

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204820Orig1s000**

**CHEMISTRY REVIEW(S)**

**ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

<b>Application:</b>	NDA 204820/000	<b>Action Goal:</b>	
<b>App Date:</b>	05-OCT-2012	<b>District Goal:</b>	30-JUL-2014
<b>Regulatory:</b>	28-SEP-2014		
<b>Applicant:</b>	HIKMA PHARMS 200 401 435 465 INDUSTRIAL WAY WEST EATONTOWN, NJ 07724	<b>Brand Name:</b>	COLCHICINE
		<b>Estab. Name:</b>	
		<b>Generic Name:</b>	COLCHICINE
<b>Priority:</b>	3	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
<b>Reg. Code:</b>	570		001; CAPSULE; COLCHICINE; .6MG

**Application Comment:**

<b>QA Contacts:</b>	C. BERTHA	Prod Qual Reviewer	3017961646
	Y. LIU	Product Quality PM	3017961926
	M. JORDAN GARNER	Regulatory Project Mgr (HFD-570)	3017964786
	ID = 105168	Team Leader	

<b>Overall Recommendation:</b>	ACCEPTABLE	on 26-JUN-2014	by E. DOBBIN	( )	2404024266
	PENDING	on 02-APR-2014	by EES_PROD		
	WITHHOLD	on 31-JUL-2013	by EES_PROD		

# ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: (b) (4)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	03-DEC-2012				LIUY
SUBMITTED TO DO	11-JAN-2013	10-Day Letter			STOCKM
DO RECOMMENDATION	11-JAN-2013			ACCEPTABLE	PHILPYE
DO RECOMMENDATION	14-JAN-2013			ACCEPTABLE	SHARPT
SUBMITTED TO OC	02-APR-2014				LIUY
DO RECOMMENDATION	03-APR-2014			ACCEPTABLE	SHARPT

# ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: 2250102 FEI: 2250102

WEST WARD PHARMACEUTICAL CORP

465/435/401/200 INDUSTRIAL WAY  
EATONTOWN, NJ 077242209

vi AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: THE MANUFACTURING (BATCH) RECORD FOR BATCH 02 MENTIONS AN EVENT WHERE A PEBBLE WAS FOUND CHIPPED IN THE (b) (4), AND A FRAGMENT ABOUT 1 CM IN DIMENSION WAS FOUND. THE APPLICANT CONSIDERS THIS TO BE A MINOR DEVIATION AND THEY STATE THAT ANY LARGE PEBBLE FRAGMENTS ARE RETAINED WITHIN THE (b) (4) OF STEP (b) (4) PRODUCTION PROCESS. PLEASE EVALUATE THIS. (on 04-DEC-2012 by SCHROEDER)  
THE APPLICANT INDICATES IN P.3.4 OF THE APPLICATION THAT THEY WILL ONLY BE PERFORMING (b) (4) (on 05-DEC-2012 by C. BERTHA ( ) 3017961646)

DUNS: 001230762

THE APPLICANT IS HIKMA PHARMACEUTICALS IN AMMAN, JORDAN, PER THE 356H FORM. THE ADDRESS LISTED IN THE EES IS FOR WEST WARD, THE US AGENT FOR THIS NDA. (on 03-DEC-2012 by Y. LIU ( ) 3017961926)

THE APPLICANT HAS BULK PACKAGING FOR THE DRUG PRODUCT AND PLANS TO HOLD BULK DRUG PRODUCT UP TO (b) (4). NO DETAILED INFORMATION ABOUT THE BULK CONTAINER CLOSURE SYSTEM NOR THE DATA SUPPORTING SUITABILITY ARE IN THE APPLICATION. AS PER OUR GUIDANCE, THESE ARE TO BE RETAINED AT THE SITE AND ARE TO BE MADE AVAILABLE DURING INSPECTION UPON DEMAND. (on 15-JAN-2013 by C. BERTHA ( ) 3017961646)

Profile: CAPSULES, PROMPT RELEASE

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	03-DEC-2012				LIUY
SUBMITTED TO DO	17-DEC-2012	Product Specific and GMP Inspection			SMITHDE
PLEASE SEE REVIEWERS COMMENTS REGARDING BATCH RECORD DEVIATION REPORTED IN APPLICATION.					
DO RECOMMENDATION	22-FEB-2013			WITHHOLD	KDORAZIO
THIS FIRM REMAINS IN OAI STATUS FOLLOWING THE MOST RECENT INSPECTION OF 8/28/12.					
DO RECOMMENDATION	11-JUN-2013			WITHHOLD	KDORAZIO
THIS NDA WAS COVERED DURING THE W/L FOLLOW-UP INSPECTION OF 4/29 - 6/7/2013. DEVELOPMENT DATA WAS NOT AVAILABLE FOR REVIEW FOR SEVERAL PROCESSING PARAMETERS AS LISTED IN THE 483. IN ADDITION THE FIRM CONTINUES TO HAVE GMP DEFICIENCIES AND THE EIR WILL BE REVIEWED BY THE DO TO DETERMINE IF THERE WILL BE A RECOMMENDATION THAT THE FIRM REMAIN IN OAI STATUS.					
DO RECOMMENDATION	31-JUL-2013			WITHHOLD	RAMANADHAMM
UNRESOLVED METAL CONTAMINATION INVESTIGATION AND CORRECTIVE ACTION. SITE IS CURRENTLY OAI.					
SUBMITTED TO OC	02-APR-2014				LIUY

10-Day Letter

**ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

~~CONFIDENTIAL~~  
JBM/CEEC/KDO

03-APR-2014

SHARPT

RECOMMENDATION

18-JUN-2014

ACCEPTABLE

KDORAZIO

THE FIRM SUBMITTED AN ADEQUATE WRITTEN RESPONSE WHICH WAS VERIFIED DURING THE GMP INSPECTION ENDING 2/26/14 CLASSIFIED AS "VAI" WITH ACCEPTABLE PROFILES. THE INSPECTION VERIFIED CORRECTION OF THE DEFICIENCIES ASSOCIATED WITH THE APPLICATION IDENTIFIED DURING THE 4/29/13 - 6/7/13 INSPECTION. A WITHHOLD RECOMMENDATION HAD BEEN SUBMITTED FOR THE APPLICATION AT THAT TIME (6/2013).

RECOMMENDATION

26-JUN-2014

ACCEPTABLE

DOBBINE



# Memorandum

Date July 29, 2013

From Vipul Dholakia, Ph.D.  
Compliance Officer  
New Drug Manufacturing Assessment Branch  
Division of Good Manufacturing Practice Assessment,  
Office of Manufacturing and Product Quality

Subject Concurrence with New Jersey District Office (NWJ-DO) Withhold Recommendation for  
NDA 204-820 Colchicine Capsules 0.6 mg

Thru Don Henry, Acting Branch Chief  
New Drug Manufacturing Assessment Branch (NDMAB)  
Division of Good Manufacturing Practice Assessment (DGMPA)

To Peri Prasad, Branch Chief, Branch VIII, ONDQA Division III

Applicant: Hikma Pharmaceuticals LLC  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Establishment: West-Ward Pharmaceutical Corp.  
465 Industrial Way  
Eatontown, NJ 07724-2209  
**FEI: 2250102**

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) and GMP inspection conducted by New Jersey District (NWJ-DO) investigators from April 29, 2013 to June 07, 2013 at the West-Ward Pharmaceutical Corp. facility. DGMPA has also reviewed the firm's June 27, 2013 written response to the FDA Form-483 observations. This inspection was initiated by NWJ-DO to provide pre-approval coverage of NDA 204-820 and also follow up inspection to the 2012 warning letter.

The West Ward Pharmaceutical Inc. was inspected in June 2011 and was classified Official Action Indicated (OAI) due to systemic CGMP deficiencies. This facility received a Warning Letter in 2012 as a result of this inspection. This site was re-inspected in July 2012 and persistent and additional CGMP deficiencies were verified and OAI classification for the site was maintained. During the current inspection NWJ-DO investigators found continuing CGMP deficiencies as observed on the previous two inspections and has recommended maintaining OAI classification.

The Division of Good Manufacturing Practice Assessment (DGMPA) concurs with New Jersey District Office's withhold recommendation for NDA 204-820. NWJ-DO recommended withholding approval of this application due the systemic CGMP deficiencies and the product specific deficiencies. The following deficiencies specific to NDA 204-820, Colchicine 0.6 mg Capsules were observed:

(b) (4)

1. The investigations into the confirmed presence of metal contamination found in metal detector rejects are not conducted.

The firm did not conduct investigations for determining the source or cause of the metal contamination identified in the metal detector rejects of Colchicine capsule 0.6 mg in exhibit batch # (b) (4). On review of the executed batch record, it was found that metal rejects tested in the laboratory identified 13 metal particles from (b) (4) in size.

Similarly metal contaminations were found in 324 tablets of Doxycycline 100 mg batch (b) (4), in 51 tablets of Doxycycline 100 mg batch (b) (4) and in 62 capsules of Doxycycline 50 mg batch (b) (4). There were no investigations conducted for the source and cause of the metal contamination in all these batches.

CDER OMPQ evaluation:

The firm stated in the response that an investigation for metal contamination is initiated if the number of metal rejects from metal detector exceeds (b) (4) % from the actual batch yield. According to the SOP PR-73, "Set Up and Operation of Metal Detectors", investigations of batches for metal particles exceeding the limit of (b) (4) % will be initiated and will include root cause analysis, impact assessment and corrective/preventive actions when appropriate. The investigations were not initiated for the above batches as none of the batches exceeded the (b) (4) % limit per SOP. The firm also stated that all (b) (4)

(b) (4) during manufacturing process. (b) (4)

It should be noted that similar deficiency for the metal contamination was observed in the previous inspection conducted in August 2012 and no investigation was performed to determine the source and root cause for metal particles in the product.

The response is not acceptable as the firm has not yet investigated the source and root cause for metal particles in the product.

2. There is no test or specification established for the visual appearance of the colchicine capsule fill for release or stability testing.

The firm did not conduct testing or documented the visual appearance of the colchicine capsule fill for release or stability. Only the appearance of the capsule was examined.

CDER OMPQ evaluation: The firm revised the specification for the visual appearance of the colchicine capsule fill for release or stability testing and also submitted an amendment to the agency for the proposed change in the visual appearance specification.

The response is adequate and will be evaluated in the next inspection.

3. There is no development data to support the parameters established for the process of the colchicine API and (b) (4) established at (b) (4).

(b) (4)

A review of the batch record for (b) (4) found that the batch record was executed through step (b) (4). The (b) (4) process starts at step (b) (4) and is (b) (4) as described in the batch record.

CDER OMPQ evaluation: The firm stated in the response that (b) (4) (b) (4)

The response is adequate and will be evaluated in the next inspection.

- 4. There is no development data to support the use of (b) (4) during the manufacturing of the product and no assurance that (b) (4) in the manufacturing area using (b) (4) during the manufacturing of the product.

The product development report and the batch records include a statement that Colchicine is (b) (4) manufacturing process. The firm stated that during the manufacture of the product, (b) (4) for the manufacture of the product.

CDER OMPQ evaluation

The firm conducted a study per protocol AR-2013-008.0 to demonstrate the use of (b) (4) The firm also submitted an amendment to the agency to specify (b) (4)

The response is adequate and will be evaluated in the next inspection.

West Ward Pharmaceuticals has been inspected in June 2011, July 2012 and classified OAI. The current inspection in June 2013 warrants maintaining the OAI classification based on the significant CGMP deficiencies including repeat deviation of failure to perform adequate investigations. The inspection classification (initial OAI) is under review within the New Jersey District Office. The district recommendation will then be reviewed by CDER/OC/OMPQ/DDDQ.

**CDER/OC/OMPQ/DGMPA Recommendation:**

Based on the above assessment of the inspection findings, the firm's response to Form 483 observations, inadequate resolution of observation 1 in this memo, and the pending OAI classification of the June 2013 inspection, OMPQ concurs with the NWJ-DO's recommendation to withhold approval of NDA 204-820 Colchicine 0.6 mg capsules. OMPQ recommends that corrective actions to the Form 483 should be verified on a follow up inspection.

If you have any questions, please contact me at (301) 796-5065 or by email at [Vipul.dholakia@fda.hhs.gov](mailto:Vipul.dholakia@fda.hhs.gov).

Vipul Dholakia, Ph.D.

**cc:**

New Jersey District Pre-Approval Manager (PAM),  
NDMAB Acting Team Leader, Mahesh Ramanadham

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/s/  
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VIPULCHANDRA N DHOLAKIA  
07/29/2013

DON L HENRY  
07/29/2013

**NDA 204820**

**Mitigare (colchicine) Capsules (0.6 mg)**

**Hikma Pharmaceuticals LLC**

**Craig M. Bertha, PhD,  
Chemist**

**Office of New Drug Quality Assessment  
Division III/Branch VIII**

**for**

**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

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# Chemistry Review Data Sheet

1. NDA 204820
2. REVIEW #: 4
3. REVIEW DATE: 26-JUN-2014
4. REVIEWER: Craig M. Bertha, PhD, Chemist
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	05-OCT-2012
Amendment (updated facility information)	06-NOV-2012
Amendment (stability data for marketed unapproved colchicine tablet)	14-NOV-2012
Amendment (updated information on facility responsibilities)	20-NOV-2012
Amendment (updated information on facility responsibilities)	14-DEC-2012
Amendment (letter of authorization for capsule manufacturer's DMF)	21-DEC-2012
Amendment (response to filing issues letter)	12-FEB-2013
Amendment (response to CMC discipline review letter)	17-APR-2013
Amendment (revised cover letter for DR response of 17-APR-2013)	18-APR-2013
Amendment (response to IR letter)	23-MAY-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission (Response to CR letter)	27-MAR-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Hikma Pharmaceuticals LLC
Address:	P.O. Box 182400 Bayader Wadi El Seer Amman, Jordan Jordan 11118

## Chemistry Review Data Sheet

U.S. Representative:	Susan Todd, Senior Manager, Regulatory Affairs West-Ward Pharmaceutical Corp. 200/401/435/465 Industrial Way West Eatontown, NJ 07724
Telephone:	732-720-2871

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mitigare (proposed)
- b) Non-Proprietary Name (USAN): Colchicine
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: S

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

## 10. PHARMACOL. CATEGORY: Prophylaxis of gout flares

## 11. DOSAGE FORM: capsules (maximum proposed dose 1.2 mg/day or two capsules)

## 12. STRENGTH/POTENCY: 0.6 mg/capsule

## 13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

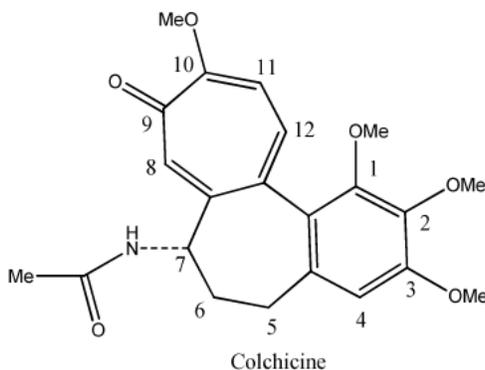
SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemistry Review Data Sheet

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



MW 399.44 g/mole

C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEWS COMPLETED	COMMENTS <sup>3</sup>
(b) (4)	II	(b) (4)	colchicine	1	Adequate	21-SEP-2010 23-NOV-2010 05-DEC-2012	
	III		(b) (4)	4			Reviewed as per ONDQA policy for bottle CCSs for solid oral drug products
	III			4			"
	III			4			"
	IV			1	Adequate	07-JAN-2013	Reviewed for composition and quality of components

<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 is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

<sup>3</sup> Include reference to location in most recent CMC review

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	78601	West-Ward Pharmaceutical Corp.	

**18. CONSULTS/CMC-RELATED REVIEWS:**

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Pre-approval inspections	03-APR-2014	ACCEPTABLE	Office of Compliance overall recommendation in EES on 26-JUN-2014
Pharm/Tox	Drug product impurities limits	29-NOV-2012	Final/L. Leshin, PhD	Limits for (b) (4)  ); Dr. Leshin recommends Hikma reduce allowed levels in drug product specification for these potentially genotoxic impurities. See response to comment 2 on p. 10 of CMC review #2.
LNC	N/A			
Methods Validation				
EA	Categorical exclusion	18-APR-2013	Final/R. Bloom, PhD	See response to DR letter comment 13 on p. 25 of CMC review #2
Microbiology	N/A			

# The Chemistry Review for NDA 204820

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is recommended to be **approved**.

#### 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 Capsules and each immediate release capsule contains 0.6 mg of colchicine. It is to be indicated for prophylaxis of gout flares in adult patients. The drug product is packaged in high density polyethylene bottles (100 and 1000 count).

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 (b) (4) (b) (4)). Colchicine that is provided by (b) (4) is an (b) (4). Colchicine is chiral but also exists as a diastereomeric mixture due to atropisomerism<sup>1</sup> resulting from steric hindrance between the A and C rings. Thus, there are two 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 (i.e., one is highly favored over the other thermodynamically).

The drug product is formulated as gelatin capsules with a formulation comprised of colchicine and the following excipients: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The manufacturing process utilizes (b) (4) of the formulation. It is important to note that one of the primary stability batches of the drug product ( (b) (4) ), was used to supply the bioequivalence study supporting the application. This batch is said to have the (b) (4)

<sup>1</sup> **Atropisomers** are stereoisomers that result from restricted rotation of single bonds due to steric hindrance such that different conformers can be isolated.

(b) (4) 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 one tablet (0.6 mg) once or twice daily. The marketed drug product will be packaged in HDPE bottles without desiccants but containing (b) (4) for filling the void space. Based on the updated stability data for the registration batches and those for the supportive tablet batch with the (b) (4), a **24 month expiration dating period** is supported.

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

N/A

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Craig M. Bertha, PhD/Chemist/Date: 26-JUN-2014  
Eric Duffy, PhD/Div. Director/Acting Branch Chief \_\_\_\_\_

#### **C. CC Block**

LLeshin/Pharm/Tox  
KHull/Clinical  
MJordan Garner/DPARP PM  
EChikhale/Biopharm  
YLiu/ONDQA PM

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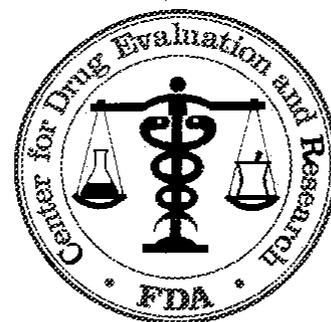
/s/  
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CRAIG M BERTHA  
06/26/2014

ERIC P DUFFY  
07/07/2014

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

**DATE:** 31-JUL-2013  
**TO:** N204820 File  
**FROM:** Craig M. Bertha, Ph.D.  
CMC Reviewer/Acting CMC Lead  
ONDQA, Division III, Branch VIII



**THROUGH:** Prasad Peri, Ph.D.  
Branch Chief  
ONDQA, Division III, Branch VIII

**SUBJECT:** Update on Establishment Evaluation Request for N204820 Mitigare (colchicine) Capsules; CMC recommendation

**SUMMARY:**

On 29-JUL-2013, the Office of Manufacturing and Product Quality in the Office of Compliance issued a memorandum which concurred with the WITHHOLD recommendation from the New Jersey District Office for NDA 204820. It is also noted that the applicant has followed up and submitted revised drug product specifications (applied at release and for stability studies) that reflect the agreement for the dissolution acceptance criterion outlined in the biopharmaceutics review dated 01-JUL-2013 (see the 02- and -08-JUL-2013, amendments), i.e.,  $Q = \frac{(b)}{(4)}\%$  at 20 minutes.

**RECOMMENDATION:** Considering the concurrence memorandum from OMPQ, the application is **not recommended for approval**.

---

Craig M. Bertha, Ph.D.  
CMC Reviewer/Acting CMC Lead

cc:  
OND/DPARP/MJordan Garner  
ONDQA/DIV 3/CBertha/31-JUL-2013  
ONDQA/DIV 3/EDuffy  
ONDQA/DIV 3/PPeri  
OND/DPARP/BChowdhury  
ONDQA/EChikhale  
ONDQA/DIV 3/YLiu  
OND/DPARP/KHull  
OND/DPARP/LLeshin  
OCP/DCPII/Sagarwal  
OB/DBII/KHamilton

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/s/  
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CRAIG M BERTHA  
07/31/2013

**NDA 204820**

**Colchicine Capsules (0.6 mg)**

**Hikma Pharmaceutical LLC**

**Craig M. Bertha, Ph.D.**

**Office of New Drug Quality Assessment/Division III/Branch  
VIII**

**for**

**Division of Pulmonary, Allergy, and Rheumatology  
Products**

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# Chemistry Review Data Sheet

1. NDA 204820
2. REVIEW #: 3
3. REVIEW DATE: 29-MAY-2013
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	05-OCT-2012
Amendment (updated facility information)	06-NOV-2012
Amendment (stability data for marketed unapproved colchicine tablet)	14-NOV-2012
Amendment (updated information on facility responsibilities)	20-NOV-2012
Amendment (updated information on facility responsibilities)	14-DEC-2012
Amendment (letter of authorization for capsule manufacturer's DMF)	21-DEC-2012
Amendment (response to filing issues letter)	12-FEB-2013
Amendment (response to CMC discipline review letter)	17-APR-2013
Amendment (revised cover letter for DR response of 17-APR-2013)	18-APR-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (response to IR letter)	23-MAY-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Hikma Pharmaceuticals LLC
Address:	P.O. Box 182400 Bayader Wadi El Seer Amman, Jordan Jordan 11118
U.S. Representative:	Susan Todd, Senior Manager, Regulatory Affairs West-Ward Pharmaceutical Corp. 200/401/435/465 Industrial Way West Eatontown, NJ 07724

## Chemistry Review Data Sheet

Telephone:	732-720-2871
------------	--------------

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mitigare (proposed)
- b) Non-Proprietary Name (USAN): Colchicine
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: S

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

## 10. PHARMACOL. CATEGORY: Prophylaxis of gout flares

## 11. DOSAGE FORM: capsules (maximum proposed dose 1.2 mg/day or two capsules)

## 12. STRENGTH/POTENCY: 0.6 mg/capsule

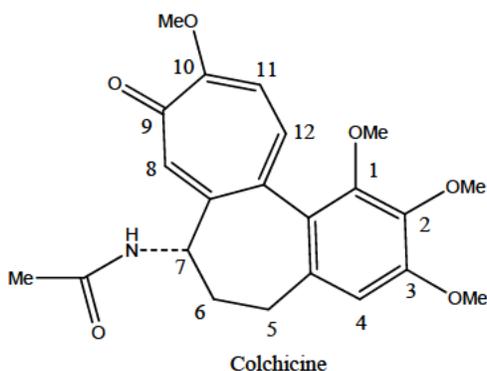
## 13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

## Chemistry Review Data Sheet



MW 399.44 g/mole

 $C_{22}H_{25}NO_6$ 

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEWS COMPLETED	COMMENTS <sup>3</sup>
(b) (4)	II	(b) (4)	colchicine	1	Adequate	21-SEP-2010 23-NOV-2010 05-DEC-2012	
	III	(b) (4)	(b) (4)	4			Reviewed as per ONDQA policy for bottle CCSs for solid oral drug products
	III	(b) (4)	(b) (4)	4			“
	III	(b) (4)	(b) (4)	4			“
	IV	(b) (4)	(b) (4)	1	Adequate	07-JAN-2013	Reviewed for composition and quality of components

<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 is enough data in the application, therefore the DMF did not need to be reviewed)<sup>3</sup> Include reference to location in most recent CMC review

Chemistry Review Data Sheet

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	78601	West-Ward Pharmaceutical Corp.	

**18. CONSULTS/CMC-RELATED REVIEWS:**

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Pre-approval inspections	03-DEC-2012	Unknown (no recommendation in EES)	
Pharm/Tox	Drug product impurities limits	29-NOV-2012	Final/L. Leshin, Ph.D.	Limits for (b) (4) ); Dr. Leshin recommends Hikma reduce allowed levels in drug product specification for these potentially genotoxic impurities. See response to comment 2 on p. 10.
LNC	N/A			
Methods Validation				
EA	Categorical exclusion	18-APR-2013	Final/R. Bloom, Ph.D.	See response to DR letter comment 13 on p. 25 of CMC review #2
Microbiology	N/A			

# The Chemistry Review for NDA 204820

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable** from a CMC perspective, as the Office of Compliance recommendation is not provided in the Establishment Evaluation System (EES).

#### 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 Capsules and each immediate release capsule contains 0.6 mg of colchicine. It is to be indicated for prophylaxis of gout flares in adult patients. The drug product is packaged in high density polyethylene bottles (100 and 1000 count).

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 (b) (4) (b) (4). Colchicine that is provided by (b) (4) is an (b) (4). Colchicine is chiral but also exists as a diastereomeric mixture due to atropisomerism<sup>1</sup> resulting from steric hindrance between the A and C rings. Thus, there are two 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 (i.e., one is highly favored over the other thermodynamically).

The drug product is formulated as gelatin capsules with a formulation comprised of colchicine and the following excipients: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The manufacturing process utilizes (b) (4) of the formulation. It is important to note that one of the primary stability batches of the drug product (b) (4), for which nine (9) months of long term data are submitted, was used to supply the bioequivalence study

<sup>1</sup> **Atropisomers** are stereoisomers that result from restricted rotation of single bonds due to steric hindrance such that different conformers can be isolated.

supporting the application. (b) (4)

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 one tablet (0.6 mg) once or twice daily. The marketed drug product will be packaged in (b) (4) bottles without desiccants but containing (b) (4) for filling the void space. Based on the stability data for the registration batches and those for the supportive tablet batch with the (b) (4), a 24 month expiration dating period is supported.

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

Currently, it is recommended that the application be given an approvable action, as an acceptable recommendation from the Office of Compliance (OC) will be necessary prior to recommendation for approval. Currently there is no recommendation from OC in the EES.

## **III. Administrative**

### **A. Reviewer's Signature**

### **B. Endorsement Block**

Craig M. Bertha, Ph.D./Chemist/Date: 29-MAY-2013  
Prasad Peri, Ph.D./Branch Chief \_\_\_\_\_

### **C. CC Block**

LLeshin/Pharm/Tox  
KHull/Clinical  
MJordan Garner/DPARP PM  
EChikhale/Biopharm  
YLiu/ONDQA PM  
RBloom/OPS

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CRAIG M BERTHA  
05/30/2013

PRASAD PERI  
06/06/2013  
I concur

**NDA 204820**

**Colchicine Capsules (0.6 mg)**

**Hikma Pharmaceutical LLC**

**Craig M. Bertha, Ph.D.**

**Office of New Drug Quality Assessment/Division III/Branch  
VIII**

**for**

**Division of Pulmonary, Allergy, and Rheumatology  
Products**

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# Chemistry Review Data Sheet

1. NDA 204820
2. REVIEW #: 2
3. REVIEW DATE: 23-APR-2013
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	05-OCT-2012
Amendment (updated facility information)	06-NOV-2012
Amendment (stability data for marketed unapproved colchicine tablet)	14-NOV-2012
Amendment (updated information on facility responsibilities)	20-NOV-2012
Amendment (updated information on facility responsibilities)	14-DEC-2012
Amendment (letter of authorization for capsule manufacturer's DMF)	21-DEC-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (response to filing issues letter)	12-FEB-2013
Amendment (response to CMC discipline review letter)	17-APR-2013
Amendment (revised cover letter for DR response of 17-APR-2013)	18-APR-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Hikma Pharmaceuticals LLC
Address:	P.O. Box 182400 Bayader Wadi El Seer Amman, Jordan Jordan 11118
U.S. Representative:	Susan Todd, Senior Manager, Regulatory Affairs West-Ward Pharmaceutical Corp. 200/401/435/465 Industrial Way West Eatontown, NJ 07724

## Chemistry Review Data Sheet

Telephone:	732-720-2871
------------	--------------

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: none proposed
- b) Non-Proprietary Name (USAN): Colchicine
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: S

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

## 10. PHARMACOL. CATEGORY: Prophylaxis of gout flares

## 11. DOSAGE FORM: capsules (maximum proposed dose 1.2 mg/day or two capsules)

## 12. STRENGTH/POTENCY: 0.6 mg/capsule

## 13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

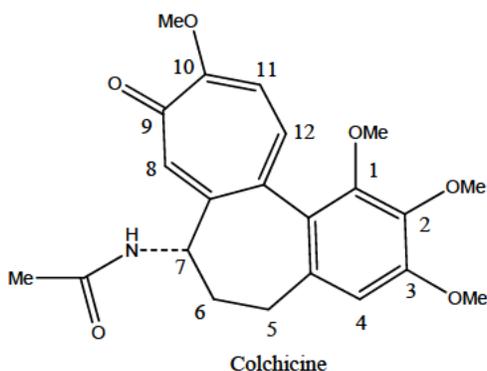
SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

## Chemistry Review Data Sheet



MW 399.44 g/mole

 $C_{22}H_{25}NO_6$ 

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. Supporting DMFs:

DMF # (b) (4)	TYPE	HOLDER (b) (4)	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEWS COMPLETED	COMMENTS <sup>3</sup>
	II		colchicine	1		21-SEP-2010 23-NOV-2010 05-DEC-2012	
	III		(b) (4)	4	Adequate		Reviewed as per ONDQA policy for bottle CCSs for solid oral drug products
	III			4			“
	III			4			“
	IV			1	Adequate	07-JAN-2013	Reviewed for composition and quality of components

<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 is enough data in the application, therefore the DMF did not need to be reviewed)<sup>3</sup> Include reference to location in most recent CMC review

Chemistry Review Data Sheet

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	78601	West-Ward Pharmaceutical Corp.	

**18. CONSULTS/CMC-RELATED REVIEWS:**

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Pre-approval inspections	03-DEC-2012	Unknown	The NWJ-DO has held a Regulatory Meeting with West-Ward on 05-OCT-2012 to discuss the results of recent inspections which "showed new and continuing GMP deficiencies."
Pharm/Tox	Drug product impurities limits	29-NOV-2012	Final/L. Leshin, Ph.D.	Limits for (b) (4) Dr. Leshin recommends Hikma reduce allowed levels in drug product specification for these potentially genotoxic impurities. See comment in draft CMC IR letter attached.
LNC	N/A			
Methods Validation				
EA	Categorical exclusion	18-APR-2013	Final/R. Bloom, Ph.D.	See response to DR letter comment 13 below on p. 25
Microbiology	N/A			

# The Chemistry Review for NDA 204820

## 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 attached draft information request (IR) letter at the end of this review. Also, the Office of Compliance recommendation is pending. **It is requested that the project manager forward the comments in the IR letter at the end of this review, to the applicant.**

#### 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 Capsules and each immediate release capsule contains 0.6 mg of colchicine. It is to be indicated for prophylaxis of gout flares in adult patients. The drug product is packaged in high density polyethylene bottles (100 and 1000 count).

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 (b) (4) (b) (4). Colchicine that is provided by (b) (4) is an (b) (4). Colchicine is chiral but also exists as a diastereomeric mixture due to atropisomerism<sup>1</sup> resulting from steric hindrance between the A and C rings. Thus, there are two 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 (i.e., one is highly favored over the other thermodynamically).

The drug product is formulated as gelatin capsules with a formulation comprised of colchicine and the following excipients: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The manufacturing process utilizes (b) (4) of the formulation. It is important to note that one of

<sup>1</sup> **Atropisomers** are stereoisomers that result from restricted rotation of single bonds due to steric hindrance such that different conformers can be isolated.

the primary stability batches of the drug product ( (b) (4) ), for which nine (9) months of long term data are submitted, was that used in the bioequivalence study supporting the application. (b) (4)

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 one tablet (0.6 mg) once or twice daily. The marketed drug product will be packaged in (b) (4) bottles without desiccants but containing (b) (4) for filling the void space. Based on the stability data for the registration batches and those for the supportive tablet batch with the (b) (4), a 24 month expiration dating period is supported.

#### **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 information request letter. 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. Also, an acceptable recommendation from the Office of Compliance will be necessary prior to recommendation for approval.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Craig M. Bertha, Ph.D./Chemist/Date: 23-APR-2013  
Prasad Peri, Ph.D./Branch Chief \_\_\_\_\_

#### **C. CC Block**

ASchroeder/CMC Lead  
LLeshin/Pharm/Tox  
KHull/Clinical  
MJordan Garner/DPARP PM  
YLiu/ONDQA PM  
RBloom/OPS

19 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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CRAIG M BERTHA  
04/23/2013

PRASAD PERI  
04/24/2013  
I concur

**NDA 204820**

**Colchicine Capsules (0.6 mg)**

**Hikma Pharmaceutical LLC**

**Craig M. Bertha, Ph.D.**  
**Office of New Drug Quality Assessment/Division III/Branch**  
**VIII**

**for**

**Division of Pulmonary, Allergy, and Rheumatology**  
**Products**

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# Chemistry Review Data Sheet

1. NDA 204820
2. REVIEW #: 1
3. REVIEW DATE: 17-JAN-2013
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission

Amendment (updated facility information)

Amendment (stability data for marketed unapproved colchicine tablet)

Amendment (updated information on facility responsibilities)

Amendment (updated information on facility responsibilities)

Amendment (letter of authorization for capsule manufacturer's DMF)

Document Date

05-OCT-2012

06-NOV-2012

14-NOV-2012

20-NOV-2012

14-DEC-2012

21-DEC-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Hikma Pharmaceuticals LLC
Address:	P.O. Box 182400 Bayader Wadi El Seer Amman, Jordan Jordan 11118
U.S. Representative:	Susan Todd, Senior Manager, Regulatory Affairs West-Ward Pharmaceutical Corp. 200/401/435/465 Industrial Way West Eatontown, NJ 07724

## Chemistry Review Data Sheet

Telephone:	732-720-2871
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## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: none proposed
- b) Non-Proprietary Name (USAN): Colchicine
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: S

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

## 10. PHARMACOL. CATEGORY: Prophylaxis of gout flares

## 11. DOSAGE FORM: capsules (maximum proposed dose 1.2 mg/day or two capsules)

## 12. STRENGTH/POTENCY: 0.6 mg/capsule

## 13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

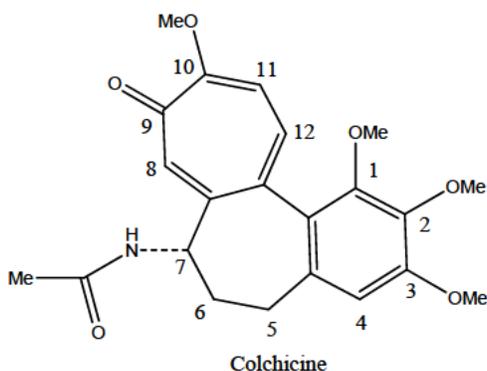
SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

## Chemistry Review Data Sheet



MW 399.44 g/mole

 $C_{22}H_{25}NO_6$ 

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEWS COMPLETED	COMMENTS <sup>3</sup>
(b) (4)	II	(b) (4)	colchicine	1	Adequate	21-SEP-2010 23-NOV-2010 05-DEC-2012	
	III	(b) (4)	(b) (4)	4			Reviewed as per ONDQA policy for bottle CCSs for solid oral drug products
	III	(b) (4)	(b) (4)	4			"
	III	(b) (4)	(b) (4)	4			"
	IV	(b) (4)	(b) (4)	1	Adequate	07-JAN-2013	Reviewed for composition and quality of components

<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 is enough data in the application, therefore the DMF did not need to be reviewed)<sup>3</sup> Include reference to location in most recent CMC review

Chemistry Review Data Sheet

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	78601	West-Ward Pharmaceutical Corp.	

**18. CONSULTS/CMC-RELATED REVIEWS:**

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Pre-approval inspections	03-DEC-2012	Pending	
Pharm/Tox	Drug product impurities limits	29-NOV-2012	Final/L. Leshin, Ph.D.	Limits for (b) (4) Dr. Leshin recommends Hikma reduce allowed levels in drug product specification for these potentially genotoxic impurities.
LNC	N/A			
Methods Validation				
EA	Categorical exclusion			Dr. Bloom has provided comments regarding the EA for the applicant that will be included in the DR letter.
Microbiology	N/A			

# The Chemistry Review for NDA 204820

## 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 discipline review letter at the end of this review. Also, the Office of Compliance recommendation is pending. **It is requested that the project manager forward the comments in the draft discipline review letter at the end of this review, to the applicant.**

#### 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 Capsules and each immediate release capsule contains 0.6 mg of colchicine. It is to be indicated for prophylaxis of gout flares in adult patients. The drug product is packaged in high density polyethylene bottles (100 and 1000 count).

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 (b) (4). Colchicine that is provided by (b) (4) is an (b) (4). Colchicine is chiral but also exists as a diastereomeric mixture due to atropisomerism<sup>1</sup> resulting from steric hindrance between the A and C rings. Thus, there are two 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 (i.e., one is highly favored over the other thermodynamically).

The drug product is formulated as gelatin capsules with a formulation comprised of colchicine and the following excipients: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The manufacturing process utilizes (b) (4) of the formulation. It is important to note that one of

<sup>1</sup> **Atropisomers** are stereoisomers that result from restricted rotation of single bonds due to steric hindrance such that different conformers can be isolated.

the primary stability batches of the drug product (b) (4), for which nine (9) months of long term data are submitted, was that used in the bioequivalence study supporting the application. (b) (4)

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 one tablet (0.6 mg) once or twice daily. The marketed drug product will be packaged in (b) (4) bottles without desiccants but containing (b) (4) for filling the void space. Based on the stability data for the registration batches and those for the supportive tablet batch with the (b) (4), a 24 month expiration dating period is supported.

#### **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 discipline review letter. 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. Also, an acceptable recommendation from the Office of Compliance will be necessary prior to recommendation for approval.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Craig M. Bertha, Ph.D./Chemist/Date: 17-JAN-2013  
Prasad Peri, Ph.D./Branch Chief \_\_\_\_\_

#### **C. CC Block**

ASchroeder/CMC Lead  
LLeshin/Pharm/Tox  
KHull/Clinical  
MJordan Garner/DPARP PM  
YLiu/ONDQA PM  
RBloom/OPS

58 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CRAIG M BERTHA  
01/17/2013

PRASAD PERI  
01/17/2013  
I concur

# Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

## APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: **N204820**  
 Applicant: Hikma Pharmaceuticals LLC, Amman, Jordan  
 (US Agent: West-Ward Pharmaceutical Corp., Eatontown, NJ)
  
2. Drug Name: Colchicine Capsules (0.6 mg)
  
3. RECEIVED DATE: October 5, 2012
  
4. RELATED REVIEW DOCUMENTS:
  - a. **Drug Master Files: none listed on 356h form, but 4 DMFs are listed in section 1.4:**

DMF #	TYP E	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Colchicine	4/02/2010	DMF previously reviewed and found adequate on 11/23/10.
	III	(b) (4)	(b) (4)	8/23/2010	
	III	(b) (4)	(b) (4)	8/23/2010	
	III	(b) (4)	(b) (4)	8/13/2009	

TEMP NOTE: DMF (b) (4) IS WRITTEN TO Westward Pharmaceutical, not to the applicant – needs to be updated

Comment: All of the LOAs indicated in the table above were written (in the original NDA) to authorize the US Agent, West-Ward Pharmaceuticals, not the applicant. They were all resubmitted to provide authorization to the applicant, Hikma Pharmaceuticals LLC at our request: see the November 20, 2012 amendment.

**b. Recommended Consults**

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CONSULT	YES	NO	COMMENTS:
Biometrics	<input type="checkbox"/>	X	very limited stability data provided
Biopharm	X	<input type="checkbox"/>	This is within ONDQA so it isn't actually a consult. The assigned Biopharm Reviewer is Dr. Elsbeth Chikhale.
EES	X	<input type="checkbox"/>	EES was entered on Dec. 3, 2012 after getting additional site clarifications from the applicant.
Pharm/Tox	X	<input type="checkbox"/>	possible
Methods Validation	<input type="checkbox"/>	X	This is not recommended unless the reviewer feels that our lab should check one or more methods for particular concerns.
EA	<input type="checkbox"/>	X	Reviewer will evaluate categorical exclusion request.
New Drug Micro	<input type="checkbox"/>	<input type="checkbox"/>	There are no microbial controls for either d.s. or d.p. This is a review issue to evaluate.
CDRH	<input type="checkbox"/>	X	
Other	<input type="checkbox"/>	<input type="checkbox"/>	

**c. Other Applications or Submissions to note (if any) listed by the applicant in the NDA:**

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	10/14/2009	78601	Colchicine Tablets USP 0.6 mg; although this IND is referenced in the NDA, West Ward Pharmaceutical is the sponsor of this IND (but not the applicant for this NDA)

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d. Previous Communications with the Applicant to note (if any):

none are listed in the NDA for this applicant.

## OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X	<input type="checkbox"/>	Note our tcon with applicant on 11/13/12 re: the very limited stability data present in the NDA. The applicant has now provided supportive stability data for tablets with the same formulation, and this is judged to be sufficient to allow review.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
X	<input type="checkbox"/>	<p>1. This pertains to the (b) (4) of the drug, and the instruction in the executed batch records to (b) (4) (b) (4) ” Provide a description of how the (b) (4) is controlled during the manufacturing process.</p> <p>2. Update section 3.2.P.3.3 to ensure that it is complete, including a detailed description of the packaging and labeling processes.</p> <p>3. Your application states that the particle size of colchicine is potentially critical, yet there do not seem to be any in process controls for particle size during/after the (b) (4) process. Provide a justification for the absence of these controls.</p> <p>4. Describe the bulk drug product containers used to store the bulk product, prior to its encapsulation and indicate the maximum amount of storage time (and storage conditions) for the bulk product, and provide stability data for longer term storage (e.g. 30 days or more).</p>

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		<p>5. The specification for uniformity of dosage units (USP &lt;905&gt;) is not complete and cannot be said to meet the USP requirement. The maximum value of (b) (4) is not indicated and there are no limits on individual values. Address this concern in your application for the specification for uniformity of dosage units.</p> <p>6. Drug product specifications list (b) (4), with reference to USP &lt;(b) (4)&gt; but specific (b) (4) and limits are not listed in the specifications. Update your specifications to include specific (b) (4) which may be potentially present.</p> <p>7. The application should be complete upon submission and your proposal to provide a future amendment with additional container closure system information and stability data for a blister package should be submitted after NDA approval as a supplement.</p> <p>8. Provide the West-Ware SOP describing time limits on the various phases of the drug product manufacturing process, or provide the equivalent information.</p> <p>9. You have indicated that you will institute written procedures for a system of (b) (4) procedures for (b) (4) that do not conform to standards or specifications, and that such (b) (4) will conform with “all established standards, specifications and characteristics.” Provide details of this (b) (4) system (or data from (b) (4)) in section P.3.3 of your NDA, in order for FDA to review these (b) (4) system.</p>
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<b>Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?</b>		
Yes	No	Biopharmaceutics Filing Issues
<input type="checkbox"/>	<input type="checkbox"/>	SEE SEPARATE BIOPHARMACEUTICS FILING REVIEW

<b>Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?</b>		
Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	SEE SEPARATE BIOPHARMACEUTICS FILING REVIEW

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**Does the submission contain any of the following elements?**

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	x	
Combination Products	<input type="checkbox"/>	x	
Nanotechnology	<input type="checkbox"/>	x	
PET	<input type="checkbox"/>	x	
QbD Elements	<input type="checkbox"/>	x	There are some QbD related terms which are used briefly, but this does not appear to be an overall QbD developed drug product.
SPOTS	X	<input type="checkbox"/>	This is a purified drug substance (single constituent): it is not therefore a SPOTS product.

**Is a team review recommended?**

Yes	No	Suggested expertise for team
<input type="checkbox"/>	X	

## CMC Summary: Critical Issues and Complexities

*(This section is formatted to expand as far as needed by author.)*

Drug Substance:

“Colchicine is a water soluble alkaloid obtained from the colchicum plant.” It is a highly potent drug (the maximum daily dose, according to the applicant, is (b) (4) mg.) CMC information about the drug substance is referred (via a letter of authorization) to DMF (b) (4) ( (b) (4) Dr. Craig Bertha last reviewed this DMF on November 23, 2010, and found it to be adequate for oral tablets. The applicant has listed (b) (4) manufacturing site for the drug substance (in (b) (4) and clarified that the corporate address for this firm is in (b) (4)

The applicant refers to DMF (b) (4) for much drug substance CMC information, however, they do provide drug substance specifications and batch results for Lot# (b) (4) Analytical procedures are referenced to USP, or

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provided in the NDA for certain chromatographic methods. Drug substance specifications meet the requirements of the USP monograph. Residual solvents ( (b) (4) ) are controlled.

Other specifications are also present, in addition to those in those in the USP monograph: e.g., specific impurities, heavy metals, particle size, bulk density, XRD, residue on ignition.

The particle size specifications for colchicine drug substance should be looked at carefully in the review: they are all written in terms of “NLT,” which allows for considerable variability. For example, the specifications would be met (b) (4) or alternatively, (b) (4). This may or may not make a difference, but dissolution is not likely to be an issue with the high water solubility of colchicine. It may be a concern for blending and content uniformity (see below).

Drug Product:

The drug product consists of gelatin capsules filled with a formulation of colchicine, microcrystalline cellulose, anhydrous lactose, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate. The applicant states that all excipients are present (in terms of maximum daily dose) in amounts within the Inactive Ingredient Guide limits for approved products in the US; this does not include the gelatin capsules which are not listed but this is not likely an issue.)

The applicant notes that they had marketed 0.6 mg colchicine tablets for over 25 years (apparently, as an unapproved product in the US). The proposed 0.6 mg encapsulated drug product contains “ (b) (4) ”  
“ (Section 2.3.P.1) It is not absolutely clear whether “tablets” refer to the unapproved tablets, previously marketed by West-Ward, but that seems to be the implication.

It is indicated that colchicine is (b) (4) and that (b) (4) This (b) (4) during the manufacturing process does not seem to be defined and controlled.

The drug product manufacturing process involves (b) (4) . It is indicated (2.3.P.2.1.1) that particle size of colchicine is potentially critical, yet there do not seem to be any in process controls for particle size during/after the (b) (4) process. Particle size is suggested to be critical due to the high potency and low strength of the capsules, and the importance of content uniformity.

The manufacturing (batch) record for batch (b) (4) mentions an “event” where a pebble

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was found chipped in the (b) (4) and a fragment about 1 cm in dimension was found. The applicant considers this to be a minor deviation and they state that “any large pebble fragments are retained within the (b) (4) of step (b) (4) production process.” This potentiality of the process allowing fragments/particles from the pebbles smaller than (b) (4) in size into the formulation should be evaluated for safety.

Drug product manufacture described in 3.2.P.3.3 doesn't include a separate process description, however, it does include a blank batch record for the largest batch ( (b) (4) capsules). This possible master batch record only includes the process up through (b) (4).” It does not include packaging the product in final to be marketed container closure systems nor does it include labeling. The applicant should update section 3.2.P.3.3 to ensure that it is complete, including the packaging and labeling processes. The bulk drug product containers are not described, nor is it indicated how many capsules are placed in a bulk container or what its size is. The applicant should describe the bulk containers including the materials of construction and size. It is noted that executed process validation records are provided in section 3.2.R.1 ( (b) (4) capsules per run), and separate executed batch records are provided for packaging and labeling.

Time limits on the various phases of the drug product manufacturing process are referenced to a West-Ward SOP which is “available for review by the FDA’s Field Investigation Staff.” This SOP is not provided to the NDA. The applicant will be asked for details of the time limits for various parts of the drug product manufacturing process.

A process validation protocol is provided, which will not be reviewed or approved in the NDA, rather it will be examined as part of the future site inspection by FDA’s field investigators.

Drug product specifications: This is just for information: drug product specifications for the proposed colchicine *capsules* meet the acceptance criteria of the USP monograph for colchicine *tablets*, for the following attributes: identification, dissolution and assay. This presumes that the applicant uses the USP monograph methods for the proposed capsules. The applicant should provide the following information. The specification for uniformity of dosage units (USP <905>) is not complete and cannot be said to meet the USP requirement. Calculation of (b) (4) is not indicated and there are no limits on individual values. Drug product specifications list (b) (4), with reference to USP <(b) (4)> but specific (b) (4) and limits are not listed in the specifications and they should be. Drug product specifications do list specified and unspecified impurities; the specified impurities/degradants are the same ones that are listed in the drug substance specifications.

Drug product will be packaged into (b) (4) white HDPE bottles, with (b) (4)

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(b) (4)

It does not appear that method (b) (4) for impurities in the capsules includes any impurity reference standards; however the validation report does utilize impurity standards for this method. This is an issue for the reviewer to consider.

Drug product (b) (4): see Section 3.2.P.3.3. There is a statement they will institute written procedures for a system of (b) (4) procedure for (b) (4) that do not conform to standards or specifications, and that such (b) (4) will conform with “all established standards, specifications and characteristics.” There aren’t any details of this (b) (4) system (or data from (b) (4)) in P.3.3 which would be needed in order for FDA to review it. These details will be requested for section P.3.3.

Following is the table discussing risk assessment in the manufacturing process, without any details as to how it was generated (the tables below are taken from Section 3.2.P.2.3):

(b) (4)

Following are the two tables listed as identifying the “design space:”

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The following table explains the different sets of experiments that were performed to collect the maximum data in order to establish the design space.

(b) (4)

**Results and Summary**

The results of the above experiments are summarized in the table below:

(b) (4)

The table illustrates that all the test results obtained for different trials are well within the limits set for this product. There seems to be no detrimental effect on the product quality and efficacy as long as the formulation and manufacturing process is maintained within the ranges selected for all three parameters.

From the physical characteristics and dissolution data collected for the above trials, potential design space was generated for the proposed drug product.

Factors	Range
(b) (4)	(b) (4)

It is stated that a

(b) (4)

Information identified as being QbD information is very limited, and QbD does not appear to be the basis for the development of this drug product in general.

See the comments in the filing review table, later in this document. This includes

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(among other issues) the concern about the very limited stability data available for this drug product.

**Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)**

*See EES for complete list of facilities related to this application.*

Site information is being clarified.

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## FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	Yes	No	N/A	Comment
1.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	X	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input type="checkbox"/>	<input type="checkbox"/>	X	No IND has been found in DARRTS for this applicant

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input type="checkbox"/>	X	<input type="checkbox"/>	The information is partially provided in sections 3.2.S.2.1 and 3.2.P.3.1 for this information. The applicant is providing the missing information.
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	<input type="checkbox"/>	<input type="checkbox"/> ?		Colchicine is obtained from a plant source. It appears that there is only one manufacturer of the drug substance. The reviewer should verify this in the drug substance DMF. The drug substance manufacturing site has been clarified by the applicant (on 11/05, 2012) as being at (b) (4) [REDACTED].

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<p>7 Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<p align="center"><input type="checkbox"/></p>	<p align="center">X</p>	<p align="center"><input type="checkbox"/></p>	<p>See 3.2.S.2.1. The NDA 2.3.S.2 lists one site for drug substance. The NDA doesn't list a specific phone number for the contact person at the site although general phone numbers are provided for the site (3.2.S.2.1) and an e-mail address is provided in the 11/05/2012 amendment. Clarification has been provided in the 11/20/12 amendment for the responsibilities of the contract testing laboratories for the drug substance.</p>
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8	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input type="checkbox"/>	X	<input type="checkbox"/>	<p>Form 356h only lists the manufacturer of the drug product, West Ward Pharmaceuticals. Contact information has been provided at our request in the 11/05/2012 amendment. See 3.2.P.3.1 for additional information about facilities: The applicant has been asked to indicate if both release and stability testing are performed at the manufacturing site (West-Ward Pharmaceutical Corp.) since the NDA just lists “testing.” See the response in the 11/20/12 amendment. Two contractors are listed as being able to perform testing on active and inactive ingredients. <u>The applicant had been asked to clarify whether</u> (b) (4)   <div style="background-color: gray; width: 150px; height: 15px; margin: 2px 0;"></div>         may perform release and/or stability testing for the drug substance. The applicant has also been asked to specify the tests to be performed at each facility. See the applicant’s response in the 11/20/12 amendment. Phone numbers have been provided but E-mail addresses have not been provided for the contacts at the contractor sites.</p>
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9	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	see listing for drug product above
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input type="checkbox"/>	x	<input type="checkbox"/>	<u>This statement should be provided for all facilities used for drug substance and drug product: this request has been sent to the applicant.</u>

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	Yes	No	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x	<input type="checkbox"/>	<input type="checkbox"/>	Section 1.12.14. The basis for the claim is 21 CFR 25.31(a). There is a claim that no extraordinary circumstances exist.

D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		<input type="checkbox"/>	See table on cover page.

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APPEARS THIS WAY ON THE ORIGINAL

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<b>E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
13.	Does the section contain a description of the DS manufacturing process?	<input type="checkbox"/>	x	<input type="checkbox"/>	see DMF
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	<input type="checkbox"/>	x	<input type="checkbox"/>	see DMF
15.	Does the section contain information on impurities?	x	<input type="checkbox"/>	<input type="checkbox"/>	see 3.2.S.3, and S.4.1, S.4.4, S.4.5; see also DMF
16.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	x	<input type="checkbox"/>	see DMF
17.	Does the section contain controls for the DS?	x	<input type="checkbox"/>	<input type="checkbox"/>	compare with DMF
18.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	x	<input type="checkbox"/>	see DMF
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	x	<input type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	x	<input type="checkbox"/>	
21.	Does the section contain container and closure information?	x	<input type="checkbox"/>	<input type="checkbox"/>	Minimal information. See also the DMF.
<b>F. DRUG PRODUCT (DP)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
22.	Does the section contain quality controls of excipients?	x	<input type="checkbox"/>	<input type="checkbox"/>	All excipients are listed as NF quality, except for the gelatin capsules. <u>The reviewer should verify that the controls which are applied do comply with all compendial controls.</u>  Specifications are provided for each excipient. Tests are also provided for the gelatin capsules.
23.	Does the section contain information on composition?	x	<input type="checkbox"/>	<input type="checkbox"/>	

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24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	<input type="checkbox"/>	<input type="checkbox"/>	a blank batch record is provided (3.2.P.3.3), but it doesn't seem to describe final packaging and labeling. See Regional Information (R) for batch records of completed batches and packaging batch records. <u>Section P.3.3 should contain a detailed description of the packaging and labeling processes.</u>
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	<input type="checkbox"/>	<input type="checkbox"/>	Controls of critical steps and intermediates are provided, although limited to the blend and the capsules, and routine production batches of the blend will only be tested for description and identification, and will not be tested for blend uniformity, bulk density or moisture. <u>This section does not provide a justification for this</u> , although these additional tests will be done on process validation batches. (Note that there are other in process controls that will be performed.) This is a review issue. The applicant refers to capsule tests for dissolution and content uniformity (apparently in process), using the same tests used for the drug product. for which validation data are available. A sampling plan is not provided for this testing; this may also be a review issue.
26.	Is there a batch production record and a proposed master batch record?	x	<input type="checkbox"/>	<input type="checkbox"/>	Section 3.2.P.3.3 provides "the largest batch record" (which is not identified as a master batch record); this is for (b) (4) capsules (the size of the proposed commercial batch); it is not an executed batch record and does not include packaging and labeling. Section 3.2.R includes three process validation batch records (separate records for manufacturing and packaging). The manufacturing records are for (b) (4) capsules each. These packaging records provided seem to state that the bottles were unlabeled for these batches; this is not clear as there is some mention of labels. It does not appear that there is a batch record identified as a master batch record.

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27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input type="checkbox"/>	X	<input type="checkbox"/>	This application is filed under section 505(b)(2). The only clinical studies were a bioavailability study (colchicine 0.6 mg capsules versus colchicine/probenecid 0.5 mg/500 mg tablets, four drug interaction studies and a food effect study. This reviewer has not discovered any investigational formulations of the proposed 0.6 mg capsules; the applicant states that no alternative formulations were investigated (2.3.P.2.2).
28.	Have any biowaivers been requested?	<input type="checkbox"/>	X	<input type="checkbox"/>	none found to date
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	Section 3.2.P.7 does not include a description of a proposed blister package, although labeling has been provided for such a package. Section R1 states that unit dose blister packaging has been carried out on Batch (b) (4) but that the results "did not meet expectations." They plan to redesign their blister package to use (b) (4). They then plan to amend the application later with this packaging information and with stability data for this package. <u>The applicant should be told that the application should be complete upon submission and this additional packaging information and data should be submitted after approval as a supplement.</u>
30.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	It is noted that (b) (4). The impurity (b) (4). <u>The reviewer should discuss this with the pharm/tox reviewer since proposed limits are NMT (b) (4) %.</u> It is noted that the (b) (4) is not mentioned and it should be included in the specifications, as appropriate.

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31.	Has stability data and analysis been provided to support the requested expiration date?	<input type="checkbox"/>	X	<p>This NDA appears to have primary stability data at room temperature only for 9 months and only for <u>one batch</u> (each for two presentations, for 100s and 1000s bottles). There are also accelerated data for this batch (6 months) at 40 deg. C/75%RH.</p> <p>There are two additional batches with 1 month of accelerated data, for each package size. No statistical analysis is provided.</p> <p>Stability attributes tested included the following: appearance, dissolution, assay, related compounds.</p> <p>Proposed expiry for the drug product is 24 months for bottles of 100 and 1000. Bulk packaged drug product will have an expiry of <sup>(b) (4)</sup>, though it isn't clear if the applicant has provided data to support this.</p> <p><u>The applicant has provided supportive tablet stability data to justify their proposed expiry with very minimal capsule drug product data; this is a review issue.</u></p>
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32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	There doesn't seem to be any significant information provided pertaining to QbD: the applicant does speak of risk assessment and defining the design space based on only one limited study. This approach doesn't seem to be the multivariate approach that we expect for defining design space, and this approach (risk assessment and "design space") is discussed on only 3 pages of the 3.2.P.2 section of the NDA. This pertains to a small number of variations in three attributes: (b) (4) It does not appear that there are any proposals for regulatory flexibility. The manufacturing process discussion contains one Ishikawa diagram for identification of process parameters.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	

G. METHODS VALIDATION (MV)					
	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	X	<input type="checkbox"/>	<input type="checkbox"/>	There is a one page package in 3.2.R.3, referring back only to sections 3.2.S.4 and 3.2.P.5. This will be inadequate if the reviewer feels a need for FDA laboratory validation of one or more NDA methods.

H. MICROBIOLOGY					
	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	X	<input type="checkbox"/>	not a sterile product.

I. LABELING					
	Parameter	Yes	No	N/A	Comment

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36.	Has the draft package insert been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	X	<input type="checkbox"/>	<input type="checkbox"/>	Established name only, no tradename.

<b>J. FILING CONCLUSION</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
39.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X	<input type="checkbox"/>	<input type="checkbox"/>	This recommendation is made with the acknowledgment of the recent amendment containing supportive stability data.
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
41.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X	<input type="checkbox"/>	<input type="checkbox"/>	See the listing of comments earlier in this review.

## REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead or CMC Reviewer  
Branch Chief

*{See appended electronic signature page}*

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/s/  
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ALAN C SCHROEDER  
12/04/2012  
IQA and filing review

PRASAD PERI  
12/05/2012  
I concur

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

<b>NDA Number</b>	204820
<b>Submission Date</b>	10/5/12
<b>Product name, generic name of the active</b>	Colchicine Capsules
<b>Dosage form and strength</b>	Capsules – 0.6 mg/capsule
<b>Route of Administration</b>	Oral
<b>Applicant</b>	Hikma Pharmaceuticals LLC c/o/West Ward Pharmaceutical Corp.
<b>Clinical Division</b>	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Type of Submission</b>	Original NDA – 505(b)(2)
<b>Biopharmaceutics Reviewer</b>	Elsbeth Chikhale, Ph.D.
<b>Biopharmaceutics Team Leader</b>	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA’s Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b><u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		<u>Proposed method:</u> Apparatus 2 (paddles), 500 mL of water with 2% SLS at 37 °C, at 75 rpm <u>Proposed acceptance criterion:</u> Q=75% at 30 minutes
3.	Does the application contain data to support the proposed dissolution acceptance criteria		x	Dissolution data to justify the proposed dissolution acceptance criterion need to be requested.
4.	Does the application contain the dissolution method development report?		x	The dissolution method development report needs to be requested
5.	Does the application contain data on the discriminating ability of the dissolution method		x	Data to show the discriminating ability of the dissolution method need to be requested as part of the dissolution method development report.
6.	Is there a validation package for the analytical method and dissolution methodology?	x		Section 3.2.P.5.3
7.	Does the application include a biowaiver request?		x	Not needed
8.	Does the application include an IVIVC model?		x	Not applicable

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

9.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not applicable
10.	Is information on mixing the product with foods or liquids included?		x	Not applicable
11.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		A comparative bioavailability study of the proposed capsules versus reference tablets (0.5 mg colchicine/500 mg probenecid) is conducted. The study will be reviewed by OCP.
12.	Does the application include <i>in vitro</i> alcohol interaction studies?		x	Not needed

### B. FILING CONCLUSION

	Parameter	Yes	No	Comment
13.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable
16.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	See <a href="#">information request</a> below sent to the Applicant on 11/20/12

West Ward has marketed 0.6 mg strength colchicine tablets for over 25 years. The proposed capsule formulation (b) (4)

The Applicant plans to rely on published literature to support the nonclinical profile, clinical pharmacology, clinical safety and efficacy of the proposed capsule drug product.

#### **Biopharmaceutics information request sent to the Applicant on 11/20/12:**

1. Please provide the dissolution method development report with complete detailed information supporting the selection of this method for the evaluation of the dissolution

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

characteristics of colchicine Capsules.

The dissolution method development report should include the following information:

- a. Solubility data for each drug substance covering the pH range;
- b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e.*, *selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). Include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e.*, 15, 20, 30, 45, & 60 minutes) and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e.*, no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;
- c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
- d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (*i.e.*, method robustness, etc.) and analytical method (*precision, accuracy, linearity, stability, etc.*).

For the setting of the dissolution acceptance criteria of your product, the following points should be considered:

- e. The dissolution profile data (*i.e.*, 15, 20, 30, 45, & 60 minutes) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your proposed drug product.
- f. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- g. The selection of the specification time point should be where  $Q = \frac{(b)}{(4)}$  % dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (*i.e.*, 15-20 minutes) and the second time point should be where  $Q = \frac{(b)}{(4)}$  % dissolution occurs.
- h. The dissolution acceptance criterion should be based on average dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criterion for your proposed product will be made during NDA review process based on the provided data.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

2. The dissolution data that you collect during your stability study should cover the complete dissolution profile (*i.e.*, 15, 20, 30, 45, & 60 minutes). Please provide these data. If you have not collected these dissolution data at all appropriate time points, you should start collecting these data and submit to the NDA.

*{See appended electronic signature page}*

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Elsbeth Chikhale, Ph.D.	<u>11/21/12</u>
Biopharmaceutics Reviewer	Date
Office of New Drug Quality Assessment	

*{See appended electronic signature page}*

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Angelica Dorantes, Ph.D.	<u>11/21/12</u>
Biopharmaceutics Team Leader	Date
Office of New Drug Quality Assessment	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELSBETH G CHIKHALE  
11/21/2012

ANGELICA DORANTES  
11/21/2012