CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-388

Chemistry Review(s)

NDA 21-388

REVIEW # 3

STERILE TALC POWDER

JOSEPHINE M. JEE
REVIEW CHEMIST
DIVISION OF ONCOLOGY
DRUG PRODUCTS
HFD-150/810

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-388

2. REVIEW #: 3

3. REVIEW DATE: 09-OCT-2003

4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA Meeting	29-MAR-2002
NDA 20-587	24-DEC-1997
NDA 21-388	23-SEP-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-388 Amendment	07-APR-2003
NDA 21-388 Amendment	02-APR-2003
NDA 21-388 Amendment	03-JUL-2003
NDA 21-388 Amendment	12-AUG-2003
NDA 21-388 Amendment	30-SEPT-2003
NDA 21-388 Amendment	09-OCT-2003

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name:	Bryan Corporation
Address:	Four Plympton Street Woburn, MA 018011-p
Representative:	Waldman Biomedical Cosultancy, Inc
Telephone:	(516) 763-1158

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ultra 2000 Talc
b) Non-Proprietary Name (USAN): Talc
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type: 3
   - Submission Priority: p

9. LEGAL BASIS FOR SUBMISSION:
RLD

10. PHARMACOL. CATEGORY:
T

1

11. DOSAGE FORM: Powder

12. STRENGTH/POTENCY: 5.0 g per bottle

NOTE: Size has been changed from — g Bottle to 5.0 g Bottle as of 07-JUL-2003

13. ROUTE OF ADMINISTRATION: Intrapleural

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

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

Talc $Mg_3Si_4O_{10}(OH)_2$ M.W. = 379.26

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
\	III	\	\	2	Adequate	26-JAN-2002	The previous reviews were for use in a
\	III	\	\	2	Adequate	06-NOV-2001	The previous review was for use in an
\	III	\	\	2	Adequate	24-MAY-2000	The previous were for use In an

[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 (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Sterile Talc Powder	NDA 21-388 Review # 1	Sterile Talc Powder
Sterile Talc Powder	NDA 21-388 Review # 2	Sterile Talc Powder
Sclerosol® Aerosol Sterile Talc	NDA 20-587	Aerosol Talc Powder Cross-referenced for drug substance CMC information

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approval	06-MAR-2003	Peiling Yang, Ph.D
EES	Approval	19-MAR-2003	PREAPPROVAL BRANCH, OC
Pharm/Tox	Approval	03-JAN-2003	M. Anwar Goheer, Ph.D.
Biopharm	Approval	13-FEB-2003	Carl-Michael Staschen, MD, PhD
Methods Validation	N/A	N/A	N/A
OPDRA	N/A	N/A	N/A
EA	N/A	N/A	N/A
Microbiology	Approval	10-SEP-2003	Vinayak Pawar, Ph.D.

The Chemistry Review for NDA 21-388

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended to be **approved from the CMC perspective.** The amended NDA application is able to demonstrate successful product sterilization validation for three Talc Powder lots. The application is also recommended for approval from the microbiological standpoint on 10-SEP-2003.

The PAI is acceptable by the Office of Compliance on Mar. 19, 2003.

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

We await Bryan's results of the study of [

]

provided and are included in this review.

II. Summary of Chemistry Assessments

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

Sterile Talc Powder will be marketed for intrapleural administration supplied in a single use 100-mL — brown glass bottle serum, sealed with a gray 20 mm stopper and covered with a Flip-off seal. Each bottle contains 5.0 g of Talc USP (Ultra 2000 Talc), either white or off-white to light gray, asbestos-free and brucite-free grade of Talc of controlled particle size.

The drug substance and the drug product are the same, no additional ingredients are added to the drug product.

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

The product will be marketed in cartons containing ten 5.0 g, single doses of Sterile Talc Powder. Each bottle containing Sterile Talc Powder is placed on a pouch and the pouch is sealed around the entire rim. The pouch is white — on the back and clear plastic film on the front. Ten pouches each containing one bottle of Sterile Talc Powder are packaged in a white vanilla box. The primary label appears on the end panel of the carton.

The recommended doses are — g administered intrapleurally via chest tube. As per the labeling, Sodium Chloride Injection, USP is added to the sterile talc powder using a 16 gauge needle attached to a 60-mL LuerLok syringe to prepare, under aseptic condition, for the talc slurry. This talc slurry is then administered intrapleurally via chest tube.

Based on the stability data provided in this application and in NDA 20-587, an expiration dating period of 24 months, when stored at controlled room temperature (25 ± 2 ^{0}C) is established for the Sterile Talc Powder in bottle, 5.0 g.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, the sponsor has provided adequate documentation for the composition of the proposed drug product, control of talc, the manufacturing process, control of critical manufacturing steps and control of the finished product. USP methods are used in this application; therefore no further validation is necessary. Sterile Talc Powder is the same as the Talc drug substance. Talc is very stable with no possible hazardous reaction and no decomposition products. No potency or assay method currently exists. Talc is considered by geological standards to be a rather old and stable material. From a Microbiology perspective, the amended NDA application is able to demonstrate successful product sterilization validation of three Talc Powder lots. The application is recommended for approval from the microbiological standpoint on 10-SEP-2003.

The PAI is acceptable by the Office of Compliance on Mar. 19, 2003.

III. Administrative

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

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/s/

Josephine Jee
12/3/03 10:37:55 AM
CHEMIST

Richard Lostritto
12/3/03 04:06:51 PM
CHEMIST

NDA 21-388

REVIEW # 2

STERILE TALC POWDER

JOSEPHINE M. JEE
REVIEW CHEMIST
DIVISION OF ONCOLOGY
DRUG PRODUCTS
HFD-150/810

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-388

2. REVIEW #: 2

3. REVIEW DATE: 21-MAR-2003

4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA Meeting	29-MAR-2002
NDA 20-587	24-DEC-1997

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-388	23-SEP-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Bryan Corporation
Address:	Four Plympton Street Woburn, MA 018011-p
Representative:	Waldman Biomedical Cosultancy, Inc
Telephone:	(516) 763-1158

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ultra 2000 Talc
b) Non-Proprietary Name (USAN): Talc
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type:
   - Submission Priority: 1-p

9. LEGAL BASIS FOR SUBMISSION:
RLD

10. PHARMACOL. CATEGORY:
L
1

11. DOSAGE FORM: Powder

12. STRENGTH/POTENCY: —g per bottle

13. ROUTE OF ADMINISTRATION: Intrapleural

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:
N/A

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

Talc $Mg_3Si_4O_{10}(OH)_2$ M.W. = 379.26

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
\	III	\	\	2	Adequate	26-JAN-2002	The previous reviews were for use in a
\	III	\	\	2	Adequate	06-NOV-2001	The previous review was for use in an
\	III	\	\	2	Adequate	24-MAY-2000	The previous were for use In an

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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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Sclerosol® Aerosol Sterile Talc	NDA 20-587	Aerosol Talc Powder Cross-referenced for drug substance CMC information

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approvable	06-MAR-2003	Peiling Yang, Ph.D
EES	Acceptable	19-MAR-2003	PREAPPROVAL BRANCH, OC
Pharm/Tox	Approvable	03-JAN-2003	M. Anwar Goheer, Ph.D.
Biopharm	Approvable	13-FEB-2003	Carl-Michael Staschen, MD, PhD
Methods Validation	N/A	N/A	N/A
OPDRA	N/A	N/A	N/A
EA	N/A	N/A	N/A
Microbiology	Approvable	20-MAR-2003	Vinayak Pawar, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-388

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable pending resolution of the sterilization validation. The applicant should provide data to show successful dose verification studies for the three validation lots. They should also show successful final sterilization of those lots to achieve — In addition, the sponsor should demonstrate the absence of — from the newly validated samples considering that the sponsor had experienced difficulty in recovering these organisms. The PAI is acceptable by the Office of Compliance on Mar. 19, 2003.

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

We await Bryan's results of the study of [redacted]

provided and are included in this review.

II. Summary of Chemistry Assessments

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

Sterile Talc Powder will be marketed for intrapleural administration supplied in a single use 100-mL — glass bottle serum, sealed with a gray 20 mm stopper and covered with a Flip-off seal. Each bottle contains — g of Talc USP (Ultra 2000 Talc), either white or off-white to light gray, asbestos-free and brucite-free grade of Talc of controlled particle size.

The drug substance and the drug product are the same, no additional ingredients are added to the drug product.

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

The product will be marketed in cartons containing ten — g, single doses of Sterile Talc Powder. Each bottle containing Sterile Talc Powder is placed on a pouch and the pouch is sealed around the entire rim. The pouch is white — on the back and clear plastic film on the front. Ten pouches each containing one

bottle of Sterile Talc Powder are packaged in a white vanilla box. The primary label appears on the end panel of the carton.

The recommended doses are —— g administered intrapleurally via chest tube.

Based on the stability data provided in this application and in NDA 20-587, an expiration dating period of 24 months, when stored at controlled room temperature (25 ± 2 ^{0}C) is established for the Sterile Talc Powder in bottle, — g.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, the sponsor has provided adequate documentation of the composition of the proposed drug products, control of talc, the manufacturing process, control of critical manufacturing steps and control of the finished product. USP methods are used in this application; therefore no validation is necessary. Sterile Talc Powder is the same as the Talc drug substance. Talc is very stable with no possible hazardous reaction and no decomposition products. No potency or assay method currently exists. Talc is considered by geologically standards as a rather old and stable material. However, from a Microbiology perspective, the application is **approvable** pending resolution of the sterilization validation. The applicant should provide data to show successful dose verification studies for the three validation lots. They should also show successful final sterilization of those lots to achieve —— In addition, the sponsor should demonstrate the absence of — from the newly validated samples considering that the sponsor had experienced difficulty in recovering these organisms. These microbiology issues are important since they are part of the drug product specifications. The PAI is acceptable by the Office of Compliance on Mar. 19, 2003.

III. Administrative

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

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/s/

Josephine Jee
3/21/03 10:54:32 AM
CHEMIST

Richard Lostritto
3/21/03 11:10:08 AM
CHEMIST

NDA 21-388

REVIEW # 1

STERILE TALC POWDER

JOSEPHINE M. JEE
REVIEW CHEMIST
DIVISION OF ONCOLOGY
DRUG PRODUCTS
HFD-150/810

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-388

2. REVIEW #: 1

3. REVIEW DATE: 08-MAR-2003

4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA Meeting	29-MAR-2002
NDA 20-587	24-DEC-1997

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-388	23-SEP-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Bryan Corporation
Address:	Four Plympton Street Woburn, MA 018011-p
Representative:	Waldman Biomedical Cosultancy, Inc
Telephone:	(516) 763-1158

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ultra 2000 Talc
b) Non-Proprietary Name (USAN): Talc
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type:
   - Submission Priority: 1-p

9. LEGAL BASIS FOR SUBMISSION:
RLD

10. PHARMACOL. CATEGORY:
[ ]

11. DOSAGE FORM: Powder

12. STRENGTH/POTENCY: — g per bottle

13. ROUTE OF ADMINISTRATION: Intrapleural

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:
N/A

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

Talc $Mg_3Si_4O_{10}(OH)_2$ M.W. = 379.26

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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\	III	\	\	2	Adequate	06-NOV-2001	The previous review was for use in an
\	III	\	\	2	Adequate	24-MAY-2000	The previous were for use In an

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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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Sclerosol® Aerosol Sterile Talc	NDA 20-587	Aerosol Talc Powder Cross-referenced for drug substance CMC information

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approvable	06-MAR-2003	Peiling Yang, Ph.D
EES	One Pending Facility	08-MAR-2003	PREAPPROVAL BRANCH, OC
Pharm/Tox	Approvable	03-JAN-2003	M. Anwar Goheer, Ph.D.
Biopharm	Approvable	13-FEB-2003	Carl-Michael Staschen, MD, PhD
Methods Validation	N/A	N/A	N/A
OPDRA	N/A	N/A	N/A
EA	N/A	N/A	N/A
Microbiology	Pending		Vinayak Pawar, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-388

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval of NDA 21-450 is recommended from a CMC perspective, pending on an acceptable EES and an acceptable Microbiology recommendation.

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

We await Bryan's results of the study of [redacted]

provided and are included in this review.

II. Summary of Chemistry Assessments

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

Sterile Talc Powder will be marketed for intrapleural administration supplied in a single use 100-mL [redacted] glass bottle serum, sealed with a gray 20 mm stopper and covered with a Flip-off seal. Each bottle contains [redacted] g of Talc USP (Ultra 2000 Talc), either white or off-white to light gray, asbestos-free and brucite-free grade of Talc of controlled particle size.

The drug substance and the drug product are the same, no additional ingredients are added to the drug product.

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

The product will be marketed in cartons containing ten [redacted] g, single doses of Sterile Talc Powder. Each bottle containing Sterile Talc Powder is placed on a pouch and the pouch is sealed around the entire rim. The pouch is white [redacted] on the back and clear plastic film on the front. Ten pouches each containing one bottle of Sterile Talc Powder are packaged in a white vanilla box. The primary label appears on the end panel of the carton.

The recommended doses are [redacted] g administered intrapleurally via chest tube.

Based on the stability data provided in this application and in NDA 20-587, an expiration dating period of 24 months, when stored at controlled room temperature (25 ± 2 ^{0}C) is established for the Sterile Talc Powder in bottle, — g.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, the sponsor has provided adequate documentation of the composition of the proposed drug products, control of talc, the manufacturing process, control of critical manufacturing steps and control of the finished product. Dr. Vinayak Pawar has not finished the review of microbiology controls; therefore the approvability of this NDA will depend on the microbiology review. USP methods are used in this application; therefore no validation is necessary. Sterile Talc Powder is the same as the Talc drug substance. Talc is very stable with no possible hazardous reaction and no decomposition products. No potency or assay method currently exists. Talc is considered by geologically standards as a rather old and stable material. Establishment inspections have not been completed as of this date and this could affect the approvability of this application.

III. Administrative

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

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/s/

Josephine Jee
3/18/03 04:34:52 PM
CHEMIST

Richard Lostritto
3/19/03 09:53:53 AM
CHEMIST

NDA FILEABILITY CHECKLIST

NDA Number: 21-388 Applicant: Bryan Corporation Stamp Date: 23-SEP-2002

Drug Name: Sterile Talc Powder

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) ___Yes ✓

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?		X	
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?		X	Submitted 1 point analysis at 3 months. However, talc is very stable and the chance of breaking down is negligible.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?			
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: Josephine M. Jee Date: 29-OCT-2002

Team Leader: Richard T. Lostritto Date:

cc:
Original NDA 21-388
HFD-150/Division File
HFD-150/J.Jee/29-OCT-2002
HFD-150/R.Lostritto
HFD-150/S.Bradley

NDA Number: 21-388 **Applicant:** Bryan **Drug Name:** Sterile Talc Powder

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Status
—	\	\	**yes**	**ok**
—	\	\	**yes**	**adequate**
none	\	\	**no**	**Justification: not direct drug contact**
—	\	\	**yes**	

APPEARS THIS WAY
ON ORIGINAL