

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-457**

**CHEMISTRY REVIEW(S)**

**NDA 021457**

**[Trade Name]<sup>®</sup> HFA (albuterol sulfate) Inhalation Aerosol**

**IVAX Research, Inc.  
4400 Biscayne Blvd.  
Miami, FL 33137**

**Vibhakar Shah, Ph.D.  
Division of Pulmonary and Allergy Drug Products  
HFD-570**



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# Chemistry Review Data Sheet

1. NDA 21457
2. REVIEW #: 2
3. REVIEW DATE: 29-OCT-2004
4. REVIEWER: Vibhakar Shah, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-Jan-03
Amendment (BZ)	05-May-03
Amendment (BC)	15-Jul-03
Amendment (BC)	10-Oct-03
Amendment (C)	15-Oct-03
Amendment (C)	20-Oct-03
Amendment (BC)	30-Oct-03
Amendment (C)	17-Nov-03

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BZ)	15-Mar-2004
Amendment (BC)	02-Apr-2004
Amendment (BC)	29-Apr-2004
Amendment (C)	09-Sep-2004
Amendment (C)	25-Oct-2004
Amendment (BC)	26-Oct-2004
Amendment (C)	27-Oct-2004

7. NAME & ADDRESS OF APPLICANT:



## CHEMISTRY REVIEW-2



### Chemistry Review Data Sheet

**Name:** IVAX Research, Inc.  
**Address:** 4400 Biscayne Blvd., Miami, FL 33137  
**Representative:** Steven M. Viti, Ph.D., Dir Reg. Affairs  
**Telephone:** 305-575-6336

#### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: [Trade Name]<sup>TM</sup> (Albuterol Sulfate, USP) HFA Inhalation Aerosol  
b) Non-Proprietary Name (USAN): Albuterol sulfate, USP Inhalation Aerosol  
c) Code Name/# (ONDC only):  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(2) of the FD&C Act

10. PHARMACOL. CATEGORY:  $\beta$ 2-Agonist (Bronchodilator)

11. DOSAGE FORM: Inhalation Aerosol (Metered Dose Inhaler or MDI)

#### 12. STRENGTH/POTENCY:

**Albuterol sulfate:** 108 mcg/actuation from the mouthpiece  
120 mcg /actuation from the valve

**Albuterol base (equiv.):** 90 mcg/actuation from the mouthpiece  
— /actuation from the valve

Maximum Daily Dose: 2 actuations every 4-6 hours  
(i.e., 1.08 mg albuterol base/12 actuations)

Actuations/Canister: 200  
Net weight/Canister: 8.5 g

13. ROUTE OF ADMINISTRATION: Oral inhalation

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

# CHEMISTRY REVIEW-2

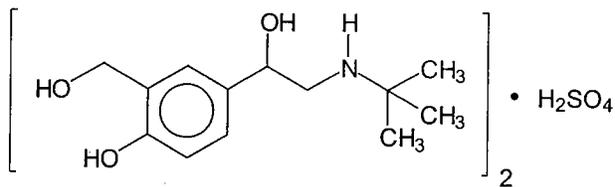
## Chemistry Review Data Sheet

  X   Not a SPOTS product

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

**Chemical Name:** 1,3-benzenedimethanol,  $\alpha^1$ -[[1,1-dimethylethyl)amino]-methyl]-4-hydroxy-, sulfate (2:1) salt, or  $\alpha^1$ -[tert-butylamino)methyl]-4-hydroxy-m-xylene- $\alpha, \alpha'$ -diol sulfate (2:1) salt

**Molecular Formula:**  $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$   
**Molecular Weight:** 576.70  
**CAS Registry No:** [51022-70-9]



Albuterol sulfate (USP 25, p 55)

### 17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:** See page 10003/V1/M1

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	REVIEW DATE *	COMMENTS <sup>3</sup>
	II		Albuterol sulfate	1, 3	Adequate	10-18-2004	DMF Chem Rev-22 See p 13 of this review
	III			1	Adequate	11-24-2003	See Chem Rev -1, page 5
	V			1	Adequate	11-25-2003	See Chem Rev-1, page 5
	III			1	Adequate	11-26-2003	See Chem Rev-1, page 5
	III			1	Adequate	09-30-2004	DMF Chem Rev. 4 See p 123 of this review
	III			1	Adequate	10-27-2004	DMF Chem Rev. 14 See p 123 of this review
	III			1	Adequate	10-18-2004	DMF Chem Rev. 2 See p 123 of this review

\*MM-DD-YYYY

<sup>1</sup> 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



# CHEMISTRY REVIEW-2



## Chemistry Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")
- <sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
- <sup>3</sup> Include reference to location in most recent CMC review

### B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 60549	IVAX Research, Inc.	Albuterol HFA-MDI 90 mcg			

### C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
/	/	/	/

### 18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Expiration dating period evaluation	-	-	None required as expiration was limited to 15 months
EES	GMP evaluation of drug substance and drug product manufacturing sites	06-13-2003	Acceptable	See EER Report dated Dec 18, 2003 and Feb 19, 2004 Also See Chem Rev-1 page 5.
Pharm/Tox	Qualification	06-15-2004	Complete 08-16-2004	See page 17 of this review.
	albuterol impurities Leachables	10-13-2004	Complete	See page 35 of this review
Biopharm	-	-	-	None
DMETS/ LNC	-	-	-	-
Methods Validation	Evaluation of Regulatory methods	To be forwarded	N/A	MVP will be forwarded to FDA labs, post-approval.
EA	Exclusion requested as per 21CFR 25.31(a)	-	Acceptable	See page 5 of Chem Review-1
Microbiology	-	-	-	Not needed.



# The Chemistry Review for NDA 21-457

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the CMC perspective, an **approval (AP)** action is recommended for this application with 15 month of expiration dating when the drug product is stored between 15°C and 25°C.

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

Not applicable at this time.

### II. Summary of Chemistry Assessments

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

The Drug Product (DP) for this application is [Trade Name]® (albuterol sulfate) HFA Inhalation Aerosol. The formulation for this suspension inhalation aerosol uses HFA-134a (1,1,1,2-tetrafluoroethane) propellant (non-CFC) and contains \_\_\_\_\_ of \_\_\_\_\_ alcohol \_\_\_\_\_. This drug product is a suspension formulation and contains *micronized* albuterol sulfate \_\_\_\_\_.

\_\_\_\_\_ Note that any formulation heterogeneity of suspension inhalation aerosols can directly impact the dosing reproducibility from actuation to actuation.

The DP delivers \_\_\_\_\_ of formulation from the valve, containing a target amount of 108 mcg of albuterol sulfate (90 mcg albuterol base), \_\_\_\_\_ of alcohol, and \_\_\_\_\_ of HFA-134a propellant. The aluminum canister \_\_\_\_\_ contains 8.5 g (target) of formulation with \_\_\_\_\_ of albuterol sulfate. The metering valve is composed of \_\_\_\_\_ components and is similar to that used in other approved and unapproved products. The actuator has an orifice with a relatively small diameter of 0.22 mm when compared to the other two recently approved albuterol sulfate HFA inhalation aerosols.

The manufacturing process : \_\_\_\_\_

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

The DP which is a conventional "press and breathe" MDI is intended for                       
                    . Proper coordination of inhalation with valve actuation (or puff) is a necessity for efficacy.

The usual dosage for adults and children 12 years and older is two puffs repeated every 4 to 6 hours.                     

Other important points to note about usage which are that the labeling include:

- shake well before each use
- instructions to wash and dry the actuator only at least once a week.
- not to use beyond 200 actuations
- prime a new unit with three sprays.
- re-prime an existing unit after sitting for two weeks with three sprays

## C. Basis for Approvability or Not-Approval Recommendation

Note:                     , a critical site used for the                       
                     was found acceptable from cGMP perspective. (Refer to EES Report dated February 19, 2004 by J. Ambrogio, Office of Compliance, HFD-322)

Currently, the application, in terms of the CMC portion, is considered adequate to recommend an approval with an expiry of 15 months. Several post-approval agreements have been reached with the applicant (see page 131 of the review) and will be confirmed to the applicant in The DPADP action letter. These agreements, which are described below pertain to the qualification of leachables, developing validated test methodologies for quantitative determination of extractables, leachables, and foreign particulates Applicant has agreed to fulfill these agreements post-approval with firm timelines as follows:

The most critical factors that recommended approval of the application include:

- All manufacturing facilities were found acceptable from cGMP perspective.
- Negotiation of the expiration dating to 15 months rather than \_\_\_\_\_ which was sought by IVAX. \_\_\_\_\_ was not supported by the stability data provided. The stability data available to assess the TO-BE-MARKETED drug product was limited to initial and \_\_\_\_\_ of data at 25°C/60% RH from three batches using all to-be-marketed processing conditions (i.e., \_\_\_\_\_ testing) Expiry is primarily based on \_\_\_\_\_ of SUPPORTIVE stability data in similarly (but not identically) processed batches (\_\_\_\_\_ processes). The risk in a strong reliance on supportive stability data to establish the shelf life was considered minimal and balanced in this particular case
- Also of note, the specifications (test method and acceptance criteria) for the performance parameters, such as *aerodynamic particle size distribution* (APSD) and *dose content uniformity* (DCU), and acceptance criteria for *leakage rate, valve delivery* and \_\_\_\_\_ have been significantly revised to be reflective of the data and to assure consistent delivery of the emitted dose to the clinically relevant stage groups of the multistage Anderson cascade impactor.
- Significant changes (addition of valve delivery and leachable testing etc.) to the stability protocol to be applied to post-approval stability program has been agreed and updated accordingly.
- An agreement to qualify \_\_\_\_\_ leachables \_\_\_\_\_ post approval with firm time commitment.
- Drug master files covering the pertinent CMC information for the drug substance, inhalation aerosol valve, canister and actuator have been found adequate.



### III. Administrative

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist Name/Date: Vibhakar Shah, Ph.D., October 29, 2004

Acting Chemistry Team Leader Name/Date:

Project Manager Name/Date: Richard Lostritto, Ph.D., October 29, 2004

**C. CC Block**

**CC:**

Orig. NDA 21-457  
HFD-570/Division File  
HFD-570/VShah  
HFD-570/RLostritto  
HFD-570/AGreen  
HFD-570/SBarnes

R/D Init. By: RLostritto \_\_\_\_

Filename/Location: C:\CDData\CMCReviews\NDAs\N21457\N21457RS\N21457CR2\_v1.doc

136 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**NDA 021457**

**Volare<sup>®</sup> HFA (albuterol sulfate) Inhalation Aerosol**

**IVAX Research, Inc.  
4400 Biscayne Blvd.  
Miami, FL 33137**

**Vibhakar Shah, Ph.D.  
Division of Pulmonary and Allergy Drug Products  
HFD-570**



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# Chemistry Review Data Sheet

1. NDA 21457
2. REVIEW #: 1
3. REVIEW DATE: 28-Nov-2003
4. REVIEWER: Vibhakar Shah, Ph.D.
5. PREVIOUS DOCUMENTS:

**Previous Documents****Document Date**

None

6. SUBMISSION(S) BEING REVIEWED:

**Submission(s) Reviewed****Document Date**

Original

30-Jan-03

Amendment (BZ)

05-May-03

Amendment (BC)

15-Jul-03

Amendment (BC)

10-Oct-03

Amendment (C)

15-Oct-03

Amendment (C)

20-Oct-03

Amendment (BC)

30-Oct-03

Amendment (C)

17-Nov-03

7. NAME & ADDRESS OF APPLICANT:

**Name:** IVAX Research, Inc.**Address:** 4400 Biscayne Blvd., Miami, FL 33137**Representative:** Steven M. Viti, Ph.D., Dir Reg. Affairs**Telephone:** 305-575-6336

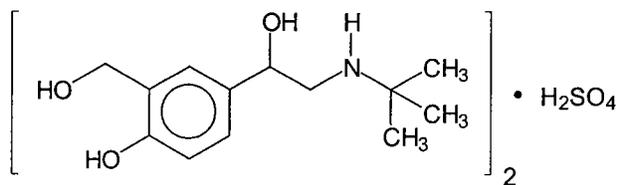
8. DRUG PRODUCT NAME/CODE/TYPE:



# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

**Molecular Formula:** (C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub>•H<sub>2</sub>SO<sub>4</sub>  
**Molecular Weight:** 576.70  
**CAS Registry No:** [51022-70-9]



Albuterol sulfate (USP 25, p 55)

### 17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:** See page 10003/V1/M1

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	REVIEW DATE *	COMMENTS <sup>3</sup>
(	II	)	Albuterol sulfate	1, 3	Adequate with IR	11-12-2003	DMF Chem Rev #19 See p 12 of this review
(	III			1	Adequate	11-24-2003	DMF Chem Rev. #4 See p 67 of this review
(	V			1	Adequate	11-25-2003	DMF Chem Rev. #1 See p 67 of this review
(	III			1	Adequate	11-26-2003	DMF Chem Rev. #5 See p 75 of this review
(	III			1	Inadequate	11-20-2003	DMF Chem Rev. #3 See p 75 of this review
(	III			1	Inadequate	11-26-2003	DMF Chem Rev. #13 See p 75 of this review
(	III			1	Inadequate	11-17-2003	DMF Chem Rev. #1 See p 75 of this review
(	III			1	Inadequate	11-17-2003	DMF Chem Rev. #1 See p 75 of this review

\*MM-DD-YYYY

<sup>1</sup> 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")

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

<sup>3</sup> Include reference to location in most recent CMC review



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 60549	IVAX Research, Inc.	Albuterol HFA-MDI 90 mcg			

### C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

### 18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
<b>Biometrics</b>	Expiration dating period evaluation	-	-	Withheld at this time until updated stability data become available.
<b>EES</b>	GMP evaluation of drug substance and drug product manufacturing sites	06-13-2003	pending	As per the email from OC, inspection for facilities (old and new) is scheduled in early December 2003. See pp. 14 and 66 of this review
<b>Pharm/Tox</b>	Qualification of albuterol impurities	09-26-2003	Complete 14-Nov-2003	Qualification studies requested for these impurities. See p 24 of this review
<b>Biopharm</b>	-	-		None
<b>DMETS/ LNC</b>	-			
	Trade Name	11-21-2003	Not Acceptable 26-Nov-2003	Refer to DFS for DMETS Memo By Denise Toyer, Phram. D.
<b>Methods Validation</b>	Evaluation of Regulatory methods	To be forwarded	N/A	MVP will be forwarded to FDA labs, once approvability issues pertaining to the drug product are adequately resolved. See p 121 of this review.
<b>EA</b>	Exclusion requested as per 21CFR 25.31(a)		Acceptable	See p 122 of this review
<b>Microbiology</b>	-	-	-	Not needed. See pp. 31, 55 and 71 of this review

# The Chemistry Review for NDA 21-457

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The recommended action for this application from the CMC perspective is **approvable (AE)**.

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

Not applicable at this time.

### II. Summary of Chemistry Assessments

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

The Drug Product (DP) for this application is Volare® HFA (albuterol sulfate) Inhalation Aerosol. The formulation for this suspension inhalation aerosol uses HFA-134a (1,1,1,2-tetrafluoroethane) propellant (non-CFC) and contains \_\_\_\_\_ of \_\_\_\_\_ alcohol \_\_\_\_\_. This drug product is a suspension formulation and contains *micronized* albuterol sulfate \_\_\_\_\_.

\_\_\_\_\_ Note that any formulation heterogeneity of suspension inhalation aerosols can directly impact the dosing reproducibility from actuation to actuation.

The DP delivers \_\_\_\_\_ of formulation from the valve, containing a target amount of 108 mcg of albuterol sulfate (90 mcg albuterol base), \_\_\_\_\_ of alcohol, and \_\_\_\_\_ of HFA-134a propellant. The aluminum canister, \_\_\_\_\_, contains 8.5 g (target) of formulation with \_\_\_\_\_ of albuterol sulfate. The metering valve is a standard version \_\_\_\_\_ components) similar to that used in other approved and unapproved products. The actuator has an orifice with a relatively small diameter of 0.22 mm when compared to the other two recently approved albuterol sulfate HFA inhalation aerosols.

The manufacturing process \_\_\_\_\_

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

The DP is intended for \_\_\_\_\_  
\_\_\_\_\_ The usual dosage for adults and children 12 years and older is two inhalations repeated every 4 to 6 hours. The proposed labeling does not recommend a more frequent administration schedule and states that one inhalation in 4 hours may be sufficient \_\_\_\_\_

Another important point to note about usage is that the labeling states that “\_\_\_\_\_ the mouthpiece be washed and dried at least once a week.” The *in vitro* cleaning study results in the application did support the cleaning of the actuator on a weekly basis but it should be kept in mind that differences between the conditions of *in vitro* dose testing done in the controlled laboratory cleaning study and actual drug delivery during patient usage might be quite distinct in terms of mouthpiece drug retention and potential orifice clogging. Discussions with the clinical team did not reveal any complaints of this nature occurring during the clinical studies but the number of patients involved was minimal when compared to the potential number of patients that will use this DP upon marketing, particularly when the established CFC products are removed from the marketplace due to the provisions of the Montreal Protocol.

## C. Basis for Approvability or Not-Approval Recommendation

Note: \_\_\_\_\_ a critical site used for the \_\_\_\_\_  
\_\_\_\_\_, is not scheduled for inspection until December 15, 2003, which is subsequent to the PDUFA goal date of November 30, 2003.

Currently the application, in terms of the CMC portion, is considered to be **approvable** pending revision as outlined in the attached draft letter at the end of



this review. In summary, the remaining comments to be addressed involve the following issues:

- Controls for the drug substance (DS) particle size distribution [redacted] are inadequate for this suspension-based formulation. In addition controls for [redacted] micronized crystalline material are lacking. It is well known that reproducibility in both dose delivery and the aerodynamic particle size distribution (APSD) of the emitted dose is generally linked to control of these [redacted] drug substance properties. APSD reproducibility is also directly related to the reproducibility of the amount of drug substance that partitions to the patient's lungs during product usage.
- Impurities specifications are inadequately permissive, particularly in light of the lack of toxicological qualification data for [redacted] identified individual impurities. Other drug substance quality specification acceptance criteria warrant tightening based on the submitted data. These corrections are necessary to assure future DS and DP reproducibility.
- It appears that the DP applicant (IVAX) may not be prepared to perform all of the necessary testing of incoming drug product components, which is particularly important for those components manufactured by firms which are not covered by our GMP inspection system.
- At the present time the institution of the necessary [redacted] is not completely described or "validated" by the provision of stability and batch yield data.
- As with the drug substance, the controls for the drug product require significant modification, both in terms of the addition of important testing parameters (e.g., valve delivery, leachables on stability), and in terms of having acceptance criteria that are reflective of the submitted data for assurance of future batch-to-batch reproducibility.
- It was also notable in the review of the data for the performance parameters of APSD and dose content uniformity (DCU) that the data for batches [redacted] Although the difference must be explained, the batches [redacted] had dose delivery more close to the desired target of 90 mcg/actuation when compared to those [redacted]
- Significant revision of the stability protocol to be applied post-approval, as well as data and statistical analysis that had been promised to the Division



by the applicant in their previous submission are being requested.

- Apart from data variability noted in the APSD dataset upon stability, the most notable stability trend is \_\_\_\_\_ Data for \_\_\_\_\_, is too limited to preclude the existence of a similar trend in stability behavior.
- Drug master files covering the pertinent CMC information for the inhalation aerosol valve and actuator were found to be inadequate and comments have been forwarded to the holders of these drug master files.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist Name/Date: Vibhakar Shah, Ph.D., November 28, 2003

Acting Chemistry Team Leader Name/Date:

Project Manager Name/Date: Craig M. Bertha, Ph.D., November 28, 2003

#### C. CC Block

**CC:**

Orig. NDA 21-457  
HFD-570/Division File  
HFD-570/VShah  
HFD-570/CBertha  
HFD-570/AGreen  
HFD-570/SBarnes

R/D Init. By: C. Bertha \_\_\_\_\_

Filename/Location: C:\CData\CMCReviews\NDAs\N21457\N21457DFS\N21457FinalCR1.doc

129 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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/s/

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Vibhakar J. Shah  
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CHEMIST

Craig Bertha  
11/28/03 11:20:20 AM  
CHEMIST  
I concur.