



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11/05/03	D Ambrogio, Janine M
Pharm/Tox	N/A		
Clinical Pharmacology and Biopharmaceuticals	Bio-waiver for Amiodarone HCl inj. 50 mg/mL in a Dilute-A-Jet Additive syringe. Recommend Approval	Review completed 4/18/03	B. Nhi Nguyen
LNC	N/A		
Methods Validation	Pending Methods will be requested from two district laboratories		
DMETS	N/A		
EA	Acceptable/Categorical exclusion	N/A	JV Advani
Microbiology	Recommend approval from microbiology perspective.	5/01/03	Dr. James McVey

The Chemistry Review for NDA 21-594

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Overall recommendation from office of Compliance regarding cGMP status is now "Acceptable".

Applicant has provided complete response to our approvable letter of September 5, 2003. The requested information for an alternate placement of the assembly diagram and Final Printed Labeling on Amiodarone HCl Injection is provided in the amendment of December 2, 2003. This application may be APPROVED from the standpoint of CMC and submitted final printed labeling.

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)

1) Drug Substance

Amiodarone Hydrochloride is a white to slightly yellow crystalline powder, and is very slightly soluble in water. It is freely soluble in _____ soluble in _____ sparingly soluble in alcohol and very soluble _____ Drug substance specifications are adequate.

Based on analysis of the provided _____ years stability data, the proposed _____ month retest period is acceptable.

Sponsor IMS has made reference to the _____ DMF _____ for pertinent CMC information on the drug substance, stability, and test specifications and tests methods. This DMF data has been found to be adequate in successive reviews from 10/2/1991 to 9/29/2001.

2) Drug Product

The drug product is an Injection manufactured in one concentration, 50 mg/mL and two Strengths, 150 mg/3 mL and 900 mg/18 mL. The drug product is a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes.

All test methods and acceptance criteria for the product are adequate. The acceptance criteria are appropriate to ensure the strength, quality, potency and purity of the finished product. Firm has impurities specifications to reflect the manufacturing experience and stability data. This is essentially a generic version of innovator brand

Cordarone also stored in vials. The only difference is that at time of administration of the product a special delivery system is used.

The drug product is a sterile solution for intravenous administration produced in sizes of 3 mL and 18 mL and are packaged — clear — glass vial,

— fitted with — rubber stopper and with — vial cap and — Dilute-A-Jet prefilled syringe respectively.

All packaging components, which are standard packaging components, are deemed adequate for protecting the drug product during the shelf life.

The sponsor has proposed 18-month of expiry based on satisfactory supporting 18 months real time stability data obtained at IMS South El Monte, CA 91733.

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

Amiodarone HCl is generally considered a Class III antiarrhythmic drug and shows considerable variation in response. It works by slowing nerve impulses in the heart and is given to treat a variety of cardiac dysrhythmias, such as ventricular and supraventricular tachycardia, atrial fibrillation, etc.

Recommended starting dosage is 150 mg (15 mg/min) over the first 10 minutes, 360 mg over the next 6 hours (1 mg/min) and 540 mg over the remaining 18 hrs (0.5 mg/ml). After the first 24 hours infusion rate of 0.5 mg/min. should be continued. Doses above 720 mg are not recommended.

Amiodarone has been used in the USA since the approval of its brand product, Cordarone, in 1995. It also has been used worldwide for years. The basis for submission of this application in lieu of a generic product is that the product is provided in a pre-filled syringe configuration. The 3 mL and 18 mL configuration are packaged as pre-filled syringe in Dilute-A-Jet Additive Syringe, for use in the preparation of pharmacy admixtures of Amiodarone HCl Injection with 5% Dextrose in water in the PVC bags.

These Configurations presumably will allow for the preparation of continuous IV infusions without the need for multiple vials, thereby reducing the number of aseptic manipulations.

C. Basis for Approvability or Not-Approval Recommendation

cGMP status is now satisfactory, therefore this application may be approved as acceptable final overall recommendation from office of compliance on cGMP status of all facilities is provided. All the other CMC information is adequate.

Previous Establishment Inspection (EI) report of IMS facility had revealed new serious deficiencies on marketed drug products. In adequate investigation into — contamination in injectable and sterile drugs. Cleaning validation didn't assess bioburden and endotoxin removal. There was failure

Failure

— and failure to perform in-process tests prior to release of 3 lots. Ineffective method of cleaning verification and failure to operate equipment within established/validated parameters.

Due to these serious deficiencies on marketed products, therefore NDA 21-594 was not covered in the establishment inspection and there was withhold due to general GMPs issues.

Labeling: FPL sample package insert is provided. The Syringe Assembly Directions are now provided in Dosage and Administration section as per our recommendation.

All issues identified in the APPROVABLE letter dated September 5, 2003, have been resolved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist JV Advani/Date: 01/21/04
ChemistryTeamLeader Kasturi Srinivasachar/Date
ProjectManagerName/Russell Forney/Date

C. CC Block

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/s/

J. V. Advani
1/23/04 02:53:31 PM
CHEMIST

Kasturi Srinivasachar
1/23/04 03:05:49 PM
CHEMIST



NDA 21-594

**Amiodarone Hydrochloride Injection
50 mg/mL, 3 mL and 18 mL (prefilled syringe)
Original NDA dated October 31, 2002 with
Amendments dated January 09, March 12, 2003,
July 21, 2003 and August 21, 2003**

International Medication Systems, Ltd.

**JV Advani
Cardio-Renal Drug Products (HFD-110)**

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Chemistry Review Data Sheet

1. NDA 21-594
2. REVIEW #: 2
3. REVIEW DATE: 9/2/03
4. REVIEWER: JV Advani
5. PREVIOUS DOCUMENTS: None

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

This review #2, is follow up of review #1. For review #1 the following submissions were reviewed

Submission(s) ReviewedDocument Date

NDA 21-594

10/31/02

NDA 21-594 (N00)BL

01/09/03

NDA 21-594 N000(BC)

03/12/03

NDA 21-594 N000(BC)

07/21/03

NDA 21-594 N000(BC)

08/21/03



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: International Medication System, Ltd.
Address: 1886 Santa Anita Avenue
South El Monte, CA 91733
Representative: Mr. Stephen A. Campbell
Vice President, Regulatory Affairs
Telephone: 626-459-5253

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN and INN): Amiodarone hydrochloride Injection
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

PHARMACOL. CATEGORY: It is a class III anti-arrhythmic drug but possesses electrophysiologic characteristics of all four Vaughan Williams classes. It is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg/mL, 3 mL and 18 mL (Prefilled Syringe)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

Chemistry Review Data Sheet

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

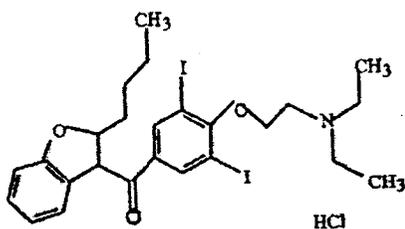
_____ SPOTS product – Form Completed

---X-----Not a SPOTS product

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

Structure of Amiodarone Hydrochloride

Structural Formula:



Molecular Formula: C₂₅H₂₉I₂NO₃ · HCl

Molecular Weight: 681.8

Chemical Name

2-butyl-3-benofuranyl 4-(2-diethylaminoethoxy)-3,5-diiodophenylketone hydrochloride

(CAS) Registry Number

1 9774-82-4



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	II	\	Drug Substance	3	Adequate	Updated review #7 dated 09/29/02 Dr. N. Samaan	
—	III	—		4	Adequate		
—	III	—	\	4	Adequate		
—	III	\	\	4	Adequate		

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")

* There is enough data in the application, there the DMF is not reviewed.

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

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	8/22/03	R. Woods and D Ambrogio, Janine M
Pharm/Tox	N/A		
Clinical Pharmacology and Biopharmaceuticals	Bio-waiver for Amiodarone HCl inj. 50 mg/mL in a Dilute-A-Jet Additive syringe. Recommend Approval	Review completed 4/18/03	B. Nhi Nguyen
LNC	N/A		
Methods Validation	Methods will be requested from two district laboratories		
DMETS	N/A		
EA	Acceptable/Categorical exclusion	N/A	JV Advani
Microbiology	Recommend approval from microbiology perspective.	5/01/03	Dr. James McVey

The Chemistry Review for NDA 21-594

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Overall recommendation from office of Compliance regarding cGMP status is to withhold.

Applicant has provided responses to the requested information on Amiodarone HCl Injection in the amendments of 3/12/03, 7/25/03 and 8/21/03. These CMC concerns have been addressed satisfactorily. Refer review #1.

This application is not approvable until satisfactory final overall recommendation from office of compliance on cGMP status of all facilities, is provided.

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)

1) Drug Substance

Amiodarone Hydrochloride is a white to slightly yellow crystalline powder, and is very slightly soluble in water. It is freely soluble in _____, soluble in _____, sparingly soluble in alcohol and very soluble in _____. Drug substance specifications are adequate.

Based on analysis of the provided _____ years stability data, the proposed _____ month retest period is acceptable.

Sponsor IMS has made reference to the _____ DMF _____ for pertinent CMC information on the drug substance, stability, and test specifications and tests methods. This DMF data has been found to be adequate in successive reviews from 10/2/1991 to 9/29/2001.

2) Drug Product

The drug product is an Injection manufactured in one concentration, 50 mg/mL and two Strengths, 150 mg/3 mL and 900 mg/18 mL. The drug product is a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes.

All test methods and acceptance criteria for the product are adequate. The acceptance criteria are appropriate to ensure the strength, quality, potency and purity of the finished product. Firm has impurities specifications to reflect the manufacturing experience and stability data. This is essentially a generic version of innovator brand

Cordarone also stored in vials. The only difference is that at time of administration of the product a special delivery system is used.

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All packaging components, which are standard packaging components, are deemed adequate for protecting the drug product during the shelf life.

The sponsor has proposed 18-month of expiry based on satisfactory supporting 18 months real time stability data obtained at IMS South El Monte, CA 91733.

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

Amiodarone HCl is generally considered a Class III antiarrhythmic drug and shows considerable variation in response. It works by slowing nerve impulses in the heart and is given to treat a variety of cardiac dysrhythmias, such as ventricular and supraventricular tachycardia, atrial fibrillation, etc.

Recommended starting dosage is 150 mg (15 mg/min) over the first 10 minutes, 360 mg over the next 6 hours (1 mg/min) and 540 mg over the remaining 18 hrs (0.5 mg/ml). After the first 24 hours infusion rate of 0.5 mg/min. should be continued. Doses above 720 mg are not recommended.

Amiodarone has been used in the USA since the approval of its brand product, Cordarone, in 1995. It also has been used worldwide for years. The basis for submission of this application in lieu of a generic product is that the product is provided in a pre-filled syringe configuration. The 3 mL and 18 mL configuration are packaged as pre-filled syringe in Dilute-A-Jet Additive Syringe, for use in the preparation of pharmacy admixtures of Amiodarone HCl Injection with 5% Dextrose in water in the PVC bags.

These Configurations presumably will allow for the preparation of continuous IV infusions without the need for multiple vials, thereby reducing the number of aseptic manipulations.

C. Basis for Approvability or Not-Approval Recommendation

cGMP status is on withhold, therefore this application is not approvable until satisfactory final overall recommendation from office of compliance on cGMP status of all facilities is provided. All the other CMC information is adequate.

Current Establishment Inspection (EI) report of IMS facility has revealed new serious deficiencies on marketed drug products. Inadequate investigation into contamination in injectable and sterile drugs. Cleaning validation didn't assess bioburden and endotoxin removal. There has been failure

Failure

— and failure to perform in-process tests prior to release of 3 lots.
Ineffective method of cleaning verification and failure to operate equipment within
established/validated parameters.
Due to these serious deficiencies on marketed products, therefore NDA 21-594 was not
covered in the establishment inspection and there is withhold due to general GMPs issues.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist JV Advani/Date: 9/02/03
ChemistryTeamLeader Kasturi Srinivasachar/Date
ProjectManagerName/Russell Forney/Date

C. CC Block

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/s/

J. V. Advani
9/3/03 01:06:51 PM
CHEMIST

Kasturi Srinivasachar
9/3/03 02:36:30 PM
CHEMIST



NDA 21-594

**Amiodarone Hydrochloride Injection
50 mg/mL, 3 mL and 18 mL (prefilled syringe)
Original NDA dated October 31, 2002 with
Amendments dated January 09, March 12, 2003,
July 21, 2003 and August 21, 2003**

International Medication Systems, Ltd.

**JV Advani
Cardio-Renal Drug Products (HFD-110)**



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1. NDA 21-594
2. REVIEW #: 1
3. REVIEW DATE: 02/02/03, 7/25/03 and 8/22/03
4. REVIEWER: JV Advani
5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

NDA 21-594

10/31/02

NDA 21-594 (N00)BL

01/09/03

NDA 21-594 N000(BC)

03/12/03

NDA 21-594 N000(BC)

07/21/03

NDA 21-594 N000(BC)

08/21/03



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: International Medication System, Ltd.
Address: 1886 Santa Anita Avenue
South EI Monte, CA 91733
Representative: Mr. Stephen A. Campbell
Vice President, Regulatory Affairs
Telephone: 626-459-5253

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN and INN): Amiodarone hydrochloride Injection
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

PHARMACOL. CATEGORY: It is a class III anti-arrhythmic drug but possesses electrophysiologic characteristics of all four Vaughan Williams classes. It is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg/mL, 3 mL and 18 mL (Prefilled Syringe)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

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

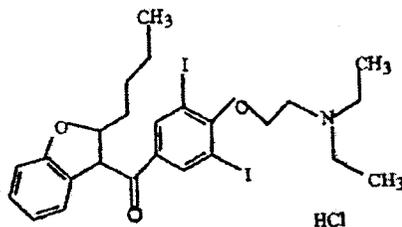
_____ SPOTS product – Form Completed

---X-----Not a SPOTS product

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

Structure of Amiodarone Hydrochloride

Structural Formula:



Molecular Formula: $C_{25}H_{29}I_2NO_3 \cdot HCl$

Molecular Weight: 681.8

Chemical Name

2-butyl-3-benofuranyl 4-(2-diethylaminoethoxy)-3,5-diiodophenylketone hydrochloride

(CAS) Registry Number

1 9774-82-4



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
-	II	/	Drug Substance	3	Adequate	Updated review #7 dated 09/29/02 Dr. N. Samaan	
-	III	-		4	Adequate		
-	III	-	/	4	Adequate		
-	III	/	/	4	Adequate		

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")

* There is enough data in the application, there the DMF is not reviewed.

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		D Ambrogio, Janine M
Pharm/Tox	N/A		
Clinical Pharmacology and Biopharmaceuticals	Bio-waiver for Amiodarone HCl inj. 50 mg/mL in a Dilute-A-Jet Additive syringe. Recommend Approval	Review completed 4/18/03	B. Nhi Nguyen
LNC	N/A		
Methods Validation	Methods will be requested from two district laboratories		
DMETS	N/A		
EA	Acceptable/Categorical exclusion	N/A	JV Advani
Microbiology	Recommend approval from microbiology perspective.	5/01/03	Dr. James McVey

The Chemistry Review for NDA 21-594

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Overall recommendation from office of Compliance regarding cGMP status of one facility is pending. Applicant has provided satisfactory responses to the requested information on Amiodarone HCl Injection in the amendments of 3/12/03, 7/25/03 and 8/21/03.

A final recommendation can only be given after office of compliance provides the overall recommendation on cGMP status of all facilities.

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)

1) Drug Substance

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Based on analysis of the provided _____ years stability data, the proposed _____ month retest period is acceptable.

Sponsor IMS has made reference to the _____ DMF _____ for pertinent CMC information on the drug substance, stability, and test specifications and tests methods. This DMF data has been found to be adequate in successive reviews from 10/2/1991 to 9/29/2001.

2) Drug Product

The drug product is an Injection manufactured in one concentration, 50 mg/mL and two Strengths, 150 mg/3 mL and 900 mg/18 mL. The drug product is a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes.

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CHEMISTRY REVIEW



Executive Summary Section

Cordarone also stored in vials. The only difference is that at time of administration of the product a special delivery system is used.

The drug product a sterile solution for intravenous administration produced in sizes of 3 mL and 18 mL and are packaged _____ clear _____ glass vial, _____ fitted with _____ rubber stopper and with _____ vial cap and _____ Dilute-A-Jet prefilled syringe respectively.

All packaging components, which are standard packaging components, are deemed adequate for protecting the drug product during the shelf life.

The sponsor has proposed 18-month of expiry based on satisfactory supporting 18 months real time stability data obtained at IMS South El Monte, CA 91733.

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

Amiodarone HCl is generally considered a Class III antiarrhythmic drug and shows considerable variation in response. It works by slowing nerve impulses in the heart and is given to treat a variety of cardiac dysrhythmias, such as ventricular and supraventricular tachycardia, atrial fibrillation, etc.

Recommended starting dosage is 150 mg (15 mg/min) over the first 10 minutes, 360 mg over the next 6 hours (1 mg/min) and 540 mg over the remaining 18 hrs (0.5 mg/ml). After the first 24 hours infusion rate of 0.5 mg/min. should be continued. Doses above 720 mg are not recommended.

Amiodarone has been used in the USA since the approval of its brand product, Cordarone, in 1995. It also has been used worldwide for years. The basis for submission of this application in lieu of a generic product is that the product is provided in a pre-filled syringe configuration. The 3 mL and 18 mL configuration are packaged as pre-filled syringe in Dilute-A-Jet Additive Syringe, for use in the preparation of pharmacy admixtures of Amiodarone HCl Injection with 5% Dextrose in water in the PVC bags.

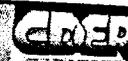
These Configurations presumably will allow for the preparation of continuous IV infusions without the need for multiple vials, thereby reducing the number of aseptic manipulations.

C. Basis for Approvability or Not-Approval Recommendation

All the CMC information is adequate. CGMP status is pending therefore no final recommendation can be given at this time.



CHEMISTRY REVIEW



Executive Summary Section

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist JV Advani/Date: 04/22/03, 7/24/03 and 8/22/03
ChemistryTeamLeader Kasturi Srinivasachar/Date
ProjectManagerName/Russell Forney/Date

C. CC Block

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/s/

J. V. Advani
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Kasturi Srinivasachar
8/22/03 05:48:30 PM
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