company, Inc.**

**Craig M. Bertha, Ph.D.  
ONDQA/DIV I for DAARP**



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# Chemistry Review Data Sheet

1. NDA 22-352
2. REVIEW #: 3
3. REVIEW DATE: 05-NOV-2008
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original  
Amendment  
Amendment

Document Date

20-JUN-2008  
27-AUG-2008  
02-OCT-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment

Document Date

31-OCT-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Mutual Pharmaceutical Company, Inc.  
Address: 1100 Orthodox Street  
Representative: Philadelphia, PA 19124  
Telephone: (215) 288-6500

8. DRUG PRODUCT NAME/CODE/TYPE:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

- a) Proprietary Name: Colstat™  
b) Non-Proprietary Name (USAN): Colchicine  
c) Code Name/# (ONDC only): N/A  
d) Chem. Type/Submission Priority (ONDQA only): N/A
- Chem. Type: 7
  - Submission Priority: P (also has orphan drug status)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: For treatment of Familial Mediterranean Fever (FMF) and gout (NDA 22-351)

11. DOSAGE FORM: tablets (maximum proposed dose 2.4 mg/day for FMF and \_\_\_\_\_ for gout flare)

b(4)

12. STRENGTH/POTENCY: 0.6 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:   X   Rx      OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

     SPOTS product – Form Completed

  X   Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT (reproduced from application):

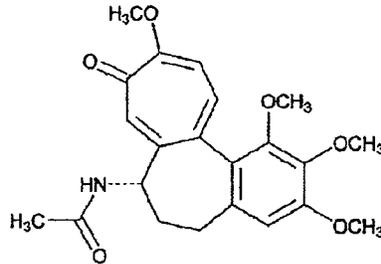
Colchicine is Acetamide, N-[5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy 9-oxobenzo[a]heptalen-7-yl], (S)-



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet



Molecular formula: C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>; Molecular weight: 399.44 g/mole

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	2			1	Adequate	28-JUL-2008 21-OCT-2008	
	2			7	N/A		Withdrawn from application in 27-AUG-2008, amendment
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			3	Adequate	19-NOV-2007	
	3			1	Adequate	29-JUL-2008 01-OCT-2008	
	4			1	Adequate	23-SEP-2008	

b(4)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75,040	colchicine tablets

### 18. STATUS:

#### ONDC:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	PAI	1-, 22, 23-JUL-2008	Pending	Forwarded by PAL, D. Christodoulou, Ph.D.
Pharm/Tox	DS/DP impurities	Via e-mail 14-JUL-2008	Pending/L. Leshin, Ph.D.	
Biopharm	N/A			
OSE	Labeling			PM has forwarded consult dated 10-JUL-2008.
Methods Validation	N/A			See p. 77 of CMC review #1
EA				See p. 78 of CMC review #1
Microbiology	N/A			



# The Chemistry Review for NDA 22-352

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is recommended for **approval** from a CMC perspective. However, the recommendation from the Office of Compliance for the application is currently pending.

The following comment should be included in the action letter regarding the expiration dating period supported by the data provided in the application:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Colchicine Tablets and each immediate release tablet contains 0.6 mg of colchicine. It is to be indicated for the treatment of Familial Mediterranean Fever (FMF) and gout. It is packaged in high density polyethylene bottles and \_\_\_\_\_, the latter for \_\_\_\_\_ only. There is a Colchicine Tablets monograph in the official edition of the USP.

b(4)

The drug substance has the USAN name "colchicine" and a monograph appears in the official edition of the USP. Information about the retest date for the drug substance is provided separately in the drug substance supplier's master file \_\_\_\_\_. Colchicine that is provided by \_\_\_\_\_; It was shown by the data included in the report from \_\_\_\_\_ that the \_\_\_\_\_ that occurs when the \_\_\_\_\_



# CHEMISTRY REVIEW



## Executive Summary Section

\_\_\_\_\_ is part of the manufacturing process, therefore the \_\_\_\_\_ in the final drug product. It is further noted that \_\_\_\_\_ of colchicine that were revealed in the \_\_\_\_\_ were \_\_\_\_\_. Because of the unique structure of colchicine, it exists as a mixture of conformers that can \_\_\_\_\_ when the compound is in solution and at ambient temperatures. The ratio of these conformers is approximately 99:1.

b(4)

The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and is coated with a proprietary coating from \_\_\_\_\_. The manufacturing process is summarized as follows. Colchicine drug substance is

\_\_\_\_\_  
\_\_\_\_\_

b(4)

It is important to note that the primary stability/registration batch BB 374 0215 of the drug product was that used in the clinical pharmacology studies supporting the application. This batch has the same formulation and is manufactured by the same process proposed for the commercial tablets. Thus, no formulation comparability studies were necessary.

### B. Description of How the Drug Product is Intended to be Used

The recommended daily dose for the colchicine product for FMF is to be \_\_\_\_\_ with a maximum daily dose of 2.4 mg (i.e., four tablets). Doses are given once a day or can be divided. The marketed drug product will be packaged in HDPE bottles with internal desiccants and with the following tablet counts: 30, 60, 100, 250, 500, 1000. The current proposed expiration dating period for the bottled product of 24 months is supported by the data provided. Whereas the applicant proposes that the \_\_\_\_\_ packaged in \_\_\_\_\_ are also to be given a \_\_\_\_\_ expiration dating period, the data provided only support and \_\_\_\_\_ expiry (see recommendation section above).

b(4)

### C. Basis for Approvability or Not-Approval Recommendation

N/A

## III. Administrative

### A. Reviewer's Signature



**B. Endorsement Block**

Craig M. Bertha, Ph.D./05-NOV-2008  
Ali Al-Hakim, Ph.D.

**C. CC Block**

Danae Christodoulou  
Margarita Tossa  
Keith Hull  
Lawrence (Steve) Leshin  
Srikanth Nallani

10 Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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/s/  
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Craig Bertha  
11/5/2008 08:08:19 AM  
CHEMIST

Ali Al-Hakim  
11/5/2008 09:29:48 AM  
CHEMIST



**CHEMISTRY REVIEW**



**NDA 22-352**

**Colchicine Tablets USP**

**Mutual Pharmaceutical Company, Inc.**

**Craig M. Bertha, Ph.D.  
ONDQA/DIV I for DAARP**



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# Chemistry Review Data Sheet

1. NDA 22-352
2. REVIEW #: 2
3. REVIEW DATE: 21-OCT-2008
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	20-JUN-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	27-AUG-2008
Amendment	02-OCT-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Mutual Pharmaceutical Company, Inc.
Address:	1100 Orthodox Street
Representative:	Philadelphia, PA 19124
Telephone:	(215) 288-6500

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Colstat™
- b) Non-Proprietary Name (USAN): Colchicine



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDQA only): N/A

- Chem. Type: 7
- Submission Priority: P (also has orphan drug status)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: For treatment of Familial Mediterranean Fever (FMF) and gout (NDA 22-351)

11. DOSAGE FORM: tablets (maximum proposed dose 2.4 mg/day for FMF and \_\_\_\_\_ for gout flare)

b(4)

12. STRENGTH/POTENCY: 0.6 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT (reproduced from application):

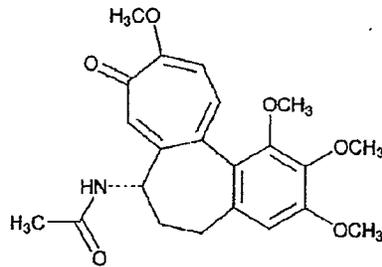
Colchicine is Acetamide, N-[5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy 9-oxobenzo[a]heptalen-7-yl], (S)-



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet



Molecular formula: C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>; Molecular weight: 399.44 g/mole

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	2			1	Adequate	28-JUL-2008 21-OCT-2008	
	2			7	N/A		Withdrawn from application in 27-AUG-2008, amendment
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
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	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			3	Adequate	19-NOV-2007	
	3			1	Adequate	29-JUL-2008 01-OCT-2008	
	4			1	Adequate	23-SEP-2008	

b(4)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75,040	colchicine tablets

### 18. STATUS:

#### ONDC:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	PAI	1-, 22, 23-JUL-2008	Pending	Forwarded by PAL, D. Christodoulou, Ph.D.
Pharm/Tox	DS/DP impurities	Via e-mail 14-JUL-2008	Pending/L. Leshin, Ph.D.	
Biopharm	N/A			
OSE	Labeling			PM has forwarded consult dated 10-JUL-2008.
Methods Validation	N/A			See p. 77 of CMC review #1
EA				See p. 78 of CMC review #1
Microbiology	N/A			



# The Chemistry Review for NDA 22-352

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is recommended for **approval** from a CMC perspective. However, the recommendation from the Office of Compliance for the application is currently pending.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

In the 02-OCT-2008, amendment, the applicant proposed to amend the application by the addition of a quantitative method for the determination of the \_\_\_\_\_ level in the drug product by the end of October 2008. Considering the GRMP deadline for completion of the primary review of 07-NOV-2008, it is likely that this amendment will not be reviewed in this cycle. If that is the case, the following comment should be included in the action letter:

b(4)

*We have received your amendment dated XX-XXX-2008, which includes the method for quantitation of \_\_\_\_\_ levels in the drug product, the associated validation data, and the updated stability data resulting from use of this method. However, due to the GRMP time frame, we have not reviewed this amendment in this cycle, but we expect your cooperation during our eventual review of this method and the associated data if any questions arise regarding their adequacy.*

b(4)

Refer to the response to comment 15 for more detailed information.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Colchicine Tablets and each immediate release tablet contains 0.6 mg of colchicine. It is to be indicated for the treatment of Familial Mediterranean Fever (FMF) and gout. It is packaged in high density polyethylene bottles and \_\_\_\_\_, the latter for \_\_\_\_\_ only. There is a Colchicine Tablets monograph in the official edition of the USP.

b(4)

The drug substance has the USAN name "colchicine" and a monograph appears in the official edition of the USP. Information about the retest date for the drug substance is provided separately in the drug substance supplier's master file \_\_\_\_\_



## CHEMISTRY REVIEW



### Executive Summary Section

\_\_\_\_\_ Colchicine that is provided by \_\_\_\_\_. It was shown by the data included in the report from \_\_\_\_\_ that the \_\_\_\_\_ that occurs when the \_\_\_\_\_ is part of the manufacturing process, therefore the \_\_\_\_\_ in the final drug product. It is further noted that \_\_\_\_\_ of colchicine that were revealed in the \_\_\_\_\_. Because of the unique structure of colchicine, it exists as a mixture of conformers that can \_\_\_\_\_ when the compound is in solution and at ambient temperatures. The ratio of these conformers is approximately 99:1.

b(4)

The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and is coated with a proprietary coating from \_\_\_\_\_. The manufacturing process is summarized as follows. Colchicine drug

b(4)

It is important to note that the primary stability/registration batch BB 374 0215 of the drug product was that used in the clinical pharmacology studies supporting the application. This batch has the same formulation and is manufactured by the same process proposed for the commercial tablets. Thus, no formulation comparability studies were necessary.

#### B. Description of How the Drug Product is Intended to be Used

The recommended daily dose for the colchicine product for FMF is to be \_\_\_\_\_ with a maximum daily dose of 2.4 mg (i.e., four tablets). Doses are given once a day or can be divided. The marketed drug product will be packaged in HDPE bottles with internal desiccants and with the following tablet counts: 30, 60, 100, 250, 500, 1000. The current proposed expiration dating period for the bottled product of \_\_\_\_\_ is supported by the data provided. \_\_\_\_\_ are to be given a \_\_\_\_\_ expiration dating period and this too, is supported by the data included in the application.

b(4)

#### C. Basis for Approvability or Not-Approval Recommendation

N/A

### III. Administrative



Executive Summary Section

**A. Reviewer's Signature**

**B. Endorsement Block**

Craig M. Bertha, Ph.D./21-OCT-2008  
Blair Fraser, Ph.D.

**C. CC Block**

Margarita Tossa  
Keith Hull  
Lawrence (Steve) Leshin  
Srikanth Nallani

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       § 552(b)(5) Deliberative Process

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Craig Bertha  
10/21/2008 09:03:02 AM  
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Blair Fraser  
10/21/2008 10:55:55 AM  
CHEMIST



**CHEMISTRY REVIEW**



**NDA 22-352**

**Colchicine Tablets USP**

**Mutual Pharmaceutical Company, Inc.**

**Craig M. Bertha, Ph.D.  
ONDQA/DIV I for DAARP**



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## CHEMISTRY REVIEW



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# Chemistry Review Data Sheet

1. NDA 22-352
2. REVIEW #: 1
3. REVIEW DATE: 25-AUG-2008
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

20-JUN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Mutual Pharmaceutical Company, Inc.
Address:	1100 Orthodox Street
Representative:	Philadelphia, PA 19124
Telephone:	(215) 288-6500

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None proposed yet
- b) Non-Proprietary Name (USAN): Colchicine
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDQA only): N/A



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

- Chem. Type: 3
- Submission Priority: P (also has orphan drug status)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: For treatment of Familial Mediterranean Fever (FMF) and gout

11. DOSAGE FORM: tablets (maximum proposed dose 2.4 mg/day)

12. STRENGTH/POTENCY: 0.6 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT (reproduced from application):

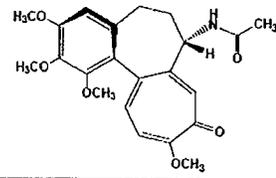
Colchicine is Acetamide, N-[5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy 9-oxobenzo[*a*]heptalen-7-yl], (S)-



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<b>Chemical Structure</b>	
<b>Molecular Formula</b>	C <sub>22</sub> H <sub>23</sub> NO <sub>6</sub>
<b>Relative Molecular Mass</b>	399.44

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	2			1	Inadequate	28-JUL-2008	Deficiency letter issued 21-AUG-2008
	2			7			<b>75 day letter will request site be removed from the application</b>
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
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	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			3	Adequate	19-NOV-2007	
	3			1	Inadequate	29-JUL-2008	Deficiency letter issued 21-AUG-2008
	4			1	To be reviewed		<b>LOA will be requested in 75 day letter</b>

b(4)

<sup>1</sup> Action codes for DMF Table:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

**1 – DMF Reviewed.**

Other codes indicate why the DMF was not reviewed, as follows:

**2 – Type 1 DMF**

**3 – Reviewed previously and no revision since last review**

**4 – Sufficient information in application**

**5 – Authority to reference not granted**

**6 – DMF not available**

**7 – Other (explain under "Comments")**

<sup>2</sup> Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75,040	colchicine tablets

### 18. STATUS:

**ONDC:**

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	PAI	1-, 22, 23-JUL-2008	Pending	Forwarded by PAL, D. Christodoulou, Ph.D.
Pharm/Tox	DS/DP impurities	Via e-mail 14-JUL-2008	Pending/L. Leshin, Ph.D.	
Biopharm	N/A			
OSE	Labeling			PM has forwarded consult dated 10-JUL-2008.
Methods Validation	N/A			See p. 77
EA				See p. 78
Microbiology	N/A			



# The Chemistry Review for NDA 22-352

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable** from a CMC perspective, pending the resolution of the issues outlined in the draft letter at the end of this review.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Colchicine Tablets and each immediate release tablet contains 0.6 mg of colchicine. It is to be indicated for the treatment of Familial Mediterranean Fever (FMF) and gout. It is packaged in high density polyethylene bottles and \_\_\_\_\_, the latter for \_\_\_\_\_ only. There is a Colchicine Tablets monograph in the current edition of the USP.

b(4)

The drug substance has the USAN name "colchicine" and a monograph appears in the current edition of the USP. Information about the retest date for the drug substance is provided separately in the drug substance supplier's master file\_\_\_\_\_. Colchicine that is provided by \_\_\_\_\_ . It was shown by the data included in the report from \_\_\_\_\_ that the \_\_\_\_\_ that occurs when the \_\_\_\_\_

\_\_\_\_\_ is part of the manufacturing process, therefore the \_\_\_\_\_ in the final drug product. It is further noted that \_\_\_\_\_ of colchicine that were revealed in the \_\_\_\_\_ were \_\_\_\_\_. Because of the unique structure of colchicine, it exists as a mixture of conformers that can \_\_\_\_\_ when the compound is \_\_\_\_\_

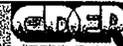
b(4)

The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and is coated with a proprietary coating from \_\_\_\_\_. The manufacturing process is summarized as follows. Colchicine drug

b(4)



## CHEMISTRY REVIEW



### Executive Summary Section

substance is

\_\_\_\_\_

\_\_\_\_\_

b(4)

It is important to note that the primary stability/registration batch BB 374 0215 of the drug product was that used in the clinical pharmacology studies supporting the application. This batch has the same formulation and is manufactured by the same process proposed for the commercial tablets. Thus, no formulation comparability studies were necessary.

#### B. Description of How the Drug Product is Intended to be Used

The recommended daily dose for the colchicine product is to be \_\_\_\_\_ with a maximum daily dose of 2.4 mg (i.e., four tablets). Doses are given once a day or can be divided. The marketed drug product will be packaged in HDPE bottles with internal desiccants and with the following tablet counts: 30, 60, 100, 250, 500, 1000. The current proposed expiration dating period for the bottled product of \_\_\_\_\_ is supported by the data provided. \_\_\_\_\_ packaged in \_\_\_\_\_ are to be given a \_\_\_\_\_ expiration dating period and this too, is supported by the data included in the application.

b(4)

#### C. Basis for Approvability or Not-Approval Recommendation

Currently, it is recommended that the application be given an approvable action. The deficiencies are outlined in the comments collated at the end of the review in the draft letter. In summary, the master file from \_\_\_\_\_ the supplier of the drug substance, was found to be deficient. A deficiency letter will be sent to the holder of this master file. Other deficiencies and requests for clarification are, on an individual basis, relatively minor in nature, but taken together as a whole, they constitute sufficient cause to recommend against approval. These issues will need to be resolved or supported with proposed post-approval agreement studies, prior to the issuance of an approval recommendation from the CMC team.

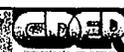
b(4)

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Craig M. Bertha, Ph.D./25-AUG-2008  
Ali Al-Hakim, Ph.D.



**C. CC Block**

Margarita Tossa  
Keith Hull  
Lawrence Leshin  
Srikanth Nallani

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       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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Craig Bertha  
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CHEMIST

Ali Al-Hakim  
8/27/2008 04:13:24 PM  
CHEMIST

**Initial Quality Assessment**  
**Division of Pre-Marketing Assessment I, Branch II**  
**Office of New Drug Quality Assessment**  
**Division of Anesthesia, Analgesia and Rheumatology Products**

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-352	
Applicant:	Mutual	
Stamp date:	June 20, 2008	
PDUFA Date:	December 20, 2008	
Trademark:	Not proposed	
Established Name:	Colchicine tablets, USP	
Dosage Form:	Coated tablets 0.6 mg	
Route of Administration:	Oral	
Indication:	Treatment of Familial Mediterranean Fever	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	—
Comments for 74-Day Letter:	<u>√</u>	—

**Summary, Critical Issues and Comments**

**A. Summary**

The application is filed as a 505(b)(2) NDA and a priority review is requested (6-month review clock). The Reference Listed Drug (RLD) is ColBenemid, NDA 12-383, approved in 1961, a combination of colchicine 0.5 mg with probenecid 500 mg. The current drug, Colchicine tablets, USP, was granted orphan designation for familial Mediterranean fever on 9/25/2007.

Colchicine is a highly poisonous natural product. It inhibits microtubule polymerization by binding tubulin and ultimately inhibits mitosis. Colchicine tablets as a single ingredient drug, has been marketed unapproved and used mostly for the treatment of gout. Colchicine has also been approved as a generic combination drug with probenecid, (probenecid 500 mg/colchicine 0.5 mg), ANDAs 40-618 (AP 2008), 83-734 and 84-279 (AP prior to 1982).

The applicant, Mutual Pharmaceuticals, held a pre-NDA meeting with the Agency on 2/4/2008, and proposed to qualify a drug substance supplier in \_\_\_\_\_, the holder of Drug Master File, \_\_\_\_\_, for colchicine HCl. However, in the current NDA submission, the applicant proposed to

**b(4)**

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_

**b(4)**

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       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

**Consults:**

The Toxicology Consult for impurities has been initiated by the primary reviewer C. Bertha, on . No other consults have been deemed necessary (see fileability template below).

Danae D Christodoulou, Ph.D.  
Pharmaceutical Assessment Lead

11/16/2007  
Date

Ali Al-Hakim, Ph.D.  
Branch II Chief

11/20/2007  
Date

**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		Resolved through the Project Manager M. Sullivan
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested as per 25.31(a)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided without statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√ [M1]	√	<b>Supporting IND:</b> 72,586 <b>Pre-IND 75,040</b> (FMF) Pre-IND ———
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	NA
16	Have all consults been identified and initiated?	√		Pharm/Tox Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology
		NA		

**b(4)**

**Have all DMF References been identified? Yes ( ) No (√ )**

DMF Number	Holder	Description	LoA Included	Status

	Yes	pending
	No	pending
	Yes	pending

b(4)

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/s/

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Danae Christodoulou  
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Initial Quality Assessment

Ali Al-Hakim  
7/18/2008 04:57:02 PM  
CHEMIST