

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-256

CHEMISTRY REVIEW(S)

10/16/08

Memorandum to File

To: NDA 22-256; Savella™ (milnacipran hydrochloride) Tablets

From: Elsbeth Chikhale, Ph.D. – Chemistry Reviewer

Subject: EER status

Date: October 16, 2008

Applicant: Cypress Bioscience Inc.

Proposed Proprietary Name: Savella

Established Name: milnacipran hydrochloride

Dosage form and strength: 12.5 mg/tablet; 25 mg/tablet; 50 mg/tablet; 100 mg/tablet

Route of Administration: oral

Indications: Treatment of fibromyalgia syndrome

Note:

The Office of Compliance has issued an overall approval recommended for this NDA. There are no remaining CMC issues and NDA 22-256 is recommended for APPROVAL from CMC perspective.

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/s/

Elsbeth Chikhale
10/16/2008 08:47:45 AM
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Blair Fraser
10/16/2008 10:03:11 AM
CHEMIST

9/2/08

Savella®
(milnacipran HCl)
Tablet

NDA 22-256

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Cypress Bioscience Inc.
4350 Executive Drive
Suite 325
San Diego, CA 92121

Indication: Treatment of fibromyalgia syndrome (FMS)

Presentation: Film-coated, immediate release, tablet for oral administration available in four strengths available as follows:

- 12.5 mg tablets are round, pink, "F" on one side, "L" on other;
- 25 mg tablets are round, white to off-white, "FL" on one side, "25" on other;
- 50 mg tablets are oval, green, "FL" on one side, "50" on other;
- 100 mg tablets are oval, blue, "FL" on one side, "100" on other;

Tablets are packaged in [] at 60 or 180 count, and in [] unit blisters.

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EER Status: Pending

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency not requested.

Original Submission: 18-DEC-2007

Post-Approval Agreements: None

Drug Substance:

The drug substance, milnacipran HCl, is a [] New Molecular Entity (NME) with an empirical formula of $C_{15}H_{23}ClN_2O$ and a molecular weight of 282.8. Milnacipran HCl has [] and is a racemic mixture of the R- and S- enantiomers. Known chemically as Z-2-aminometnyl-1-phenyl-N, N- diethylcyclopropane -carboxamide, hydrochloride, it is a white to almost-white, [] powder with a melting range of 179°C. It is freely soluble in water, methanol, ethanol, [] chloroform, methylene chloride, and very slightly soluble in ether. The []

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The chemistry, manufacturing, and controls information for the drug substance is appropriately referenced, is described in Pierre Fabre Medicament – Plantes et Industrie Type II Master File 11,501, has been reviewed, and is concluded to be adequate.

The structure of milnacipran HCl was elucidated using several analytical and spectrophotometric techniques, including elemental analysis, infrared spectroscopy (IR), multinuclear (¹H and ¹³C) magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, mass spectrometry, single-crystal X-ray crystallography, and X-ray powder diffraction spectroscopy (XRPD).

The proposed release specification for milnacipran HCl includes appearance, solubility, identification by IR spectroscopy, identification by reverse phase – high performance liquid chromatography (RP-HPLC), identification by angular (optical) rotation, chloride identification, melting range, water content by [] heavy metals, residue on ignition, residual solvents by gas chromatography (GC), impurities and related substances by RP-HPLC, [] content by thin layer chromatography and assay by RP-HPLC. The proposed regulatory methods are either compendial or were developed and validated for their intended purpose. The primary reference standard for drug substance, manufactured by commercial process, has been characterized by the proposed regulatory methods as well as additional methods. The impurity and degradation profiles have been investigated.

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Adequate stability data were provided to support a [] test period for the bulk drug substance stored inside [] contained in cardboard boxes at controlled room temperature, 25°C /60%RH.

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Conclusion: Drug substance is acceptable.

Drug Product:

Savella (milnacipran HCl) tablets are film-coated, immediate release, tablets available in four strengths of 12.5 mg, 25 mg, 50 mg, and 100 mg. Tablets are uniquely colored and labeled on both sides to distinguish the various strengths. Tablets are packaged in [] bottles, at 60 or 180 count and in [] unit blisters.

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The drug product is manufactured beginning with []

[] final packaging. Adequate information on the drug product manufacture has been provided.

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The composition of the 12.5 mg strength, round tablet is milnacipran HCl (12.5 mg), [] dibasic calcium [] USP [] povidone [] USP [], carboxymethylcellulose calcium USP [] colloidal silicon dioxide USP [] magnesium stearate NF [] and talc USP [] to give a core tablet weight of [] Following [] film-coating, the total film-coated tablet weight is [] The four strengths are composed of this [] which leads to film-coated tablet weights of [] for the 25 mg strength, [] mg for the 50 mg strength, and [] mg for the 100 mg strength.

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The release specification for drug product includes: description, identification by RP-HPLC, identification by UV, content uniformity, water content, assay by RP-HPLC, degradation products by RP-HPLC, and dissolution. The milnacipran HCl reference standard for drug

product is the same as that for drug substance. The proposed regulatory methods are either compendial or were developed and validated for their intended purpose.

The stability data support the requested expiration dating of 24 months for all strengths of drug product stored at controlled room temperature conditions [25° C (77° F)]; excursions permitted to 15-30° C (59-86° F)], and packaged in [] bottles and [] unit blisters.

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Conclusion: Drug product is acceptable.

Additional Items:

- The applicant agreed to continue the primary stability studies on the three commercial scale lots of each presentation of drug product to firmly establish the proposed shelf life.
- The sponsor agreed to place on stability the first three commercial production lots of each presentation of drug product of drug product, following the approved stability protocol.
- The sponsor agreed to place on stability at least one commercial production lot of each presentation of drug product, per year, following the approved stability protocol.
- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
- The analytical methods used for testing (release, stability, and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.
- Master batch records were provided electronically in amendments (28-FEB-2008 and 2-SEP-2008) and deemed acceptable.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval**, pending an overall acceptable recommendation from the Office of Compliance.

Blair A. Fraser, Ph.D.
Director
DPA /ONDQA

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Blair Fraser
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8/29/08



CHEMISTRY REVIEW



NDA 22-256

**Savella®
(milnacipran HCl)
Tablets**

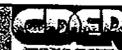
Cypress Bioscience, Inc.

**Elsbeth Chikhale, Ph.D.
ONDQA – DPA I – Branch II
for
Division of Anesthesia, Analgesia and Rheumatology
Products**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment.....	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Milnacipran HCl, Pierre Fabre Medicament].....	10
P DRUG PRODUCT [-----, Tablets]	14
A APPENDICES.....	66
R REGIONAL INFORMATION.....	66
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	67
A. Labeling & Package Insert	67
B. Environmental Assessment Or Claim Of Categorical Exclusion	67
III. List Of Information Requests Communicated	68



Chemistry Review Data Sheet

1. NDA 22-256
2. REVIEW #: 1
3. REVIEW DATE: 29-AUG-2008
4. REVIEWER: Elsbeth Chikhale, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	18-DEC-2007
Amendment to original ¹	17-APR-2008
Amendment to original ²	28-JUL-2008

- 1) The 4/17/08 amendment provides for updated stability dated and statistical analysis of the data as requested in the filing communication dated 2/20/2008.
- 2) The 7/28/08 amendment provides for a response to an information request from the Agency dated 7/21/08.

7. NAME & ADDRESS OF APPLICANT:

Name: Cypress Bioscience, Inc.
Address: 4350 Executive Drive, Suite 325
San Diego, CA 92121
Representative: Michael Olchaskey, PharmD (Director, Regulatory
Affairs of Forest Laboratories Inc.: Agent)
Telephone: (201) 386 – 2142 (Agent: Forest Laboratories, Inc)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Non proposed
b) Non-Proprietary Name (USAN): Milnacipran HCl
c) Code Name/#: F2207 for racemic milnacipran HCl
CAS 101152-94-7 (Milnacipran HCl)
CAS 92623-85-3 (for free base)

d) Chem. Type/Submission Priority:

- Chem. Type: 1 (new molecular entity)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.

10. PHARMACOL. CATEGORY: norepinephrine and serotonin reuptake inhibitor

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 12.5 mg/tablet, 25 mg/tablet, 50 mg/tablet, and 100 mg/tablet

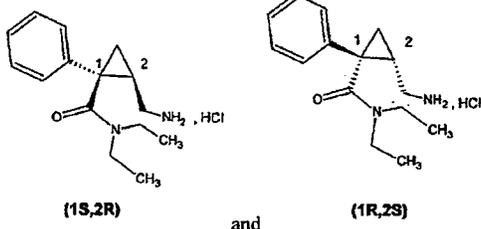
13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product Form Completed
 Not a SPOTS product

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





CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemical name: Z-2-aminomethyl-1-phenyl-N, N-diethylcyclopropane-carboxamide, hydrochloride

Molecular Formula: C₁₅H₂₃ClN₂O

Molecular Weight: 282.8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
11501	II	Pierre Fabre Medicament-Plates & Industrie	Melnacipran HCl Drug substance	1	Adequate	April 29, 2008	Reviewed by Craig Berta, Ph.D.
[]	IV			1	Adequate	August 29, 2008	Reviewed by Elsbeth Chikhale, Ph.D.
[]	III			3	Adequate	April 20, 2004	Reviewed by Sarah Pope, Ph.D.
[]	III			4	N/A		
[]	III			3	Adequate	December 7, 2004	Reviewed by Rapti Madurawe, Ph.D.
[]	III			1	Adequate	July 31, 2008	Reviewed by Elsbeth Chikhale, Ph.D.
[]	III			3	Adequate	September 15, 2000	Donald Klein, Ph.D. as part of []
[]	III			3	Adequate	September 1, 1999	
[]	III			3	Adequate	March 12, 1996	Reviewed by Andrew Langowski, Ph.D.
[]	III			3	Adequate	November 19, 2007	Reviewed by Yichun Sun, Ph.D.

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

[]	III

4	N/A		
3	Adequate	December 8, 2006	Reviewed by Gene Holbert, Ph.D.
4	N/A		
3	Adequate	January 7, 2004	Reviewed by Monica Cooper, Ph.D.
3	Adequate	April 20, 2004	Reviewed by Sarah Pope, Ph.D.
4	N/A		

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- ¹ Action codes for -
- 1 - DMF Reviewed.
 - Other codes indicate why the DMF was not reviewed, as follows:
 - 2 - Type 1 DMF
 - 3 - Reviewed previously and no relevant 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)

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,736	Milnacipran HCl capsules

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	Acceptable	8/29/08	Elsbeth Chikhale, Ph.D.
DMEDP	pending		
DDMAC	Labeling comments are provided in the review	4/18/08	Michelle Safarik, PA-C
EA	Categorical exclusion granted (consult not needed)	8/29/08	Elsbeth Chikhale, Ph.D.
Microbiology	N/A		

19. ORDER OF REVIEW: N/A

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The Chemistry Review for NDA 22-159

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for APPROVAL pending final labeling (which will be done in coordination with the clinical division) and pending an overall acceptable recommendation from OC.

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 and Drug Substance

1) Drug Product

The drug product is an immediate release film-coated tablet for oral administration, with 4 dose-proportional strengths: 12.5 mg/tablet, 25 mg/tablet, 50 mg/tablet, and 100 mg/tablet. This NDA is submitted electronically as a 505(b)1. The proposed drug product is indicated for the treatment of Fibromyalgia Syndrome. In the clinical development program, milnacipran capsules were used in phase 1 and pivotal phase 3 studies. On August 14, 2006 the applicant has requested a waiver to conduct *in vivo* bioequivalence studies between milnacipran HCl immediate release capsules and the proposed tablets (IND 63,736 amendment #176). Because, milnacipran HCl is a highly soluble and highly permeable and because the *in vitro* dissolution data show that milnacipran capsules and tablets dosage forms are rapidly dissolving, a biowaiver was granted by FDA on December 13, 2006. The container closure system for the 12.5 mg and 25 mg strength tablets consists of 60-count and 180-count,

The container closure system for the 50 mg strength tablets consists of 60-count and 180-count bottle with . The container closure system for the 100 mg strength tablets consists of 60-count bottle with . In addition, a blister unit packaging configuration is also proposed presented in a

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X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Ali Al-Hakim
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1/25/08

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

OND Division: Anesthesia, Analgesia and Rheumatology
NDA: 22-256
Applicant: Forest Research Laboratories
Stamp date: December 19, 2007
PDUFA Date: October 19, 2008
Trademark: Not proposed yet
Established Name: Milnacipran HCl
Dosage Form: Coated tablet
Route of Administration: Oral
Indication: Treatment of fibromyalgia syndrome (FMS)

Pharmaceutical Assessment Lead: Danae Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	<u>√</u>	—
Comments for 74-Day Letter:	<u>√</u>	—

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A. Summary

Background

The active pharmaceutical excipient (API), Milnacipran, is a New Chemical Entity (NME); it is a novel norepinephrine-serotonin reuptake inhibitor (NSRI) being co-developed by Forest Research Institute and Cypress Bioscience, Inc.

Milnacipran is proposed for oral administration for the treatment of fibromyalgia syndrome (FMS).

Milnacipran HCl, 12.5 mg, 25 mg, 50 mg, and 100 mg are immediate release film-coated tablets. The tablets of the four strengths are compositionally proportional.

The inactive ingredients consist of dibasic calcium phosphate, povidone, carboxymethylcellulose calcium, colloidal silicon dioxide, talc, magnesium stearate and coatings. A qualitative and quantitative listing of the components used in the manufacture of milnacipran HCl tablets, along with the function and quality standard of each component is provided in the NDA.

The drug product will be packaged in two packaging configuration: bottles and blister packs.

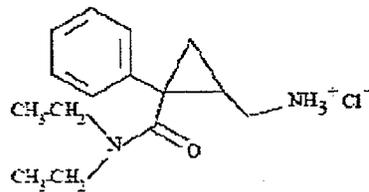
Milnacipran (Z-2-aminomethyl-1-phenyl-N, N-diethylcyclopropane-carboxamide, hydrochloride [HCl]), a reuptake inhibitor of both norepinephrine (NE) and serotonin (5-hydroxytryptamine [5-HT]), in vitro, ex vivo, and in vivo, is a cis-(d,l) racemate (Z form) composed of two (d- and l-) enantiomers. See chemical structure below.

Drug Substance:

The drug substance, Milnacipran HCl, DMF # 11501, includes detailed description of the synthesis, manufacturing process, process controls and process validation for milnacipran HCl. Letter of authorization was provided for this DMF in the NDA. However, the NDA contains some information related to the drug substance which includes:

Name: (1RS, 2SR)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride

Structure, molecular formula and molecular weight:



Molecular Formula: C₁₅H₂₃ClN₂O

Molecular Weight: 282.8

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General Physical and chemical properties for the API which include:

- Partition Coefficient
- Crystalline form
- pH and pKa
- Hygroscopicity
- Solubility (freely soluble in water, methanol, ethanol, chloroform and methylene chloride and very slightly soluble in diethyl ether).
- Appearance
- Polymorphism (no polymorphic forms by X-ray analysis)

The applicant reported that the synthesis process of Milnacipran as described in Drug Master File 11501 yields only the [] Therefore, DMF 11501 needs to be reviewed and evaluated accordingly because this is a new DMF and there is no CMC review on file.

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The manufacture, analytical testing and release of milnacipran HCl drug substance is performed at the following site:

Pierre Fabre Medicament
Plantes & Industrie
16 rue Jean Rostand
81603 Gaillac Cedex
France

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X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

D. Comments for 74-day Letter:

1. Provide confirmation that all sites are ready for cGMP inspection.
2. Provide statistical analysis of the stability test data in SAS format during early stage of the review cycle.
3. Provide a master (blank) batch record for the [redacted] of the 12.5 mg and 100 mg tablets and selected representative executed batch records. If provided in the NDA, identify the Module and Section of the NDA which includes the batch records.

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- E. Recommendation for fileability:** The NDA is fileable based on sufficient amount of CMC information for the drug substance and drug product. The data were provided according to FDA and ICH guidelines for submitting CMC information for a New Drug Application. See also fileability template, below.

Recommendation for Team Review: The NDA is recommended to be reviewed by two reviewers. The drug substance is an NME with a new Drug Master File, and the drug product contains significant pharmaceutical development, even though it is a solid oral, immediate release dosage form. Alternatively, a single, senior reviewer should be able to review the whole submission depending on the nature of his/her workload.

Consults:

The reviewer, in conjunction with the PAL should initiate the following consults/requests as early as possible (see file ability template below).

Danae Christodoulou
Pharmaceutical Assessment Lead

01/25/2008
Date

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

01/25/2008
Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?		√	This will be requested in the 75 day letter.
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested as per 21 CFR 25.31(b)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data with statistical analysis provided
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Reference to IND 63,736
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated?	√ √ √ NA		Clin. pharm Statistics DMETS/ODS Microbiology

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

DMF Number/Type	Holder	Description	LOA Included	Status
11501 II	Plantes & Industrie	Drug Substance	Yes	Pending
			Yes	Pending
			Yes	NA

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Danae Christodoulou
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Initial Quality Assessment

Ali Al-Hakim
1/25/2008 12:51:27 PM
CHEMIST