CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-181

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: November 21, 2007

To: NDA 22-181

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-181 Kuvan (Sapropterin Dihydrochloride) Tablets, BioMarin Pharmaceutical Inc.

I have assessed the ONDQA review of NDA 22-181, and the review amendment for the manufacturing site acceptability. I concur with the approval recommendation from a CMC perspective.

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/s/

Elaine Morefield
11/21/2007 02:30:25 PM
CHEMIST

MEMORANDUM

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

DATE: **November 21, 2007**

TO: **NDA 22-181**

FROM: **Yichun Sun**
Review Chemist, ONDQA

SUBJECT: **Update of Establishment Evaluation Status**
NDA 22-181, Kuvan™ (sapropterin dihydrochloride) Tablets

Recommendation and Conclusion on Approvability:

This application (NDA 22-181) is recommended for approval from the perspective of Chemistry, Manufacturing, and Controls. All manufacturing and testing facilities were found to be acceptable by the Office of Compliance as recommended by C. Cruz on November 21, 2007. The EER Summary Report is attached below:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application: NDA 22-181/000 Sponsor: BIOMARIN PHARMACEUTICALS
Org Code: 180 NO CITY, XX
Priority: 1P
Brand Name: SAPROPTERIN DIHYDROCHLORIDE
Stamp Date: 25-MAY-2007 Estab. Name:
PDUFA Date: 25-NOV-2007 Generic Name: SAPROPTERIN DIHYDROCHLORIDE
Action Goal: Dosage Form: (TABLET)
District Goal: 25-JAN-2008 Strength: 100 MG

FDA Contacts:	L. MULLINS ATHEY	Project Manager (HFD-800)	301-796-2096
	Y. SUN	Review Chemist	301-796-1388
	M. KOWBLANSKY	Team Leader	301-796-1390

Overall Recommendation: ACCEPTABLE on 21-NOV-2007 by C. CRUZ (HFD-323) 301-827-9013

Establishment: CFN: FEI:

BIOMARIN PHARMACEUTICALS INC
46 GALLI DRIVE
NAVATO, CA 94949

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 21-NOV-07
Decision: ACCEPTABLE
Reason:

Establishment: CFN: FEI:

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 08-NOV-07
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [redacted] FEI: [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTX OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 08-JUN-07
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Establishment: CFN: 1224701 FEI: 1000513191

LYNE LABORATORIES INC
10 BURKE DR
BROCKTON, MA 02301-5505

DMF No: AADA:

Responsibilities: [redacted]

Profile: TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 15-OCT-07
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [redacted] FEI: [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JUN-07
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI:

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 19-NOV-07
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [redacted] FEI: [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 15-JUL-07
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [redacted] FEI: [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

[redacted]

Profile: CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 11-JUN-07
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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/s/

Yichun Sun
11/21/2007 02:30:21 PM
CHEMIST

Elaine Morefield
11/21/2007 02:32:27 PM
CHEMIST
Signing for Moo-Johng Rhee.

NDA 22-181

Kuvan™ (sapropterin dihydrochloride) Tablets

BioMarin Pharmaceutical Inc.

Yichun Sun Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 22-181
For the Division of Gastroenterology Products
(HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA: #22-181

2. REVIEW #: 1

3. REVIEW DATE: 13-November-2007

4. REVIEWER: Yichun Sun Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 69,708	13-August-2004
EOP 2 meeting Memorandum (IND 69,708)	22-November-2004
Pre-NDA meeting minutes (IND 69,708)	12-October-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-May-2007
Amendment (BC)	30-July-2007
Amendment (BC)	29-August-2007
Amendment (BC)	24-September-2007
Amendment (BL)	27-September-2007
Amendment (BC)	10-October-2007
Amendment (BC)	26-October-2007
Amendment (BL)	29-October-2007
Amendment (BC)	16-November-2007

7. NAME & ADDRESS OF APPLICANT:

Name: BioMarin Pharmaceutical Inc.

Address: 105 Digital Drive
Novato, CA 94949

Representative: Ruhi Ahmed Ph.D.

Telephone: 415-506-6735

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Kuvan™
b) Non-Proprietary Name (USAN): Sapropterin Dihydrochloride
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Priority Review

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

10. PHARMACOL. CATEGORY: Phenylalanine hydroxylase-directed cofactor, indicated to treat Phenylketonuria

11. DOSAGE FORM: Immediate Release Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

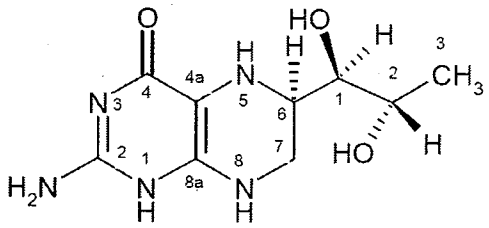
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

(6R)–2–amino–6[(1R,2S)–1,2–dihydroxypropyl]–5,6,7,8–tetrahydro–4(1H)–pteridinone dihydrochloride. (Chemical Abstracts Service Nomenclature).

(6R)–2–amino–6(3R,2S)–dihydroxypropyl]–4–oxo–5,6,7,8–tetrahydropteridine dihydrochloride. (IUPAC Nomenclature)



• 2 HCl

Structural Formula of Sapropterin Dihydrochloride

Empirical formula: $C_9H_{15}N_5O_3 \cdot 2HCl$

Molecular weight: 314.17

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			4	Adequate	NA	
	III			4	Adequate	NA	
	III			1	Adequate	12-Nov.-2007	Y. Sun
	III			1	Adequate	12-Nov.-2007	Y. Sun
	III			1	Adequate	12-Nov.-2007	Y. Sun
	III			4	Adequate	NA	

[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: NA

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	N/A	----	----
DMETS	N/A	----	----
EA	Categorical Exclusion Acceptable	See Review Date Above	Y. Sun
Microbiology	N/A	----	----

The Chemistry Review for NDA 22-181

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval from the Chemistry, Manufacturing, and Controls perspective with Establishment Evaluation pending.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance, sapropterin dihydrochloride, used in Kuvan™ (sapropterin dihydrochloride) Tablets, is a synthetic analog of the dihydrochloride salt of naturally-occurring tetrahydrobiopterin (6R-BH4). It is only biochemically active in the R enantiomer form. The chemical name of sapropterin dihydrochloride is: (6R)–2–amino–6[(1R,2S)–1,2–dihydroxypropyl]–5,6,7,8–tetrahydro–4(1H)–pteridinone dihydrochloride. Sapropterin dihydrochloride drug substance appears as off-white to light yellow crystals or crystalline powder. Sapropterin dihydrochloride is very soluble in water (> 1 g/mL). It is sparingly soluble in methanol (10 mg/mL) and ethanol (0.9 mg/mL), and practically insoluble (<0.1 mg/mL) in aprotic solvents such as diethyl ether. [redacted]

[redacted] The drug substance is stable in solid, however, it is not stable in aqueous solutions especially at relatively high pHs. Degradation pathways is predominately oxidative, with [redacted] Sapropterin dihydrochloride manufactured by Daiichi Suntory Pharma is the approved drug substance used in a commercially-available drug product, Biopten® Granules in Japan to treat patients with primary BH4 deficiency.

Drug Product

The drug product, Kuvan™ (sapropterin dihydrochloride) Tablets, is a round, off-white to light yellow mottled tablet, debossed with "177" on one side. Each tablet is 3/8-inch (9.5 mm) in diameter and 4 – 5 mm in thickness, and contains 100 mg of sapropterin dihydrochloride

(equivalent to 76.8 mg of sapropterin). The sapropterin dihydrochloride tablets are manufactured by [redacted] The sapropterin dihydrochloride tablets are packaged into high density polyethylene bottles to permit distribution of 120 tablets per bottle.

Several changes were made to the to-be-marketed sapropterin dihydrochloride tablets from the tablets used in Phase III clinical trials. The changes are summarized in the following Table.

Summary of Changes Made between Tablets Used in Phase III Clinical Studies and Tablets for Commercial Production

Description of changes	Tablets (Formulation A) used in pivotal studies		Tablets (Formulation B) of the commercial product	Level defined in SUPAC IR
	PKU-003	PKU-006		
[redacted]				
[redacted]				
Sodium stearyl fumarate	[redacted]			
Tablet debossment	[redacted]		Debossed with "177"	
Manufacturing site	[redacted]		Lyne	
Manufacturing process	[redacted]			
Manufacturing scale	[redacted]		production	

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

The sapropterin dihydrochloride tablets are indicated to reduce blood phenylalanine (Phe) levels [redacted] in patients with hyperphenylalaninemia (HPA) due to Phenylketonuria (PKU). The dosage should be adjusted within the range of 5 to 20 mg/kg/day according to the goals of therapy and the needs of the patient. Blood Phe must be monitored regularly during the therapy. The required number of sapropterin dihydrochloride tablets for daily dose should be dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice and taken within 15 minutes after dissolution.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval from the perspective of Chemistry, Manufacturing, and Controls (with Establishment Evaluation pending) based on the following basis:

Drug Substance:

- The chemical structure of the drug substance, sapropterin dihydrochloride, has been elucidated. The physicochemical properties of the drug substance have also been studied.
- The quality of the drug substance is ensured by controlling the starting materials and intermediate materials, implementing adequate in-process controls during manufacturing, and setting appropriate specifications.
- The specifications for the drug substance have been justified.
- The reference standard used for quality control of the drug substance has been qualified.
- The test methods used for identification, and quantitation of the drug substance and its impurities have been validated.
- The primary container [redacted] used for drug substance conforms to 21 CFR 177.1520.
- Stability data provided indicates that the drug substance is stable for at least 12 months [redacted]

Drug Product:

- The sponsor provided adequate information for the composition of the drug product, sapropterin dihydrochloride tablets. The drug substance and excipients are controlled to ensure the quality and performance of the drug product.
- Adequate in-process controls are implemented to ensure the quality of the drug product.
- The test methods used for identification and quantitation of the drug product and its impurities were validated.
- The proposed specifications are adequate for ensuring the safety and quality of the drug product.
- The packaging materials chosen are safe; and can adequately hold and protect the drug product.
- An expiration period of 18 months for tablets in bottles is recommended based on 9 month stability data provided.

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer _____ Date

Marie Kowblansky, Ph.D.
Pharmaceutical Assessment lead _____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief _____ Date

Linda Athey
Project Manager _____

C. CC Block

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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/s/

Yichun Sun
11/19/2007 11:26:38 AM
CHEMIST

Moo-Jhong Rhee
11/19/2007 12:22:01 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division:	Division of Gastroenterology Products
NDA:	22-181
Applicant:	Biomarin Pharmaceuticals
Stamp Date:	5/25/2007
Received by PAL:	6/5/2007
Review Date:	6/29/2007
PDUFA Date:	11/25/2007
Filing Meeting:	7/13/2007
Proposed Trademark:	To be determined
Established Name:	sapropterin dihydrochloride
Dosage Form:	Immediate release tablets
Route of Administration:	oral
Indication:	phenylketonuria, tetrahydrobiopterin deficiency
P.A.L:	Marie Kowblansky, PhD

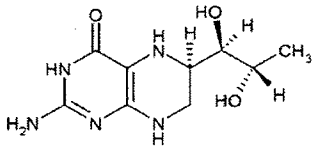
	YES	NO
ONDQA Fileability:	☒	
Comments for 74-Day Letter		☒

A. Summary

Sapropterin Dihydrochloride Tablets is an immediate release product intended for oral administration to reduce blood phenylalanine levels in patients with Phenylketonuria [redacted] The tablets contain 100 mg sapropterin dihydrochloride (equivalent to 76.8 mg sapropterin base) and are to be administered once daily based on patient body weight (100 mg/kilogram). Administration instructions call for swallowing the tablets [redacted] dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice. This product has been studied under IND 69,708, granted Orphan Drug Status in January of 2004, and designated Fast Track in January of 2006

Drug Substance

Sapropterin dihydrochloride,



• 2 HCl

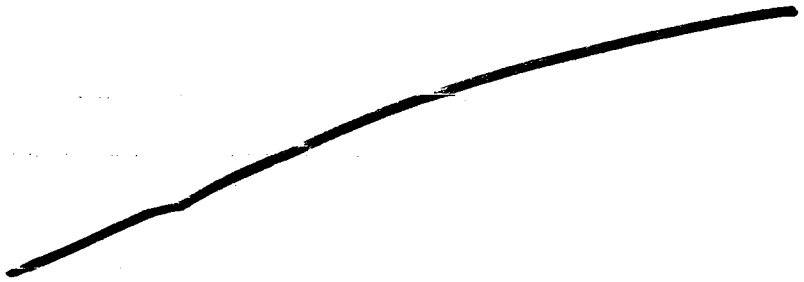
the active drug substance, is the dihydrochloride salt of synthetically prepared tetrahydrobiopterin. The name sapropterin is specific to the 6-R diastereomer of tetrahydrobiopterin. According to the applicant, the 6R form is the biologically active diastereomer, being a cofactor of phenylalanine hydroxylase (PAH);

[redacted]

Sapropterin dihydrochloride is a crystalline powder, which is very soluble in both acidic and basic aqueous solution, sparingly soluble in methanol or ethanol, and practically insoluble in aprotic solvents. It is hygroscopic and needs protection from moisture during storage. Although it exhibits polymorphism, [redacted] While it is highly soluble in aqueous solution, it exhibits a low degree of absorption. Consequently, it is classified as a Class 3 material in the Biopharmaceutics Classification System (BCS).

The drug substance will be manufactured by two alternate suppliers, [redacted] but both will use the same route of synthesis (as appended to this review).

[redacted]



Drug Product

Sapropterin dihydrochloride Tablets (100 mg) will be marketed as an immediate-release solid oral dosage form, with the following composition

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim) 100 mg tablet	
		Amount per tablet (mg)	Percentage per tablet (%)
Sapropterin dihydrochloride	Active ingredient	100.00	[redacted]
Ascorbic acid, USP/Ph. Eur.	[redacted]		
Crospovidone, USP/Ph. Eur.			
Dibasic calcium phosphate, [redacted] USP/Ph. Eur.			
[redacted]			
Riboflavin, USP/Ph. Eur.			
Sodium stearyl fumarate, NF/Ph. Eur.			
Total		300.00 mg	100.00%

The tablets will be round, off-white to light yellow, and debossed with "177" on one side. They will be manufactured by Lyne Laboratories in Massachusetts, using the above formulation and a

From this preliminary evaluation of the NDA it is not clear whether this proposed commercial formulation was actually used in clinical trials or not. This will need to be determined during the complete review of the NDA.

. In support of this request, three months of stability data are provided for batches manufactured at Lyne Laboratories, using drug substance from and packaged in the commercial container/closure system (120-count bottle). Additional stability data for these batches (i.e., nine months of real-time and six months of accelerated data) will be provided while the application is under review. Also provided are of supportive stability data (real time and accelerated) from the clinical lots. However, data may or may not be useful as supporting data, since it is for product with a slightly different formulation, made by a different manufacturer, possibly using a different manufacturing method, and packaged in a different packaging configuration This will need to be closely scrutinized during the full NDA review.

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.)

B. Critical issues for review

-- The most critical issue requiring close evaluation in this application relates to all the different drug substance suppliers product manufacturers formulations, and manufacturing methods that were used in preparing the clinical supplies for the Phase 3 studies. The submitted information should be closely scrutinized to ensure that the proposed commercial product is comparable to the products used in pivotal clinical trials. At the end-of phase2 meeting in October of 2006, the sponsor indicated that a different method of manufacture would be used for the commercial product than used to prepare the phase 3 clinical supplies and the following advice was given by FDA:

> *"...The critical factor to consider is that the evaluations provide a linkage between the properties of the product used in clinical trials and the product that is produced at the proposed manufacturing sites. If the clinical samples were produced , you will need to provide a linkage through bioequivalence studies. However, if you can*

demonstrate that the drug substance is categorized as a Class I material in the Biopharmaceutics Classification System (BCS) system, the bioequivalence studies will not be necessary."

The fact that the drug substance has been categorized as a Class 3 compound requires not only CMC evaluation, but coordination with the Biopharm reviewer to determine if the proposed commercial product is sufficiently comparable to the product used in clinical trials.

-- The applicant defines ' [redacted] . It is not clear at which point in the manufacturing process the applicant plans to start expiration dating of the packaged product. This should be closely examined and made consistent with FDA practice.

-- Administration instructions call for dissolution of the tablet in water or apple juice. The stability of the product in these solvents should be demonstrated.

C. Comments for 74-Day Letter -- None

Marie Kowblansky, PhD Pharmaceutical Assessment Lead	6/29/2007 Date
Moo-Jhong Rhee, PhD Branch Chief	6/29/2007 Date

1 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

NDA 22-181 **Manufacturing Sites**

Drug Substance:

Name and Address	Technical Responsibility	FDA Establishment Number	Responsible Head
[redacted]			
[redacted]			
[redacted]			
[redacted]			
BioMarin Pharmaceutical Inc. 46 Galli Drive and 300 Bel Marin Keys Novato, CA 94949	Release Testing Stability Testing	3004079983	Robert Baffi, Ph.D. Senior Vice President, Technical Operations 105 Digital Drive Novato CA 94949

Drug Substance (continued)

Name and Address	Technical Responsibility	FDA Establishment Number	Responsible Head
[redacted]			
BioMarin Pharmaceutical Inc. 46 Galli Drive and 300 Bel Marin Keys Novato, CA 94949	Release Testing Stability Testing	3004079983	Robert Baffi, Ph.D. Senior Vice President, Technical Operations 105 Digital Drive Novato CA 94949

Drug Product

Name and Address	Technical Responsibility	FDA Establishment Number	Responsible Head
Lyne Laboratories 10 Burke Drive Brockton, MA 02301	[redacted]	1224701	Robert E. Tarallo Vice-President, Research and Development Lyne Laboratories 10 Burke Drive Brockton, MA 02301 508-583-8700 (phone) 508 583-9120 (fax) rtarallo@lyne.com
BioMarin Pharmaceutical Inc. 46 Galli Drive and 300 Bel Marin Keys Novato, CA 94949	Release and Stability Testing	3001226485	Robert Baffi. Ph.D. Senior Vice-President, Technical Operations 105 Digital Drive Novato CA 94949 Phone: 415-506-6790 Fax: 415-382-7889 rbaffi@bmrn.com
[redacted]			

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/s/

Marie Kowblansky
7/9/2007 09:38:14 AM
CHEMIST

Moo-Jhong Rhee
7/9/2007 04:06:58 PM
CHEMIST
Chief, Branch III