CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-585

CHEMISTRY REVIEW(S)

REV 3

NDA 21-585

Mucinex D
Guaifenesin and Pseudoephedrine HCl
Extended Release Tablets
(1200 mg/120 mg and 600 mg/60 mg)

Adams Laboratories

J. Salemme, Ph.D.
for
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-585
2. REVIEW #: 3
3. REVIEW DATE: 18-May-2004
4. REVIEWER: J. Salemme, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	4-Feb-2003
Response to 74-Day letter	30-Apr-2003

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date
Response to the Approvable Letter	24-Nov-2003
Amendment	6-May-2004

1. NAME & ADDRESS OF APPLICANT:

Name:	Adams Laboratories, Inc.
Address:	14801 Sovereign Road Fort Worth, TX 76155-2645
Representative:	D. Jeffrey Keyser, VP Development and Regulatory Affairs
Telephone:	817-786-1243

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name (Proposed): Mucinex D Regular Strength and Mucinex D Maximum Strength Extended Release Tablets

b) Non-Proprietary Name (USAN): Guaifenesin and Pseudoephedrine HCl Extended

c) Code Name/# (ONDC only): None

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not applicable
10. PHARMACOL. CATEGORY: expectorant and decongestant
11. DOSAGE FORM: Extended release tablets

12. STRENGTH/POTENCY:
Maximum strength: Guaifenesin (1200 mg) and pseudoephedrine hydrochloride (120 mg)
Regular strength: Guaifenesin (600 mg) and pseudoephedrine hydrochloride (60 mg)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx __X_OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM:
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

Guaifenesin:
See USP 26 for other chemical names, the structural formula, molecular formula, and molecular weight.

Pseudoephedrine hydrochloride:
See USP 26 for other chemical names, the structural formula, molecular formula, and molecular weight.

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs: See Chemistry Review No. 1. All were considered adequate.
B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER or Comment
Biometrics	Review not required.		
EES	Acceptable	16-Apr-2003	
Pharm/Tox	N/A		
Biopharm	Approved	Mar 2004 and May 2004	S. Suarez-Sharp, Ph.D.
LNC	N/A		
Methods Validation	See Chemistry Review #1.		
OPDRA	Acceptable		
EA	Acceptable		
Microbiology	Review not required.		

The Chemistry Review for NDA 21-585

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for approval with an expiration dating period of 18 months for drug product stored at controlled room temperature.

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 the Two Drug Substances

Mucinex D extended release tablets are uncoated, oval, bi-layer tablets. One layer, white in color, is an immediate release formulation that releases guaifenesin. The other layer, colored pink for Maximum strength and orange for Regular strength, is an extended release formulation that releases both pseudoephedrine hydrochloride and guaifenesin. Two strengths are proposed. These are Maximum strength tablets with 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride and a tablet weight of 1.6 g, and Regular strength tablets with 600 mg guaifenesin and 60 mg pseudoephedrine hydrochloride, tablet weight of 0.8 g. For both strength tablets, the white, immediate release layer is of identical size and composition. The strengths differ in the amount of material used to form modified release layer and in the colorant used in the modified release layer, with FD&C Red #40 used for maximum strength tablets and FD&C Yellow #6, used for regular strength tablets. Additionally, the strengths differ by the embossing that is performed on the immediate release layer, 1200 and 600 for the strengths, respectively.

The quality of the drug product is adequately controlled by the specification with tests for appearance, average tablet weight, average tablet thickness, friability, loss on drying, identification, assay, and dissolution for guaifenesin, identification, assay, and dissolution for pseudoephedrine, degradation products and content uniformity.

Stability data for batches of drug product produced with manufacturing changes show that friability failures observed with the original batches have been eliminated. Stability data provided to - months at [redacted] RH and to - months at [redacted] for these batches support an 18 month expiration dating period for drug product stored a controlled room temperature.

The drug substances, guaifenesin and pseudoephedrine hydrochloride, have been used in a number of OTC and approved products. DMF [redacted] describes the chemistry, manufacturing, and controls for guaifenesin, DMF [redacted] describes the chemistry, manufacturing, and controls for pseudoephedrine hydrochloride manafactured by [redacted] and DMF [redacted] describes the chemistry, manufacturing, and controls for pseudoephedrine hydrochloride manufactured by [redacted] The DMFs have been reviewed and the information is found to be acceptable.

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

The drug product is an extended release tablet containing an expectorant (guaifenesin) and a decongestant (pseudoephedrine hydrochloride). The maximum daily dose is 2400 mg guaifenesin and 240 mg pseudoephedrine hydrochloride.

C. Basis for Approvability or Not-Approval Recommendation

The CMC deficiencies conveyed to the sponsor in the Approvable letter have been satisfactorily addressed. Satisfactory release and stability data for both strengths of drug product manufactured with the improved manufacturing changes have been provided. Therefore, the application is recommended for approval with an 18-month expiration date for drug product stored at 25°C.

III. Administrative

A. Reviewer's Signature

ChemistName/Date:
J. Salemme, Ph.D., 18-May-2004

B. Endorsement Block

ChemistryTeamLeaderName/Date:	R. Lostritto, Ph.D.
ProjectManagerName/Date	Colette Jackson

C. CC Block

13 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- REV III

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/s/

Jean Salemme
5/27/04 12:25:34 PM
CHEMIST

Richard Lostritto
5/27/04 04:26:07 PM
CHEMIST

R+V2

NDA 21-585

Mucinex D
Guaifenesin and Pseudoephedrine HCl
Extended Release Tablets
(1200 mg/120 mg and 600 mg/60 mg)

Adams Laboratories

J. Salemme, Ph.D.
for
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-585
2. REVIEW #: 2
3. REVIEW DATE: 1-Oct-2003
4. REVIEWER: J. Salemme, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	4-Feb-2003
Response to 74-Day letter	30-Apr-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	30-June-2003
Response to IR letter	18-Aug-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Adams Laboratories, Inc.
Address:	14801 Sovereign Road Fort Worth, TX 76155-2645
Representative:	D. Jeffrey Keyser, VP Development and Regulatory Affairs
Telephone:	817-786-1243

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name (Proposed): Mucinex D Regular Strength and Mucinex D Maximum Strength Extended Release Tablets

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Guaifenesin and Pseudoephedrine HCl Extended Release Tablets

c) Code Name/# (ONDC only): None

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: NS

9. LEGAL BASIS FOR SUBMISSION: Not applicable
10. PHARMACOL. CATEGORY: expectorant and decongestant
11. DOSAGE FORM: Extended release tablets

12. STRENGTH/POTENCY:
Maximum strength: Guaifenesin (1200 mg) and pseudoephedrine hydrochloride (120 mg)
Regular strength: Guaifenesin (600 mg) and pseudoephedrine hydrochloride (60 mg)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx __X_OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM:
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

Guaifenesin:
See USP 26 for other chemical names, the structural formula, molecular formula, and molecular weight.

Pseudoephedrine hydrochloride:
See USP 26 for other chemical names, the structural formula, molecular formula, and molecular weight.

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs: See Chemistry Review No. 1. All were considered adequate.
B. Other Documents: None

1. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER or Comment
Biometrics	For batches mfd prior to manufacturing changes: A [redacted] month expiry based on assay is estimated for both strengths.		T. Gao September 2003
EES	See Chemistry Review 1. Acceptable as of 16-Apr-2003.		
Pharm/Tox	N/A		
Biopharm	Pending		S. Suarez
LNC	N/A		
Methods Validation	Will not be requested in this review cycle.		
OPDRA	See Chemistry Review 1.		
EA	See Chemistry Review 1		
Microbiology	No review necessary.		

The Chemistry Review for NDA 21-585

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is "Approvable." A review of the CMC section showed that the manufacturing process used to make the biobatches and the primary stability batches was not adequate to assure the future quality of drug product, specifically with respect to friability. While the sponsor has indicated in-process improvements have been made since the manufacture of the primary stability batches that have improved the friability characteristics of both strengths of Mucinex D, they have not provided any release or stability data for batches made after the manufacturing improvements. Furthermore, as the manufacturing changes made to resolve friability failures included changing the [redacted] of tablets, a dissolution profile comparison of the tablets to the dissolution profiles of the biobatches was not done. Additionally, although the friability issue may have been corrected by [redacted], the dissolution profile at the new high end of the proposed acceptance criteria for [redacted] is unknown and therefore requires additional data to support the proposal.

With no data provided for review, a decision could not be made that the proposed manufacturing improvements produced tablets that showed the same dissolution profiles at release and during stability as the biobatches. Furthermore, as no stability data were provided, an expiration dating period could not be granted. Release and stability data for drug product manufactured with the manufacturing changes, and a dissolution profile comparison, are required for review. The application is approvable pending submission of adequate dissolution, release and stability data, and a satisfactory review of the data.

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 the Two Drug Substances

Mucinex D extended release tablets are uncoated, oval, tablets that are composed of two components or pieces pressed together. One piece is an immediate release formulation that releases guaifenesin, and the other piece is an extended release formulation that

releases pseudoephedrine hydrochloride and guaifenesin. Two strengths are proposed. These are Maximum strength tablets that contain 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride and Regular strength tablets that contain 600 mg guaifenesin and 60 mg pseudoephedrine hydrochloride. Both strength tablets are composed of a white, immediate release component of identical size and composition. The strengths differ in the amount of material used to form modified release layer and in the colorant used in the modified release layer, with FD&C Red #40 used for maximum strength tablets, which colors the layer pink, and FD&C Yellow #6, which colors the layer orange, used for regular strength tablets. Additionally, the strengths differ by the embossing that is performed, with the maximum strength tablets showing the number 1200 on the immediate release layer and the regular strength tablets showing the number 600 on the immediate release layer; the modified release layers of both strengths have the name Adams on the modified release layer.

The quality of the drug product is controlled by the specification with tests for appearance, average tablet weight, average tablet thickness, friability, loss on drying, identification, assay, and dissolution for guaifenesin, identification, assay, and dissolution for pseudoephedrine, degradation products and content uniformity.

The sponsor provided stability data to — months at ——— and —months at ——— RH for the primary stability batches, which are three pilot-scale batches of each strength in 30-cc and 75-cc —— bottles. A ——— expiry was requested for the to-be-marketed product. Friability failures, up to greater than —— and sporadically occurring during stability, have occurred during stability for both maximum and regular strength tablets of these primary stability batches. Because of the friability failures, the sponsor adjusted tableting manufacturing parameters and produced additional pilot scale batches after the primary stability batch manufacture. No release or stability data for batches made with the improved parameters have been provided in the original application or in the amendment of 18-Aug-2003. Therefore, acceptance criteria for the dissolution test performed at release and during stability could not be reviewed, and an expiration dating period could not be determined.

The drug substances, guaifenesin and pseudoephedrine hydrochloride, have been used in a number of OTC and approved products. DMF —— describes the chemistry, manufacturing, and controls for guaifenesin, DMF —— describes the chemistry, manufacturing, and controls for pseudoephedrine hydrochloride manafactured by ———, and DMF —— describes the chemistry, manufacturing, and controls for pseudoephedrine hydrochloride manufactured by ——— The DMFs have been reviewed and the information is found to be acceptable.

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

The drug product is an extended release tablet containing an expectorant (guaifenesin) and a decongestant (pseudoephedrine hydrochloride). The maximum daily dose is 2400 mg guaifenesin and 240 mg pseudoephedrine hydrochloride.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, this application is approvable pending satisfactory release and stability data for both strengths of drug product manufactured with the improved manufacturing changes and pending a demonstration that the dissolution profiles of these batches are comparable to the dissolution profiles of the biobatches.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	J. Salemme, Ph.D., 1-Oct-2003
ChemistryTeamLeaderName/Date:	Guirag Poochikian, Ph.D.
ProjectManagerName/Date	Colette Jackson

C. CC Block

21 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- REV II

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/s/

Jean Salemme
10/6/03 11:41:52 AM
CHEMIST

Guiragos Poochikian
10/6/03 11:54:04 AM
CHEMIST

CHEMISTRY REVIEW

P. 1 1

NDA 21-585

Mucinex D
Guaifenesin and Pseudoephedrine HCl
Extended Release Tablets
(1200 mg/120 mg and 600 mg/60 mg)

Adams Laboratories

J. Salemme, Ph.D.
for
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-585

2. REVIEW #: 1

3. REVIEW DATE: 2-June-2003

4. REVIEWER: J. Salemme, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Stamp Date
Original NDA	4-Feb-2003
Amendment	1-May-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Adams Laboratories, Inc.
Address:	14801 Sovereign Road Fort Worth, TX 76155-2645
Representative:	D. Jeffrey Keyser, VP Development and Regulatory Affairs
Telephone:	817-786-1243

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name (Proposed): Mucinex D Regular Strength and Mucinex D Maximum Strength Extended Release Tablets

b) Non-Proprietary Name (USAN): Guaifenesin and Pseudoephedrine HCl Extended Release Tablets

c) Code Name/# (ONDC only): None

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: NS

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: expectorant and decongestant

11. DOSAGE FORM: Extended release tablets

12. STRENGTH/POTENCY:
Maximum strength: Guaifenesin (1200 mg) and pseudoephedrine hydrochloride (120 mg)
Regular strength: Guaifenesin (600 mg) and pseudoephedrine hydrochloride (60 mg)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx __X_OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Guaifenesin:
See USP 25 for other chemical names, the structural formula, molecular formula, and molecular weight.

Pseudoephedrine hydrochloride:
See USP 25 for other chemical names, the structural formula, molecular formula, and molecular weight.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED or Comment
	II		Mfr of Guaifenesin	1	Adequate	May 2003 by J. Salemme
	II		Mfr of Pseudoephedrine HCl	1	Adequate	May 2003 by J. Salemme
	II		Mfr of Pseudoephedrine HCl	1	Adequate	May 2003 by J. Salemme
	III	[redacted]		3	Adequate	1-g: Aug-2002 by G. Holbert
	III			3	Adequate	August 2001 by P. Peri
	III		[redacted]	3 3	Adequate	August 1999 by J. Vidra (and approved for use in Mucinex in 2002) March 2000 by D. Christodoulou
	III			3	Adequate	April 2002 by J. Boal

Chemistry Review Data Sheet

	III		3	Adequate	September 2000 by D. Klein with DMF

[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 (Enough data are in the application; therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER or Comment
Biometrics	Consult will be requested upon receipt of updated stability data.		
EES	All seven sites are acceptable.		See Appendix 4 of this review.
Pharm/Tox	Not reviewed.		Guaifenesin impurities were reviewed in Mucinex. The impurities of PSE comply with ICH Q3A/B.
Biopharm	Dissolution method and data not yet reviewed.		
LNC	N/A		
Methods Validation	To be submitted once method related issues are resolved.		
OPDRA	Not consulted.		Mucinex is approved (21-

Chemistry Review Data Sheet

			282); "D" is for use of pseudoephedrine as a decongestant
EA	Requested and approved		J. Salemme May 2003
Microbiology	No review necessary.		

Executive Summary Section

The Chemistry Review for NDA 21-585

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is approvable pending resolution of the deficiencies conveyed to the sponsor in the Deficiency Letter. A conclusion will be made regarding approvability after a review of the responses to the deficiencies, which will include release and stability data for commercial scale drug product manufactured with modified tableting manufacturing parameters

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 and the Two Drug Substances

Mucinex D extended release tablets are uncoated, oval, bi-layer tablets. One layer is an immediate release formulation that releases guaifenesin, and the other layer is an extended release formulation that releases pseudoephedrine hydrochloride and guaifenesin. Two strengths are proposed. These are Maximum strength tablets that contain 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride and Regular strength tablets that contain 600 mg guaifenesin and 60 mg pseudoephedrine hydrochloride. Both strength tablets are composed of a white, immediate release layer of identical size and composition. The strengths differ in the amount of material used to form modified release layer and in the colorant used in the modified release layer, with FD&C Red #40 used for maximum strength tablets, which colors the layer pink, and FD&C Yellow #6, which colors the layer orange, used for regular strength tablets. Additionally, the strengths differ by the embossing that is performed, with the maximum strength tablets showing the number 1200 on the immediate release layer and the regular strength tablets showing the number 600 on the immediate release layer; the modified release layers of both strengths have the name Adams on the modified release layer.

The quality of the drug product is controlled by the specification with tests for appearance, average tablet weight, average tablet thickness, friability, loss on drying, identification, assay, and dissolution for guaifenesin, identification, assay, and dissolution for pseudoephedrine, degradation products and content uniformity.

Limited stability data to ~ months at real-time conditions for three pilot-scale batches of each strength in 30-cc and 75-cc —— bottles have been provided to the NDA with a request for a —— expiry for the to-be-marketed product. Friability failures are reported during stability for the maximum strength tablets. Because of the friability failures, the sponsor adjusted tableting manufacturing parameters after the pilot-scale batch manufacture in an attempt to solve friability problems during stability. No release or stability data for batches made with the improved parameters have been provided in the original application.

The drug substances, guaifenesin and pseudoephedrine hydrochloride, have been used in a number of OTC and approved products. DMF —— describes the chemistry, manufacturing, and controls for guaifenesin, DMF —— describes the chemistry, manufacturing, and controls for pseudoephedrine hydrochloride manafactured by —— and DMF —— describes the chemistry, manufacturing, and controls for pseudoephedrine hydrochloride manufactured by —— The DMFs have been reviewed and the information is found to be acceptable.

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

The drug product is an extended release tablet containing an expectorant (guaifenesin) and a decongestant (pseudoephedrine hydrochloride). The maximum daily dose is 2400 mg guaifenesin and 240 mg pseudoephedrine hydrochloride.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, this application is approvable pending resolution of the issues outlined in the Deficiency Letter.

III. Administrative

A. Reviewer's Signature

Executive Summary Section

B. Endorsement Block

ChemistName/Date:	J. Salemme, Ph.D., 30-May-2003
ChemistryTeamLeaderName/Date:	Guirag Poochikian, Ph.D.
ProjectManagerName/Date	Colette Jackson

C. CC Block

48 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- REV I

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/s/

Jean Salemme
6/5/03 04:21:18 PM
CHEMIST

Guiragos Poochikian
6/5/03 04:39:50 PM
CHEMIST