CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-587

CHEMISTRY REVIEW(S)

DIVISION OF ONCOLOGIC DRUG PRODUCTS HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-587 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 23-DEC-1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment AZ	13-NOV-1997	17-NOV-1997	3-DEC-1997 (response to def. ltr. 27-OCT)
Amendment BC	5-DEC-1997	09-DEC-1997	

NAME & ADDRESS OF APPLICANT: Bryan Corporation
Four Plympton Street
Woburn, MA 01801

Responsible Official: Frank Abrano, Chief Executive Officer
1-800-343-7711

DRUG PRODUCT NAME

Proprietary:	SCLEROSOL Intrapleural Aerosol
Nonproprietary/USAN:	Sterile Talc Powder
Code Name/#:	
Chem.Type/Ther.Class:	1-P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: sclerosing agent indicated for malignant pleural effusion secondary to malignancies having spread to the pleural space

DOSAGE FORM: sterile aerosol suspension
STRENGTHS: 4.0 gm per canister
ROUTE OF ADMINISTRATION: intrapleurally, via pleural trocar
DISPENSED: __xx__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Name: Talc: hydrated magnesium silicate
Chlorite: magnesium and aluminum silicate

(Talc and Chlorite is a natural association.)

Molecular Formula: (with CAS Nos.)
Talc, CAS #14807-96-4 $Mg_3Si_4O_{10}(OH)_2$ M.W. = 379.26
Chlorite, CAS#1318-59-0 $(Mg, Fe)_5\ Al\{AlSi_3O_{10}\}\{OH\}_8$

See Previous review for structure

RELATED DOCUMENTS:

EIR Form 481(E)-CG on Bryan Corporation, Woburn, MA, dated 10-December 1997, submitted by Constance DeSimone of Boston District Office with a recommendation of approval as distributor. In that report, she called for a meeting of the representatives of Bryan Corporation with the district regarding the NDA requirements for record keeping. This reviewer concurs with that recommendation.

Sciarra Laboratories, responsible for the manufacture, release tesing and stability testing of the finished product has been inspected for CGMP compliance and was found acceptable by Investigator Robert Horan dated 10 December 1997.

the supplier of the bulk talc was previously found acceptable on 8-August-1997.

SUPPORTING DOCUMENTS:

DMF
DMF

Consults:

1. A microbiological consult was issued for review of the sterilization of the product.

2. Establishment re-evaluations have been requested of both Bryan Corporation and Sciarra Laboratories. An FDA 483 was issued to Sciarra Laboratories, Inc. based on the inspection which occurred between 13th-19th of August 1997.

   a) Bryan Corporation was found acceptable (NAI) by Investigator Constance DeSimone on 9-December 1997.

   b) Sciarra Laboratories was found acceptable on 10-DEC-1997 by Investigator Robert Horan.

REMARKS/COMMENTS:

1. In the amendment dated 23-AUG-1997, the applicant notified the Agency that the new supplier of the bulk talc, designated and the new manufacturer of the finished drug product would be Sciarra Laboratories, Inc. Hicksville, NY.

2. The components and suppliers of the container/closure have not changed and remain as follows:

   i) the 36 mL aluminum aerosol canister will be supplied by
   ii) a 20 mm continuous flow valve assembly will be supplied by

   iii) an actuator & two delivery tubes of 15 cm and 25 cm length for use with the product will be supplied by
   iv) a canister cap (dust cover) for the product will be supplied by

3. The product propellant will be CFC-12 (dichlorodifluoromethane) supplied by

   The propellant as supplied by was found acceptable.

4. will be used to sterilize the finished aerosol product and delivery tubes. This operation will be performed by , a new contractor. The facility is considered acceptable on HFD-324 recommendation date 30-JUN-1997.

5. Microbiological release testing of the finished product will be performed by

6. Final labeling for outside sterile pack (overwrap), and package will require review subsequent to approval.

CONCLUSIONS & RECOMMENDATIONS:

With the meeting of CGMP requirements by Sciarra Laboratories, the application is considered approved with a commitment to satisfactorily address the remaining CMC questions.

/S/

Robert P. Barron
Review Chemist, HFD-150

/S/

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

12/04/97

cc: Orig. NDA #20-587
HFD-150/Division File
HFD-150/RPBarron
HFD-150/AMartin,MD
HFD-150/RHWood
HFD-150/DCatterson
R/D Init by:

DIVISION OF ONCOLOGIC DRUG PRODUCTS HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-587 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 8-SEP-1997
Revised: 21-OCT-1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT AZ	23-APR-1997	29-APR-1997	13-MAY-1997
AMENDMENT BZ	06-AUG-1997	07-AUG-1997	12-AUG-1997

NAME & ADDRESS OF APPLICANT: Bryan Corporation
Four Plympton Street
Woburn, MA 01801

Responsible Official: Frank Abrano, Chief Executive Officer
1-800-343-7711

DRUG PRODUCT NAME

Proprietary:	SCLEROSOL Intrapleural Aerosol
Nonproprietary/USAN:	Sterile Talc Powder
Code Name/#:	
Chem.Type/Ther.Class:	1-P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: sclerosing agent indicated for malignant pleural effusion secondary to malignancies having spread to the pleural space

DOSAGE FORM: sterile aerosol suspension
STRENGTHS: 4.0 gm per canister
ROUTE OF ADMINISTRATION: intrapleurally, via pleural trocar
DISPENSED: __XX__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Name: Talc: hydrated magnesium silicate
Chlorite: magnesium and aluminum silicate

(Talc and Chlorite is a natural association.)

Molecular Formula: (with CAS Nos.)
Talc, CAS #14807-96-4 $Mg_3Si_4O_{10}(OH)_2$ M.W. = 379.26
Chlorite, CAS#1318-59-0 $(Mg, Fe)_5 Al\{AlSi_3O_{10}\}\{OH\}_8$

See Previous review for structure

SUPPORTING DOCUMENTS:

DMF
DMF

Consults:

1. The amendment AZ dated 28-APR-199 was delivered to the reviewing microbiologist, Dr. David Hussong, on 29-APR-1997. However, a formal microbiological consult to HFD 160 was issued until 8-14-97.

2. A microbiological consult was issued 8-14-97 for amendment BZ.

3. Establishment evaluations have been requested for (bulk talc supplier), Sciarra Laboratories (drug product manufacturing), and . As of this report, the inspections have been conducted and found acceptable, either based on site visits or profile data, for all establishments expect Sciarra Laboratories, for which a withhold recommendation was issued as documented on Form FDA-483. A re-inspection will be necessary before an acceptable recommendations can be reached.

REMARKS/COMMENTS:

1. The amendment BZ dated 6-AUG-1997 was the result of the information request based on the initial review of amendment AZ. This request was faxed to the firm on 13-JUN-1997 for a response.

2. Under information submitted in amendment AZ, the applicant has changed the supplier of the bulk talc, designated the manufacturer of the drug product to Sciarra Laboratories, Inc. Hicksville, NY.

3. The components and suppliers of the container/closure have not changed and remain as follows:
   I) the 36 mL aluminum aerosol canister will be supplied by
   ii) a 20 mm continuous flow valve assembly will be supplied by
   iii) an actuator & two delivery tubes of 15 cm and 25 cm length for use with the product will be supplied by
   iv) a canister cap for the product will be supplied by

4. The product propellant will be CFC-12 (dichlorodifluoromethane) supplied by

5. will be used to sterilize the finished aerosol

product and delivery tubes. This operation will be performed by

6. Microbiological release testing of the finished product will be performed by

7. Draft labeling for outside sterile pack (overwrap), and package insert have been provided. Minor revisions are required and will be include in a separate review.

CONCLUSIONS & RECOMMENDATIONS:

Approvable, subject to complete and satisfactory answers to all outstanding deficiences and an acceptable CGMP inspection.

/S/

Robert P. Barron
Review Chemist, HFD-150

10-27-97 /S/

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

Please refer to my comments dated 10-27-97

cc: Orig. NDA #20-587
HFD-150/Division File
HFD-150/RPBarron
HFD-150/AMartin,MD
HFD-150/RHWood
HFD-150/DCatterson
R/D Init by:

June 5, 1997

Preliminary CMC Review for Completeness of Submission

Document: **Amendment AZ** dated 28-APRIL-1997

NDA 20-587 Sclerosol Intrapleural Aerosol

Reviewer: R. P. Barron RB

The following responses to the Agency letter of 9 AUGUST 1996 are considered incomplete or inadequate:

1. With regard to the Environmental Assessment requirements of the submission, the previous EA statement must be revised to reflect the new manufacturer, suppliers, etc. for the product. The revised document should include the additional information provided in this amendment.

   In addition, a copy should be provided of the current mining permit or other governmental document/statement indicating that the mining operation is in compliance with the environmental laws of the region. This would be a statement similar to the document provided for the previous French supplier.

2. Item 2, p. 114. The lot number and quantity of the talc which will serve as the reference standard should be specified. Additional information on the material should include the following:

   A. Source and supplier of the material
   B. Results of analysis of the material including:
      - Name and address of testing laboratory
      - Date of analysis
      - USP test results
      - Composition/Elemental Analysis
      - Purity
      - Physical properties
      - Particle size distribution
      - Moisture content
      - Volatiles
   C. Special tests used to further qualify the material as a reference standard
   D. Storage conditions of the material
   E. Container/closure for the standard
   F. Scheduled retest date

3. Item 5, p. 127. The limits (acceptable range) of the measured particle diameter at 90%, 50% and 10% of cumulative mass, for instance, should be specified in order to reproducibly determine the lot to lot consistency of the material for use in the product. Other means, such as curve fitting, for determining the use of this technique for qualification purposes may be acceptable.

4. Item 6, p. 132. The Specifications for Talc that were supplied by assay results for mineralogical composition. as the talc supplier, will not perform this test. Provide justification if this test will not be included in the specifications and methods for the material.

5. Item 8, p. 134. Provide and compare the results of analyses on (a) the CFC propellant supplied by and (b) the material provided by the previous supplier as a means of qualifying the new material and supplier.

6. Item 12. P. 210-1. Under the stability protocol, the specification limits, and items listed as "To be Determined" must be furnished. These include Particle Size, Level of Extractables, and Microbial Testing.

7. Microbiological comments, p. 217, the test procedures (p. 223 and p.228) will require a review by HFD-160 microbiologists. However, a more definite testing schedule, other than periodically, must first be established.

8. The applicant must demonstrate the comparability of talc which is processed by the use of and the material processed by the previously used. Equivalency needs to be demonstrated with regard to particle size distribution and particle morphology.

9. Three grades of talc, i.e. Grades 1, 2, and 3 are listed on p. 107 as being available from The raw material specifications (p. 110) list the crude talc as The basis for the selection of Grade #2, presumed from the above, i.e., should be explained and the selection justified.

10. The differences, if any, between deep mined and surface mined talc should be discussed and the type of mine which will be the source of talc for the product should be specified.

RHW
6-12-97

CC: ORIG. NDA 20-587
HFD-150/DIV FILE
RBARRON
RWOOD
DCATTERSON

MAY 7 1996

DIVISION OF ONCOLOGIC DRUG PRODUCTS HFD-150

Review of Chemistry, Manufacturing and Controls

NDA #: 20-587 Chem. Review #: 3 Review Date: 29-JAN-1996 (draft)
5-MAR-1996

Submission Type	Document Date	CDER Date	Assigned Date
Original	11-AUG -1995	15-AUG-1995	25-AUG-1995
NC	8-NOV-1995	9-NOV-1995	15-FEB-1996

Name & Address of Applicant: Bryan Corporation
Four Plympton Street
Woburn, MA 01801

Drug Product Name
- Proprietary : Sclerosol
- Non-proprietary: Sterile Aerosol Talc
- Code Name: none
- Chem Type/Ther Class 1-P

Pharmacol. Category/Indication: sclerosing agent indicted for malignant pleural effusion secondary to malignancies having spread to the pleural space

Dosage Form: sterile aerosol suspension
Strengths: 4.0 gm per canister
Route of Administration: intrapleurally
Dispensed: Rx

Chemical Name, Structural Formula, Molecular Formula, Mol. Wt.:

Name: Talc: hydrated magnesium silicate
Chlorite: magnesium and aluminum silicate

(Talc and Chlorite is a natural association and in the Trimouns orebody, the chlorite content varies from 2.5% to 6.0%, based on sample analyses.)

See Chemistry Review #1 for structure.

Supporting Document: None

Related Documents (if applicable): See Chemistry Review #1

Consults: None for this review. A consult to the Nomenclature Committee is pending.

Remarks/Comments: This review addresses the labeling for the product found on pp. 1 028 to 1 031.

Conclusion & Recommendations:

The comments on the draft labeling for the name, description and how supplies section for the product should be forwarded to the applicant for incorporation into the final draft labeling.

/S/

Robert P. Barron
Review Chemist, HFD-150

/S/ 5-7-96

Rebecca H. Wood, Ph.D.
Chemistry ~~Oncology~~ Team Leader HFD-150
Division of New Drug Chemistry I

cc: Orig. NDA 20-587
HFD-150/Div File
HFD-150/RPBarron
HFD-150/DCatterson
HFD-150/AMartin
HFD-150/LLARSON

JAN 5 1996

DIVISION OF ONCOLOGIC DRUG PRODUCTS HFD-150

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-587 **CHEM.REVIEW #:** 1 **REVIEW DATE:** November 8, 1995

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11-AUG-1995	15-AUG-1995	25-AUG-1995

NAME & ADDRESS OF APPLICANT: Bryan Corporation
Four Plympton Street
Woburn, MA 01801

Responsible Official: Frank Abrano, Chief Executive Officer
1-800-343-7711

DRUG PRODUCT NAME

Proprietary:	Requested of applicant
Nonproprietary/USAN:	Sterile Aerosol Talc
Code Name/#:	
Chem.Type/Ther.Class:	1-P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: sclerosing agent indicated for malignant pleural effusion secondary to malignancies having spread to the pleural space

DOSAGE FORM: sterile aerosol suspension
STRENGTHS: 4.0 gm per canister
ROUTE OF ADMINISTRATION: intrapleurally, via pleural trocar
DISPENSED: __XX__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Name: Talc: hydrated magnesium silicate
Chlorite: magnesium and aluminum silicate

(Talc and Chlorite is a natural association and in the Trimouns orebody, the chlorite content varies from 2.5% to 6.0% based on sample analyses.)

Molecular Formula: Talc #14807-96-4 $Mg_3Si_4O_{10}(OH)_2$ M.W. = 379.26
(with CAS Nos.) Chlorite #1318-59-0 $(Mg, Fe)_5\ Al\{AlSi_3O_{10}\}\{OH\}_8$

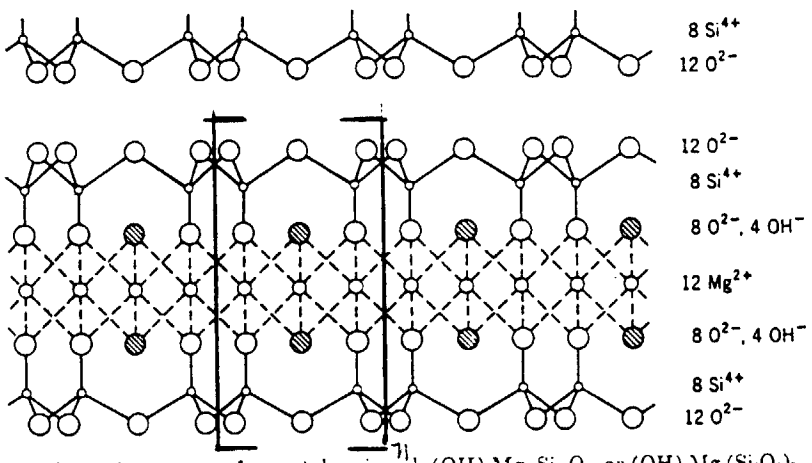

Fig. 2. Crystal structure of pure talc mineral, $(OH)_8Mg_{12}Si_{16}O_{40}$ or $(OH)_2Mg_3(Si_2O_5)_2$.

SUPPORTING DOCUMENTS:

1. DMF

2. Summary of findings with five exhibits of the Establishment Inspection (EI) on March 13 and 14, 1995, of the firm, as supplier of bulk talc, submitted by Jose A. Alicea, Investigator, SJN-DO, and Azza Talaat, Chemist, Det-DO.

3. Summary of findings of EI of (sterilization) on March 16 and 17th, 1995.

4. Summary of findings with exhibits of EI of on March 16 and 17th, 1995.

5. Summary of findings with exhibits of EI on March 16 and 17th, 1995 on

6. Memorandum of March 3, 1995 from Branch Chief, Investigations & Compliance Evaluation Br, HFD-324 to Associate Director, ITOB, HFC-134. Subject: in Aerosol Cans; 2nd Revision

RELATED DOCUMENTS (if applicable):

1. Waiver of application fees assessable under User Fee Act of 1992 dated April 21, 1995 by Amanda Peterson, Chief Mediator and Ombudsman.

2. FR notice of proposed rule to add sterile aerosol talc to the list of essential uses of CFC's drafted by the Office of General Counsel in response to Citizen Petition by Bryan Corp. Clearance record dated 10/6/95.

3. Proposed monograph on Talc appearing in Pharmacopeial Forum, 21(5), Sept.-Oct., 1995, pp. 1235-9.

CONSULTS:

1. Microbiological Consult to HFD-160, dated September 1, 1995 for review of the sterility aspects of NDA as found in DMF

2. EERs issued to HFD-324 on September 29, 1995 for inspection on the following firms associated with the NDA:

3. The applicant, Bryan Corporation, has previously been inspected and found in violation of CGMP regulations. Re-inspection to determine if the firm has taken remedial action was requested.

REMARKS/COMMENTS:

1. Given the patient population, malignancy related indications and route of administration, the product is not envisioned for chronic use. As a result, certain regulatory requirements will be weighted differently, or waived, for this drug product which are normally required of metered dose inhalers for chronic use and administered by inhalation

2. The submission, part 2.3, states talc is used widely today in the US, Europe and the Middle East as a sclerosing agent in the treatment of pleural effusions (for sixty years) but has not been approved for this use by any government regulatory body. Documents from indicate the propriety name in the European arena is "Mucosol Aerosol." A history or production (p. 1 041) indicates canisters of finished product have been manufactured since 1989 without any recalls.

3. The microbiological review is pending as of the date of this review.

4. The CGMP inspection of Bryan Corporation remains open with outstanding deficiencies from the previous inspection.

5. Due to the specialized nature of analytical methods, methods validation will not be required for the bulk drug substance.

CONCLUSIONS & RECOMMENDATIONS:

From a CMC standpoint, the application is considered approvable contingent upon the satisfactory response to the deficiencies outlined in draft letter to the applicant.

/S/ 12/22/95

Robert P. Barron
Review Chemist, HFD-150

/S/ 12-22-95

Rebecca H. Wood, Ph.D.
Supervisory Chemist, HFD-150

cc: Orig. NDA #20-587
HFD-150/Division File
DISTRICT OFFICE
HFD-150/RPBarron
HFD-150/AMartin, MD
HFD-150/DCatterson
HFD-102/ [#1 only]
R/D Init by:
filename: