

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205065Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: November 21, 2013
FROM: Caroline Strasinger, Ph.D., Review Chemist, Branch IV/ONDQA
THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV/ONDQA
TO: CMC Review #1 for NDA 205065
SUBJECT: Final Recommendation

The previous CMC Review #1, dated 9-OCT-13, noted the following two deficiencies, and therefore made a recommendation of not approval of this NDA:

1. All labels and labeling (Description and How Supplied sections) have not been finalized yet.
2. An overall “Acceptable” recommendation has *not* been made by the Office of Compliance.

Regarding the Item #1, CMC comments and recommendations regarding the labels/labeling were communicated to the Applicant on 06-NOV-2013. The Applicant accepted all changes to the labeling. For the immediate container closure the Applicant stated on 07-NOV-2013 that the (b) (4) to include the requested addition of the words “sapropterin dihydrochloride” to the equivalency statement (**Appendix 1**). Because the carton label includes all the required information, the container label with the abbreviated equivalency statement as requested by the Applicant due to the limited space (b) (4) is deemed acceptable.,

All the labels and labeling are now **adequate (see the Appendix 3)**.

Additional Comment: The Applicant provided the following information to support the labeling in an amendment on 22-Jul-2013. The information confirms expected stability of the constituted powder formulation. Results show acceptable recovery of the drug substance after incubation for up to one hour at controlled room temperature. Results also demonstrate that Kuvan powder for oral solution can be mixed with hot or cold liquids without loss of potency.

Table 3.2.P.2.2.3.1: Representative Results of Liquid Compatibility Assessments

Media Type	Media	Drug Substance Recovery ¹	
		T=0	T=1 hour
Liquid	Water	(b) (4)	
	Apple Juice		
	Boiling Water		

¹ Calculated relative to reported drug substance content from the drug product certificate of analysis.

Regarding the Item #2, An overall “ACCEPTABLE” recommendation for the facilities involved in the manufacture and testing of the drug product was made by the Office of Compliance on 21-NOV-2013 (See **Appendix 2** for the updated EES report).

Conclusion and Recommendation:

The labels and labeling for the drug product are now adequate. Additionally, the Office of Compliance has issued an overall “ACCEPTABLE” recommendation for all facilities involved.

From the ONDQA perspective, this Application is now recommended for APPROVAL.

APPENDIX 1: Email from Applicant discussing the label

From: Elizabeth Moyle [<mailto:EMoyle@bmrn.com>]
Sent: Thursday, November 07, 2013 12:15 AM
To: Manisha Deshmukh; Benjamin, Jessica
Subject: RE: NDA 205065 - container label comment
Importance: High

Dear Jessica,

Thank you very much for providing feedback on the container label for the Kuvan Powder for Oral Solution dosage form.

Regarding the request to revise the equivalency statement to read ***100 mg sapropterin dihydrochloride equivalent to 76.8 mg of sapropterin**, BioMarin has evaluated this change and requests the original proposed text remain as is since the presentation of the equivalency statement is directly associated with the total strength statement and because of limited space due to the small container size.

The current container label primary display panel presentation has the following statement, ** Equivalent to 76.8 mg of sapropterin*, which is located directly below the total strength 100 mg (see below and attached for ease of reference). Since the equivalency statement is located next to the total strength, the additional text does not seem necessary. Additionally, the primary container printable space is too small to adequately accommodate the additional text. To accommodate the additional text, significant modifications may be needed to the container text. Considering these points BioMarin proposes to keep the wording of the equivalency statement as is.

Please let me know if you have any questions or would like to discuss this further.

Kind regards,
Elizabeth A. Moyle
Director, Regulatory Affairs - Global Labeling

BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949
Tel: (415) 506-3225
Cell (b) (6)

APPENDIX 2: EES report 21-NOV-2013

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

Application:	NDA 205065/000	Sponsor:	BIOMARIN PHARM
Org. Code:	180		105 DIGITAL DR
Priority:	3		NOVATO, CA 94949
Stamp Date:	08-FEB-2013	Brand Name:	KUVAN (SAPROPTERIN)
PDUFA Date:	08-DEC-2013	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	09-JUN-2013	Product Number; Dosage Form; Ingredient; Strengths	

001; POWDER, FOR ORAL SOLUTION; SAPROPTERIN DIHYDROCHLORIDE; 100MG

FDA Contacts:	C. STRASINGER	Prod Qual Reviewer	(HFD-800)	3017963776
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800)	3017963877
	J. BENJAMIN	Regulatory Project Mgr	(HFD-180)	3017963924
	M. KOWBLANSKY	Team Leader		3017961390

Overall Recommendation:	ACCEPTABLE	on	(b) (4)	by R. WITTORF	()	
	PENDING	on		by EES_PROD		
	ACCEPTABLE	on		by R. PRABHAKARA	()	3017964668
	PENDING	on		by EES_PROD		
	PENDING	on		by EES_PROD		

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

DMF No: AADA:

Responsibilities:

- FINISHED DOSAGE LABELER
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE OTHER TESTER
- FINISHED DOSAGE PACKAGER
- FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3004079983
BIOMARIN PHARMACEUTICALS

DMF No: NOVATO, , UNITED STATES 949495706 AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO"
(DRUGS) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-AUG-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

CAROLINE STRASINGER
11/22/2013

MOO JHONG RHEE
11/22/2013
Chief, Branch IV



NDA 205065

Kuvan (sapropterin dihydrochloride) Powder for Oral Solution
100mg

BioMarin Pharmaceutical Inc.

Caroline Strasinger, Ph.D.
Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC Review of NDA 205065
For the Division of Gastroenterology Drug Products**

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Chemistry Review Data Sheet

1. NDA 205065
2. REVIEW #: #1
3. REVIEW DATE: 6-OCT-2013
4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

08-FEB-2013

Amendment

08-MAY-2013

Amendment

22-JUL-2013

7. NAME & ADDRESS OF APPLICANT:

Name: BioMarin Pharmaceutical Inc
Address: 105 Digital Drive
Novato, CA 94949
Representative: Manisha Deshmukh, Associate Director,
Regulatory Affairs
Telephone: 415-506-6788

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Kuvan

Executive Summary Section

- b) Non-Proprietary Name (USAN): sapropterin dihydrochloride
c) Code Name/#: NA
d) Chem. Type/Submission Priority:
• Chem. Type: 3
• Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Phenylalanine Hydroxylase ^{(b) (4)} activator (or
PAH ^{(b) (4)} activator)

11. DOSAGE FORM: powder for oral solution

12. STRENGTH/POTENCY: 100 mg sapropterin
dihydrochloride (base
equivalent 76.8 mg)

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

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

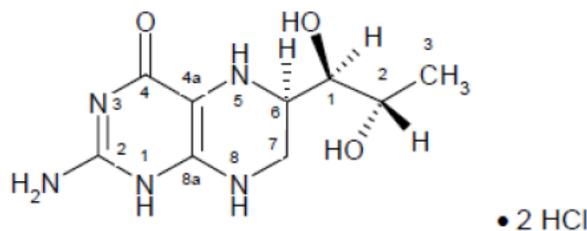
Sapropterin dihydrochloride:

(6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1H)-pteridinone dihydrochloride

C₉H₁₅N₅O₃•2HCl
MW = 314.17

Executive Summary Section

6R Form (Active) – 4(1H) conformation



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A

¹ 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")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22181	Kuvan Tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	8/21/13	Office of Compliance



CHEMISTRY REVIEW



Executive Summary Section

Pharm/Tox	N/A		
Biopharm	Adequate	10/8/13	Kelly Kitchens
LNC	N/A		
Methods Validation	To be done per ONDQA's policy		
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	03/22/13	Dr. Caroline Strasinger
Microbiology	N/A		

The Chemistry Review for NDA 205065

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

An overall “Acceptable” recommendation has *not* been made by the Office of Compliance.

All labels and labeling (Description and How Supplied sections) have not been finalized yet.

Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b) (6),(13) until the pending issues are resolved.

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

None

II. Summary of Chemistry Assessments

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

Drug product:

KUVAN (sapropterin dihydrochloride) powder for oral solution is packaged in single use (b) (4) containing 100 mg sapropterin dihydrochloride equivalent to 76.8 mg of sapropterin. The drug product is manufactured at (b) (4). Several additional companies have been listed as excipient testing and packaging facilities.

Sapropterin dihydrochloride was previously approved as a 100 mg tablet; Kuvan® Tablets under NDA 22181. BioMarin is the Applicant for both this NDA and NDA 22181. Kuvan powder for oral solution dosage form was developed to facilitate administration of the drug product with various liquids. It offers the benefit of short reconstitution time and solution clarity upon powder dissolution.

Executive Summary Section

The quality of the drug product is controlled by tests for identity, appearance, (b) (4), (b) (4), content uniformity, dissolution, assay, related substances and microbial purity.

The commercial container closure system is an individual, two inch square, four color, printed, (b) (4) laminate heat sealed packet. The (b) (4) Thirty packets are packaged to each carton. The Applicant is requesting 18 months of expiration dating; it is granted based on registration and supportive stability data provided during the review cycle indicating the product is stable through 9 months.

Drug substance:

No information for the drug substance, sapropterin dihydrochloride, has been provided in this NDA. The drug substance used to manufacture the drug product is the same drug substance as that used to manufacture commercial KUVAN® tablets (NDA 22181). The manufacturer, method of manufacture, and specification for the drug substance (b) (4) commercial KUVAN® tablets. Complete information regarding the CMC of sapropterin dihydrochloride drug substance is provided in NDA 22181. No letter of authorization is necessary to reference the information as BioMarin is the Applicant for both NDA 205065 and NDA 22181. NDA 22181 was most recently reviewed on 18-DEC-2013 and found adequate.

According to NDA 22181, the drug substance has a retest date of (b) (4) months and has been shown to be stable up to (b) (4) months.

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

KUVAN (sapropterin dihydrochloride) powder for oral solution, 100 mg is an orally administered dissolvable powder for the treatment of phenylketonuria (PKU). Labeling instructions recommend dissolving the contents of each packet in 4-8 oz. of liquid and taken within 30 minutes of dissolution. Kuvan should be administered orally with food to increase absorption, preferably at the same time each day. A missed dose should be taken as soon as possible, but 2 doses should not be taken on the same day. The product should be stored at room temperature and protected from moisture.

C. Basis for Not-Approvability Recommendation:

21 CFR 314.125(b)(13)

- An "Acceptable" site recommendation from the Office of Compliance has *not* been made. (see the **Appendix 1** on P. 39)

21 CFR 314.125(b)(6)

- Labels/Labeling have not been finalized yet.



Executive Summary Section

(see the **List of Deficiencies** on p. 38)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Caroline Strasinger, PhD	06-OCT-2013
ChemistryTeamLeaderName/Date: Marie Kowblansky, PhD	06-OCT-2013
ProjectManagerName/Date: Catherine Tran-Zwanetz	06-OCT-2013

C. CC Block

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/s/

CAROLINE STRASINGER
10/09/2013

MOO JHONG RHEE
10/09/2013
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Gastroenterology and Inborn Error Products
NDA: 205065
Applicant: BioMarin Pharmaceutical Inc.
Stamp Date: 02/08/2013
Review Date: 03/18/2013
PDUFA Date: 12/08/2013
Filing Meeting: 03/19/2013
Proposed Trademark: KUVAN
Established Name: Sapropterin dihydrochloride
Dosage Form: powder for oral solution
Route of Administration: Oral
Indication: hyperphenylalaninemia (HPA)

CMC LEAD: Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	

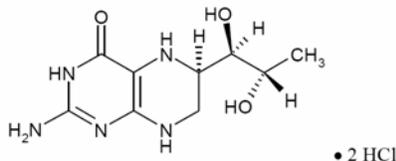
A. Summary

Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution is indicated for reduction of blood phenylalanine levels in patients with hyperphenylalaninemia. The product will be packaged in single dose packets containing 100mg of sapropterin dihydrochloride (equivalent to 76.8 mg sapropterin base). Biomarin currently markets KUVAN® as a tablet formulation, with administration instructions calling for dissolving the tablet in 4 to 8 oz. (120-240 mL) of water or apple juice. According to the applicant, this new powder formulation is designed to improve the taste and appearance of sapropterin dihydrochloride. This is being filed as a 505(b)(1) application with some cross referencing to the Kuvan Tablet NDA (22-181). Since this is a new dosage form of a currently approved drug substance, this is classified as a Type 3 application.

No clinical studies were conducted for this NDA and the company has requested a biowaiver for conducting BA/BE studies. The sponsor's justification for the biowaiver is being reviewed by Dr. Kelley Kitchens, the ONDQA Biopharm. reviewer.

Drug Substance

Sapropterin dihydrochloride,



All information regarding the drug substance is referenced to BioMarin's approved NDA 22-181.

Drug Product

Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution is a white to yellow powder that will be marketed in an individual, two inch square, (b) (4) white, printed, multi-layered, (b) (4) laminate packet which is heat sealed on four sides.

Components	Pharmacopoeial Standard	Function	Quantity (mg/packet)
Sapropterin dihydrochloride	NA	Active ingredient	100.0
Mannitol	USP/ Ph. Eur.	(b) (4)	(b) (4)
Potassium Citrate	USP/ Ph. Eur.	(b) (4)	(b) (4)
Sucralose, NF	NF	(b) (4)	(b) (4)
Ascorbic acid	USP/Ph. Eur.	(b) (4)	(b) (4)
Total			(b) (4)

All components are USP/NF and therefore, acceptable.

Release and stability testing involves reasonable testing for this product: (b) (4) (b) (4) and impurities, the limits for which conform to ICH recommendations.

Biomarin appropriately claims categorical exclusion from filing an environmental assessment on the basis that the estimated concentration of the substance at the point of entry into the aquatic environment will be below one part per billion

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

Proposed name: Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution

The full CMC review of this NDA will be done by Dr. Caroline Strasinger.

B. Critical issues for review

--The applicant requests an 18-month expiration dating period, but has submitted only three months of stability data. Since the applicant was advised at a meeting with FDA in June of 2012 (see meeting minutes in DARRTS) that three months of data would be sufficient, we will accept this application with its limited stability data set and will base expiration dating on additional stability data that will be provided within the first three months of the review clock.

--Since the application claims that the container is (b) (4)

- (b) (4)

--Since administration instructions call for dissolution of the powder in water or apple juice (and possibly other vehicles), the application should be scrutinized to determine whether

sufficient stability studies have been conducted to establish stability of the product in all recommended dissolution media over the required time frame.

--It is interesting that the release specification requires testing for (b) (4). Since this is an excipient (b) (4) it should be interesting to determine why this testing is required

D. Comments for 74-day letter

You have submitted only three months of stability data, which is insufficient for expiration dating your product. We will accept additional stability data while the product is under review using the submission schedule you propose in the submission: *stability results through nine months of storage under long-term conditions and six months of storage under accelerated conditions can be submitted during the first 3-months of application review.*

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

4/9/2013
Date

Moo-Jhong Rhee, PhD
Branch Chief

Name and Address	Contact	Registration Number (CFN)	DMF number	Manufacturing Steps and/or Type of Testing
(b) (4)			NA	<u>Manufacture:</u> Drug substance <u>Control testing:</u> Drug Substance - In-process testing and Release testing
			NA	<u>Manufacture:</u> Drug substance <u>Control testing:</u> Drug substance - In-process testing and Release testing
			NA	<u>Manufacture:</u> Drug product <u>Control:</u> In-process release and excipients testing. Drug product - Labeling and Packaging.

Name and Address	Contact	Registration Number (CFN)	DMF number	Manufacturing Steps and/or Type of Testing
BioMarin Pharmaceutical Inc. BioMarin Novato Campus 46 Galli Drive, Novato, CA 94949	Robert Baffi, Ph.D. Executive Vice President, Technical Operations 105 Digital Drive Novato CA 94949 Tel 415-506-6790 Fax 415-382-7889 rbaffi@bmm.com	3004079983	NA	<u>Control testing:</u> Drug substance and drug product - Release testing and Stability testing
(b) (4)			NA	<u>Finished Product:</u> Warehousing and Distribution
			NA	NA

NA = not available

NDA Number: 205-065 **Supplement Number and Type:** Original **Established/Proper Name:** sapropterin dihydrochloride
Applicant: BioMarin Pharmaceutical Inc. **Letter Date:** **Stamp Date:** February 8, 2013

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	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
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? This question is not applicable for synthesized API.			Not applicable

7.	<p>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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	√		By reference to NDA 22181
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		By reference to NDA 22181
14.	Does the section contain information regarding the characterization of the DS?	√		By reference to NDA 22181
15.	Does the section contain controls for the DS?	√		By reference to NDA 22181
16.	Has stability data and analysis been provided for the drug substance?	√		By reference to NDA 22181
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	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?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?	√		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		Data has been provided as agreed in a meeting between the company and FDA
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		No separate validation package has been submitted, but there appears to be sufficient methods validation information in the body of the submission

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not required

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	√		

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

April 9, 2013
 Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Branch Chief
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

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/s/

MARIE KOWBLANSKY
04/09/2013

MOO JHONG RHEE
04/09/2013
Chief, Branch IV

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	205065
Submission Date	February 7, 2013
Product name, generic name of the active	Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution
Dosage form and strength	Powder for Oral Solution, 100 mg
Route of Administration	Oral
Applicant	BioMarin Pharmaceutical Inc.
Clinical Division	Division of Gastroenterology Drug Products
Type of Submission	505 (b)(1) NDA
Biopharmaceutics Reviewer	Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Team Leader	Tapash Ghosh, 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).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		Section 3.2.P.2.2.3 Physicochemical and Biological Properties
2.	Is the dissolution test part of the DP specifications?	x		Section 3.2.P.5, Specifications Table 3.2.P.5.1.1, Drug Product Release Specifications
3.	Does the application contain data to support the proposed dissolution acceptance criteria		x	N/A, the acceptance criteria are the same for the approved Kuvan (sapropterin dihydrochloride) Tablets, 100 mg NMT ^(b) ₍₄₎ % (Q) at 15 minutes
4.	Does the application contain the dissolution method development report?		x	The Applicant used the dissolution method approved for Kuvan (sapropterin dihydrochloride) Tablets
5.	Does the application contain data on the discriminating ability of the dissolution method		x	See previous comment
6.	Is there a validation package for the analytical method and dissolution methodology?		x	See previous comment
7.	Does the application include a biowaiver request?	x		The Applicant requested a biowaiver per 21 CFR 320.22 (b)(3)(i), and per the Type C meeting for NDA 022181, Kuvan (sapropterin dihydrochloride) Tablets (June 21, 2012)
8.	Does the application include an IVIVC model?		x	

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

9.	Is information such as BCS classification mentioned, and supportive data provided?		x	
10.	Is information on mixing the product with foods or liquids included?	x		Comparative osmolarity data in water and apple juice were submitted for Kuvan Tablets and Kuvan Powder for Oral Solution. The draft labeling indicates that Kuvan Oral Powder should be administered orally with food, which is similar to the approved label for Kuvan Tablets.
11.	Is there any <i>in vivo</i> BA or BE information in the submission?		x	
12.	Does the application include <i>in vitro</i> alcohol interaction studies?		x	

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
13.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing 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 filing comments to be sent to the Applicant.			Not applicable
16.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See potential review issues described below

BIOPHARMACEUTICS GENERAL SUMMARY:

BioMarin currently markets an approved Kuvan (sapropterin dihydrochloride) Tablet, 100 mg, under NDA 022181 (approved December 13, 2007). Kuvan Tablets should be dissolved in 4 – 8 oz. (120 – 140 mL) of water or apple juice and taken within 15 minutes of dissolution. Kuvan tablets are administered orally with food to increase absorption. BioMarin has developed a new powder formulation for administration as an oral solution to be packaged in a unit dose packet. Kuvan powder formulation is designed to improve the taste, flavor and appearance of sapropterin dihydrochloride, and is expected to

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

offer a convenient alternative to tablets. The powder formulation comprises ingredients that dissolve completely in water and offers the benefit of short reconstitution time and solution clarity upon powder dissolution. Kuvan Powder is packaged in an individual two inch square, white, printed, multi-layered, (b) (4) laminate packet which is heat sealed on four sides. A comparison of the Kuvan Tablet and Powder compositions is below:

Ingredient	Kuvan Powder Formulation for Oral Solution		Kuvan Tablet	
	%	Amount per packet (mg)	%	Amount per tablet (mg)
Sapropterin dihydrochloride	(b) (4)	100.0	(b) (4)	100.00
Mannitol	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Crospovidone	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Dibasic Calcium Phosphate (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Riboflavin (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Stearyl Fumarate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucralose	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Potassium Citrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Ascorbic acid	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total	100.0%		100.00%	

A Type C meeting was held on June 21, 2012 to discuss the Biowaiver for Kuvan Powder.¹ In response to the Applicant's query if Kuvan Powder is eligible for a biowaiver, the FDA requested the Applicant submit information/justification to address the following concerns:

1. There is evidence in the scientific literature, although not totally conclusive, that sucralose may potentially affect the absorption and bioavailability of drugs (Abou-Donia et al. 2008, Brusic et al. 2009). This may apply to your product depending on the elimination pathway of sapropterin dihydrochloride.
2. Your proposed product (after it is dissolved in water or apple juice) may have a markedly different osmolarity compared to the reference product, potentially impacting the bioavailability of sapropterin dihydrochloride.

¹ DARRTS: NDA 022181, TRAN-ZWANETZ, CATHERINE A, Submit/Final Date: 07/20/2012, COR-MEET-03(Meeting Minutes)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Potential review issues to be forwarded to the Applicant for the 74-day letter:

1. Please submit the complete dissolution data for Kuvan (sapropterin dihydrochloride) Powder for oral solution, which include the individual data, mean, % CV, dates of dissolution testing, and dissolution profiles.
2. Please submit the dissolution method validation report for the Kuvan powder drug product.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 205065 is fileable. The ONDQA Biopharmaceutics team will further assess this NDA to determine if the biowaiver may be granted.

{See appended electronic signature page}

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

03/14/13
Date

{See appended electronic signature page}

Tapash Ghosh, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

03/14/13
Date

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/s/

KELLY M KITCHENS
03/14/2013

TAPASH K GHOSH
03/14/2013