Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To:	Jane Campbell/Alan Waldman	**From:**	Sean Bradley, CSO
Fax:	845-469-4212/516-536-7628	**Fax:**	310-827-4590
Phone:	845-469-4289	**Phone:**	301-594-5770
Pages, including cover sheet:	1	**Date:**	September 30, 2003
Re:	NDA 21-388-Information Request		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your July 3, 2003 NDA resubmission for Sterile Talc Powder, number 21-388.

We also refer to our September 25, 2003 information request, in particular question number 1 where we asked you, "What is the total weight of the new 5 gram finished Sterile Talc product?" **To clarify, we are asking you to provide updated specifications for the 5 gram fill weight bottle (e.g. fill weight range).**

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Jane Campbell/Alan Waldman	**From:** Sean Bradley, CSO
Fax: 845-469-4212/516-536-7628	**Fax:** 310-827-4590
Phone: 845-469-4289	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** September 26, 2003
Re: NDA 21-388-Labeling	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your July 31, 2003 FPL submission for Sterile Talc Powder, number 21-388.

We have completed our review of this FPL and conclude that it is approvable pending the changes outlined on the following page.

Please review these changes and if your are in agreement, please submit an updated FPL incorporating these changes.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.
Regulatory Project Manager

1 pages redacted from this section of the approval package consisted of draft labeling

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To:	Jane Campbell/Alan Waldman	**From:**	Sean Bradley, CSO
Fax:	845-469-4212/516-536-7628	**Fax:**	310-827-4590
Phone:	845-469-4289	**Phone:**	301-594-5770
Pages, including cover sheet:	1	**Date:**	September 25, 2003
Re:	NDA 21-388-Information Request		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your July 3, 2003 NDA resubmission for Sterile Talc Powder, number 21-388.

We are currently reviewing your application and request the following:

1. **What is the total weight of the new 5 gram finished Sterile Talc product?**
2. **Are you using the same bottles and closure systems that were used for the –gram Sterile Talc product?**

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.
/S/
Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-388

Bryan Corporation
C/O
Waldman Biomedical Consultancy, Inc.
P.O. Box 575
Oceanside, NY 11572

Attention: Alan A. Waldman, Ph.D.
President

Dear Dr. Waldman:

We acknowledge receipt on July 7, 2003 of your July 3, 2003 resubmission to your new drug application for Sterile Talc Powder.

We consider this a complete, class 2 response to our March 24, 2003 action letter. Therefore, the user fee goal date is January 7, 2004.

If you have any question, call Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 594-5770.

Sincerely,

{See appended electronic signature page}

/S/

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sean Bradley
8/13/03 03:51:25 PM
Signing off for Dotti Pease

Waldman Biomedical Consultancy, Inc.

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SUPPL NEW CORRES
SNC

FACSIMILE TRANSMISSION

ORIGINAL

To: Mr. Sean Bradley
CDER/DODP
301-594-5770

From: Dr. Alan A. Waldman
Ms. Jane B. Campbell
Waldman Biomedical Consultancy, Inc.

RECEIVED
AUG 13 2003
DDR-150/CDER

Date: August 12, 2003

2 Pages (including this Header) in this submission

If there are any problems with this transmission please call (845) 468-4289

RE: Response to request from Dr. Pawar for dates of manufacture of the Sterile Talc Powder lots that were part of the Sterilization Validation study

Dear Mr. Bradley,

Today we received a call from Dr. Pawar, the Microbiology reviewer for the NDA for Bryan Corporation's Sterile Talc Powder. Dr. Pawar requested that we provide the dates of manufacture for the three lots of Bryan Corporation's Sterile Talc Powder that were included in the validation studies required by the FDA Action Letter for NDA 21-388. After checking our files we called Dr. Pawar to relay that -

Lot 3E013 was manufactured on May 7, 2003.
Lot 3E014 was manufactured on May 8, 2003.
Lot 3E015 was manufactured on May 8, 2003.

He was satisfied with this information and asked that this be sent to him by Fax for his files. We have done this. We are hereby sending a copy to you for inclusion in the file for NDA 21-388.

Hopefully this will clear the way for the approval for this submission, which, as you know, we are anxiously awaiting.

If there are any further questions please don't hesitate to call on us.

Best regards,

DDR,
Please process this as a SNC. See NDA 21-388.
Thanks
SAB

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 •

Waldman Biomedical Consultancy, Inc.℠

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July 31, 2003

ORIGINAL

RECEIVED

AUG 7 2003

DDR-150/CDER

Document Mail Center
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products
(HFD-150)
1451 Rockville Pike
Rockville, MD 20852

Attn: Mr. Sean Bradley

RE: **FPL**
Final Printed Package Insert for Sterile Talc Powder - NDA 21-388

Dear Mr. Bradley,

As directed in the FDA's Action Letter for of Sterile Talc Powder NDA 21-388 that was received in a FAX dated 3/24/03, Bryan Corporation is hereby providing 20 paper copies of the FPL, Final Printed Package Insert. Ten of the 20 copies have been individually mounted on heavy-weight paper. The additional 10 copies are provided in a closed file envelope.

In addition, also as directed in the FDA's Action Letter, we will be providing under separate cover to the Division of Drug Marketing, Advertising and Communications, two copies of the package insert.

If there are any questions regarding this labeling or if additional copies are desired, please don't hesitate to contact us at (516) 763-1158 or at the contact points in the letterhead.

Best regards,

Yours truly,

Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

ENC.

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7620

21/45 DAY FILING MEETING

NDA# 21-388

Date Received: September 20, 2002 **PDUFA Due Date:** July 23, 2003

Drug Name: Sterile Talc Powder

Sponsor: Bryan Pharmaceuticals

Proposed Indication:

Assigned Reviewer and Team Leaders

Clinical:	Scher/Griebel
Statistical:	Yang/Chen
Pharm/Tox:	Goheer/Leighton
Biopharmaceutical:	Williams/Rahman
Chemistry:	Jee/Lostritto
Microbiology:	Pawar/Cooney

Discussion Points

1. Clinical

   Is there a waiver for the demographic review of safety and efficacy?
   Methodology of literature review received.

2. Statistical

   No study design to review. We will review the Sclerosol (NDA 20-954) submission and do a joint review with medical.

3. Pharmacolgy/Toxicology

   Based upon historic use of the product, it meets minimal filability.

4. Biopharmaceutics

   OK from a filing perspective.

5. Chemistry

Nomenclature	Request 90 Days prior to due date (*Consult sent-Pending*)
EA	categorical exclusion requested?/*YES*
EER	
Stability statistics	*No. N/A. If stability data is available please request from sponsor.*

6. Microbiology

Volume 1 and Volume 2 Part A & B were submitted for microbiology review. Upon screening the material submitted for review it was revealed that three latest production lots [2E003, 2E004 and 2E005] were manufactured by Bryan Corporation on 4/15/02. However, the sponsor has submitted data only on a representative production Lot 2E003. For Microbiology review we would like to see a summary of (1) bioburden results for all three lots at the bulk stage (2) [redacted] dose results for all three lots (3) sterility results for all three lots. (4) Endotoxin Test results for three lots. A summary of each of the above in a table form will do.

Division Goals

1. Classification: *Priority*

2. ODAC?: *No*

3. Sign-off at Division Level: *To Pazdur by March 14, 2003*

Waldman Biomedical Consultancy, Inc.

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July 3, 2003

ORIGINAL

ORIG AMENDMENT

N-000 (EE)

AZ

RECEIVED

JUL - 7 2003

HFD-150 / CDER

Dr. Richard Pazdur, MD
FDA, Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
Office of the Director
1451 Rockville Pike
Rockville, MD 20852

Attn: Mr. Sean Bradley

Re: Amendment to Original New Drug Application - 21-388 for Sterile Talc Powder
Responding to FDA Action Letter dated March 24, 2003

Dear Mr. Bradley,

In response to the FDA's Action Letter for NDA 21-388 that was received by Bryan Corporation in a FAX dated 3/24/03, we are hereby filing an amendment to our NDA 21-388 addressing the issues noted in this letter.

Eight copies of this Amendment are being provided. Each contains a copy of the original Action Letter from the FDA, and a discussion of the actions Bryan Corporation has taken to address the Agency's concerns regarding sterility of the product, and the product insert.

We provide a description of, and tables that summarize the data collected from, the studies agreed upon by the Agency (submitted on April 7, 2003, accepted on May 15, 2003) regarding sterility of Sterile Talc Powder.

We also provide a copy of the final text for the Product Insert labeling. This has been amended to reflect the change in product size from – g to 5 g. As soon as final printed copies become available they will be provided to the Agency as requested along with any promotional materials developed for use with this product.

If there are any questions regarding the information provided, or if the Agency would like any additional copies of this amendment, please don't hesitate to call on us at (516) 763-1158 or at the contact points in the letterhead. We look forward to receiving final approval for Sterile Talc Powder.

Best regards.

Yours truly,

Alan A. Waldman

Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

ORIGINAL

N-000-C

Waldman Biomedical Consultancy, Inc.

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FACSIMILE TRANSMISSION

To: Mr. Sean Bradley, CSO
Division of Oncology Drug Products
ODE 1/ CDER
FAX (301) 594-0498

RECEIVED
APR 15 2003
HFD-150 / CDER

From: Dr. Alan A. Waldman
Ms. Jane B. Campbell
Waldman Biomedical Consultancy, Inc.

Date: April 7, 2003

Number of Pages (including this Header): 5

If there are any problems with this transmission please call (845) 468-4289

RE: Proposal for Responding to NDA 21-388 FDA Action Letter

Dear Mr. Bradley,

As discussed, Bryan Corporation plans to comply with the requests of the Agency in the Action Letter. In order to do this correctly, Bryan Corporation would like to obtain guidance from the Agency on their plans for satisfying the FDA's requests for additional information concerning the sterilization of Sterile Talc Powder.

It is our understanding that we could either request a teleconference to discuss these issues or we could provide them in a FAX to the Agency with a request for a response. In order to help speed the process, we have decided to provide our questions in a FAX.

In the attached letter we have provided a brief outline of the protocol for the planned study to validate the sterilization procedure, along with a list of our concerns and questions. We ask that you share this with the appropriate staff and get back to us with advice on the suitability of our plans and with responses to our questions. If the Agency feels it is necessary to have a teleconference to discuss these matters we will be happy to do so and will try to make ourselves available at a time that is convenient to the Agency.

Three hard copies of the attached letter are being sent to the Agency by courier. If additional copies are needed or if you would like to discuss this further, please don't hesitate to call on us.

Best regards.

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628

ORIGINAL
N-000-C

Waldman Biomedical Consultancy, Inc.

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FACSIMILE TRANSMISSION

To: Mr. Sean Bradley, CSO
Division of Oncology Drug Products
ODE 1/ CDER
FAX (301) 827-4598

RECEIVED
APR 15 2003
HFD-150 / CDER

From: Dr. Alan A. Waldman
Ms. Jane B. Campbell
Waldman Biomedical Consultancy, Inc.

Date: April 2, 2003

Number of Pages (including this Header): 3

If there are any problems with this transmission please call (845) 468-4289

RE: Response to NDA 21-388 FDA Action Letter

Dear Mr. Bradley,

Attached is a letter which notifies the Agency that Bryan Corporation intends to file an amendment responding to the deficiencies noted in the Agency's Action Letter for NDA 21-388.

As discussed, Bryan Corporation plans to comply with the requests of the Agency in the Action Letter. We would however first like to obtain guidance from the Agency about a change made to the labeling by the Agency regarding the usual dose. We are submitting this first because it may affect our plans for addressing the Agency's concerns related to the validation of the sterilization.

It is our understanding that we could provide this request in a FAX to the Agency with a request for a speedy review and response from the Agency.

Three hard copies of the attached letter are being sent to the Agency by courier. If additional copies are needed or if you would like to discuss this further, please don't hesitate to call on us.

Best regards,

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Alan Waldman, PhD	**From:** Sean Bradley, CSO
Fax: 516-536-7628	**Fax:** 310-827-4590
Phone: 516-763-1158	**Phone:** 301-594-5770
Pages, including cover sheet: 10	**Date:** March 21, 2003
Re: NDA 21-388-FDA Action Letter	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

Attached is a copy of the FDA Action Letter for this application. The official hard copy is being forwarded to you via the US Postal Service.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Regards,

Sean Bradley, R.Ph.

Regulatory Project Manager

Redacted 1

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secret and/or

confidential

commercial

information

Waldman Biomedical Consultancy, Inc.SM

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March 17, 2003

N-000-XP ORIGINAL

Dr. Richard Pazdur, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
Office of the Director
1451 Rockville Pike
Rockville, MD 20852

Attn: Mr. Sean Bradley

RECEIVED
MAR 1 8 2003
HFD-150 / CDER

Re: Informational Amendment - C - Patents Statement
For New Drug Application - 21388
Bryan Corporation's Sterile Talc Powder

Dear Dr. Pazdur,

The original NDA submission for Bryan Corporation's Sterile Talc Powder, N 21388, addresses Patents by indicating "NOT APPLICABLE". As requested by the Agency, on behalf of Bryan Corporation of Woburn, Massachusetts, we are hereby submitting two copies of this letter, which contains the attached "No Relevant Patents Statement" to be added to the above NDA Patent Certification.

If additional copies are needed, or if there are any questions regarding this matter, please don't hesitate to contact either Dr. Alan Waldman, President of Waldman Biomedical Consultancy (WBC) or Ms. Jane Campbell, Senior Consultant for Regulatory Affairs for WBC us at the address noted in the letterhead.

Best regards.

Yours truly,

Alan A. Waldman

Dr. Alan A. Waldman, Ph.D.
Acting as Agent for
Bryan Corporation

Waldman Biomedical Consultancy, Inc.℠
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March 17, 2003

Dr. Richard Pazdur, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
Office of the Director
1451 Rockville Pike
Rockville, MD 20852

Attn: Mr. Sean Bradley

Re: Informational Amendment - C - Orphan Drug Extension
For New Drug Application - 21-388
Bryan Corporation's Sterile Talc Powder

Dear Dr. Pazdur,

As requested, on behalf of Bryan Corporation of Woburn, Massachusetts we are hereby submitting two copies of a letter we received from the Office of Orphan Products Development. A copy of this submission has also been provided to the Agency via FAX..

In October of 2001 Bryan Corporation submitted a request for Orphan Drug Designation for Sterile Talc Powder. This letter explains that the original orphan drug designation for Sclerosol Sterile Talc Powder, granted on September 18, 1995 applies to the sterile talc regardless of the dosage form.

If additional copies are needed, or if there are any questions regarding this matter, please don't hesitate to contact either Dr. Alan Waldman, President of Waldman Biomedical Consultancy (WBC) or Ms. Jane Campbell, Senior Consultant for Regulatory Affairs for WBC us at the address noted in the letterhead.

Best regards.

Yours truly,

Alla A. Waldman

Dr. Alan A. Waldman, Ph.D.
Acting as Agent for
Bryan Corporation

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

March 11, 2003

Waldman Biomedical Consultancy, Inc.
P.O. Box 575
Oceanside, NY 11572

Attention: Alan A. Waldman, PhD
Agent for Bryan Corporation

Dear Dr. Waldman:

This is in response to the correspondence dated January 10, 2002, in which you request the withdrawal of the orphan drug designation request for sterile talc powder indicated for the treatment of malignant pleural effusion, on behalf of the Bryan Corporation, submitted October 8, 2001 (request # 01-1519)

The reason for the withdrawal request is that orphan-drug status had previously been granted for sterile talc powder. Bryan Corporation received orphan-drug status September 18, 1995, for sterile talc powder for the treatment of malignant pleural effusion, designation request # 95-0915. Orphan designation is specific for an active drug moiety and indication without regard to dosage form or delivery system. Subsequent New Drug Application (NDA) submissions for sterile talc powder for the treatment of pleural effusion, regardless of dosage form, should be eligible for a waiver of the PDUFA Fee.

Effective as of this date, the Office of Orphan Products Development considers your orphan drug designation request # 01-1519 withdrawn.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Waldman Biomedical Consultancy, Inc.

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FACSIMILE TRANSMISSION

To: Dr. Vinnie Pawar
Reviewer, Microbiology

From: Dr. Alan A. Waldman
Waldman Biomedical Consultancy, Inc.

Date: March 4, 2003

Number of Pages (including this Header): 41

If there are any problems with this transmission please call (516) 763-1158

RE: Response to NDA 21-388 Information Request
FDA Request, 030304, Regarding Further Information on — on Changes in Microbiology Testing

Dear Dr. Pawar,

As agreed during our telephone discussion of this morning, we are sending, attached, information which we believe will help clarify the matter of — being found in validation lots of Sterile Talc Powder, even after low levels of gamma irradiation, as well as the steps that have been taken by Bryan Corporation to prevent such contamination being an issue in the future. A copy of this material is also being shared with Mr. Sean Bradley, Regulatory Project Manager for this NDA.

With regard to — itself, we understand that

Please note that — is stated —

With regard to actions taken to prevent such contamination, we are attaching the Report, including Attachments (total of 33 pages), presenting the results of the investigation, the actions taken on this matter, and the resulting new testing SOP that is now in place.

(continued overleaf...)

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628
Web Site http://www.waldmanbiomed.com • e-Mail consultancy@waldmanbiomed.com

We hope the information provided resolves any concerns about this matter. Please do not hesitate to contact us at the contact points in the letterhead if further information or discussion on this matter is desired.

Best regards.

Alan Waldman, PhD
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

Cc: Mr. Sean Bradley
Regulatory Project Manager

Waldman Biomedical Consultancy, Inc.℠
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February 11, 2003

DUPLICATE
ORIG AMENDMENT
N-000 E

RECEIVED
FEB 12 2003
HFD-150 / CDER

Document Mail Center
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852

Attn: Mr. Sean Bradley

RE: **Response to NDA 21-388 FDA Information Request dated February 6, 2003, including analysis of Sclerosol safety experience and copies of literature referenced in Section 9**

Dear Mr. Bradley,

As requested in your FAX dated 2/6/03 (see copy attached), we are hereby providing 3 copies of this letter which includes an analysis of the past safety history for Sclerosol and copies of all of the literature articles referenced in Section 9 of NDA 21-388 for Bryan Corporation's Sterile Talc Powder.

In a separate submission, Bryan Corporation has provided 3 copies of Section 9.

With regard to the second request for information, concerning adverse events related to the currently approved and marketed product, Sclerosol, and an analysis of how this experience may support the safety of Sterile Talc Powder, we can provide the following information:

a. Sclerosol, which contains the same talc as Sterile Talc Powder, provides the talc in a packaging which delivers the talc, in aerosolized form, through a trocar, during thoracoscopy.
b. There have been two incidents, one in 2001, one in 2002, of transient adverse effects during or following the incorrect application of Sclerosol through a chest tube, rather than as labeled, through a trocar during thoracoscopy.
c. Both of these events were reported to Bryan Corporation, and after review were determined to be related to the aerosol spray, rather than to the talc itself.
d. No other adverse events have been reported to Bryan Corporation.

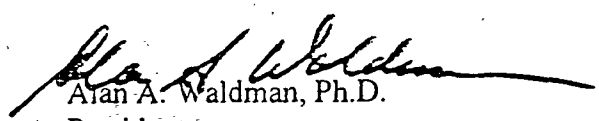
Based on this record of lack of any adverse events related to talc itself, it is felt that the use of Sterile Talc Powder, which is to be instilled through a chest tube in slurry form, will be a safe procedure, and will not result in any adverse effect on treated patient.

With regard to the third request, for copies of references not previously provided, we are submitting them in the attached. For ease in review, we are also including another copy of the review articles by Sahn and by Light previously submitted in Section 9.1.

If the Agency would like any additional copies or would like to discuss this matter further with us, please don't hesitate to contact us at the contact points in the letterhead.

Best regards,

Yours truly,



Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

Enclosure: Literature references

DUPLICATE

Waldman Biomedical Consultancy, Inc.

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February 9, 2003

N-000-C

Document Mail Center
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852

RECEIVED
FEB 11 2003
HFD-150 / CDER

Attn: Mr. Sean Bradley

RE: Response to NDA 21-388 Information Request
FDA Request dated February 6, 2003, Regarding Section 9

Dear Mr. Bradley,

As requested in your FAX dated 2/6/03 we are hereby providing 3 copies of Section 9 from NDA 21-388 for Bryan Corporation's Sterile Talc Powder. To the best of our knowledge, we have not inadvertently omitted any sections of this NDA.

In a separate submission, Bryan will respond to the requests for an analysis of the adverse events associated with Sclerosol and for copies of the literature referenced in Section 9.

If the Agency would like any additional copies or would like to discuss this matter further with us, please don't hesitate to contact us at the contact points in the letterhead.

Best regards,

Yours truly,

Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Jane Campbell	**From:** Sean Bradley, CSO
Fax: 845-469-4212	**Fax:** 310-827-4590
Phone: 845-469-4289	**Phone:** 301-594-5770
Pages, including cover sheet: 3	**Date:** February 6, 2003
Re: NDA 21-388-Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

We are currently reviewing your application and would like to have a teleconference with your Bryan's CMC group to discuss the attached issues regarding the — used for sterile talc powder.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

Regulatory Project Manager

Redacted 2

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confidential

commercial

information

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Jane Campbell	**From:** Sean Bradley, CSO
Fax: 845-469-4212	**Fax:** 310-827-4590
Phone: 845-469-4289	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 6, 2003
Re: NDA 21-388-Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

We are currently reviewing your application and request the following:

1. Section 9 and attachment 9.1 are missing from volume 6 of your NDA submission. Please submit this information expeditiously. In addition, please verify that you have not inadvertantly omitted any other sections of the paper NDA, particularly from volume 6.

2. We refer to our fax of May 7, 2001, item 2C where we advised you to "cross-reference NDA #20587 and provide safety data from the aerosol product". We cannot find specific reference in the paper NDA submission to adverse events associated with Sclerosol. Please provide this information and an analysis of how the Sclerosol safety experience may support the safety of Sterile Talc Powder.

3. We request that you forward to us, for inclusion in the NDA, copies of the papers from the literature referenced in section 9 ("safety update"). Of the 10 references cited, you have only provided the Kennedy article (Chest 1994).

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.
Regulatory Project Manager

TEAM MEETING

NDA# 21-388 February 6, 2003

Date Received: September 20, 2002 **PDUFA Due Date:** March 21, 2003

Drug Name: Sterile Talc Powder

Sponsor: Bryan Pharmaceuticals

Proposed Indication: [redacted]

Assigned Reviewer and Team Leaders

Clinical:	Scher/Farrell
Statistical:	Yang
Pharm/Tox:	Goheer
Biopharmaceutical:	Staschen
Chemistry:	Jee/Lostritto

Discussion Points

1. Clinical

   Response measurements were not given and no incisive analysis of the data. The dose descriptions in the labeling need to be revised. Would like to review ODAC minutes for Sclerosol (NDA 20-587) from 1995

2. Biopharmaceutics

   A bio-waiver was granted for this submission, therefore a review is not required.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Jane Campbell	**From:** Sean Bradley, CSO
Fax: 845-469-4212	**Fax:** 310-827-4590
Phone: 845-469-4289	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** January 28, 2003
Re: NDA 21-388-Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

We are currently reviewing your application and request the following:

An electronic copy of the Sclerosol Intrapleural Aerosol package insert and volumes 1 and 6 (not including the copied references from the literature) of the Sterile talc powder NDA submission. The electronic copy of Volume 6 should include the clinical data (section 8 and attachments 1, 2, and 3).

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

TEAM MEETING

NDA# 21-388 **Date:** January 24, 2003

Date Received: September 20, 2002 **PDUFA Due Date:** March 21, 2003

Drug Name: Sterile Talc Powder

Sponsor: Bryan Pharmaceuticals

Proposed Indication:

Assigned Reviewer and Team Leaders

Clinical:	Scher/Farrell
Statistical:	Yang/Chen
Pharm/Tox:	Goheer/Leighton
Biopharmaceutical:	Staschen/Rahman
Chemistry:	Jee/Lostritto
Microbiology:	Pawar/Cooney

Discussion Points

1. Clinical

   Due to the nature of this product and the NDA being literature based, the review process should have a low threshold
   Would like to review ODAC minutes for Sclerosol (NDA 20-587) from 1995

2. Statistical

   We will refer to the Sclerosol NDA for information and will work with the medical team on this review.

3. Pharmacolgy/Toxicology

   Review is completed and signed off
   Suggest changes to be made to the labeling (highlighted in review) because there were no literature/GLP studies available to support a statement

4. Biopharmaceutics

   No issues at this time

5. Chemistry

   Nomenclature Request 90 Days prior to due date (request sent to ODS)

   Site Inspections:
   1. [redacted] - Inspection was assigned on 12/2/02 - Pending
   2. [redacted] - " " " on 12/2/02 - Pending
   3. [redacted] " " " on 11/12/02 - Pending

6. Microbiology

   No comments at this time

Division Goals

1. **Classification**..Priority Review: Due March 21, 2003

2. **ODAC**- NO

3. **Sign-off**: Division Level, give to Dr. Pazdur March 14, 2003

Meeting Dates:

06FEB03	Team meeting
12FEB03	Team/labeling
20FEB03	Team/labeling
27FEB03	Team/labeling
06MAR03	Team/labeling
11MAR03	Team/labeling

DUPLICATE

Waldman Biomedical Consultancy, Inc.

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ORIG AMENDMENT

N- 000 (BN)

November 22, 2002

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Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852

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NOV 25 2002
HFD-150 / CDER

Attn: Mr. Sean Bradley

RE: Response to NDA 21-388 Information Request
FDA Request, 021120, Regarding Analysis of Efficacy and Safety Data Presented by Gender, Age and Racial Subgroups

Dear Mr. Bradley,

As requested in your FAX dated 11/20/02, we are hereby responding to the request for questions regarding analysis of efficacy and safety data presented by gender, age and racial subgroups.

The original signed copy, along with one review copy, is being provided to your attention.

Please note that a FAX of this submission was sent earlier today.

If the Agency would like additional copies or would like to discuss this matter further with us, please don't hesitate to contact us at the contact points in the letterhead.

Best regards.

Yours truly,

Alan A. Waldman

Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Jane Campbell	**From:** Sean Bradley, CSO
Fax: 845-469-4212	**Fax:** 310-827-4590
Phone: 845-469-4289	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** November 20, 2002
Re: NDA 21-388-Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

We are currently reviewing your application and request the following information:

In a final rule effective August 10, 1998, amended 21 CFR 314.50(d)(5)(v) and 314.50.50(d)(5)(vi)(a) the FDA required sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in NDA applications.

Please provide an analysis of the efficacy and safety data in your NDA presented by gender, age and racial subgroups. Provide this as soon as possible by fax and officially to the NDA.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Thank you for your prompt attention to this matter.

Sean Bradley, R.Ph.
Sean x Bradley
Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

11/14/02

NDA 21-388

Bryan Corporation
C/O
Waldman Biomedical Consultancy, Inc.
P.O. Box 575
Oceanside, NY 11572

Attention: Alan A. Waldman, Ph.D.
President

Dear Dr. Waldman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Sterile Talc Powder
Review Priority Classification:	Priority (P)
Date of Application:	September 20, 2002
Date of Receipt:	September 23, 2002
Our Reference Number:	NDA 21-388

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2002 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 23, 2003.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Document Room 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 594-5770.

Sincerely,

/S/

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sean Bradley
11/14/02 08:24:57 AM
Signing off for Dotti Pease

Waldman Biomedical Consultancy, Inc.℠

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November 13, 2002

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Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852

ORIG AMENDMENT
BI

Attn: Mr. Sean Bradley

RE: Response to NDA 21-388 Information Request
FDA Questions, 021112, Regarding Testing of Sterile Talc Powder Lots 2E003, 2E004, and 2E005

Dear Mr. Bradley,

As requested in your FAX dated 11/12/02, we are hereby responding to the questions concerning the testing of Sterile Talc Powder Lots 2E003, 2E004, and 2E005.

The original signed copy, along with one review copy, is being provided to your attention.

Please note that a FAX of this submission was sent earlier today.

If the Agency would like additional copies or would like to discuss this matter further with us, please don't hesitate to contact us at the contact points in the letterhead.

Best regards.

Yours truly,

Alan A. Waldman

Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628
Web Site http://www.waldmanbiomed.com • e-Mail consultancy@waldmanbiomed.com

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Jane Campbell	**From:** Sean Bradley, CSO
Fax: 845-469-4212	**Fax:** 310-827-4590
Phone: 845-469-4289	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** November 12, 2002
Re: NDA 21-388-Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

We are currently reviewing your application and request the following information:

For production lots [2E003, 2E004 and 2E005] please provide a summary of:

(1) bioburden results for all three lots at the bulk stage
(2) — irradiation dose results for all three lots
(3) sterility results for all three lots
(4) Endotoxin Test results for all three lots

A summary of each of the above in a table form will be acceptable.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Thank you for your prompt attention to this matter.

Sean Bradley, R.Ph.
S
Regulatory Project Manager

DUPLICATE

Waldman Biomedical Consultancy, Inc.

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FACSIMILE TRANSMISSION

To: Mr. Sean Bradley
DHHS/FDA/CDER/OND/DODP
FAX - 301-594-0498

From: Dr. Alan A. Waldman
Ms. Jane B. Campbell
Waldman Biomedical Consultancy, Inc.

Date: November 7, 2002

NC

Number of Pages (including this Header): 4

If there are any problems with this transmission please call (845) 468-4289

RE: Addition of Financial Disclosure Statement to NDA 21-388

Dear Mr. Bradley,

As requested, on behalf of Bryan Corporation we have prepared and are providing a new section (Section 19) for inclusion in the NDA 21-388 for Bryan Corporation's Sterile Talc Powder. Section 19 has been created to address Financial Disclosure by clinical investigators. For this application this requirement is not applicable.

We are also including a new Index for Volume 7 that reflects the inclusion of this new section.

Two copies of this letter and attachments are being sent to the Agency today via FedEx, addressed to your attention.

Please let us know if we can be of any further help in this matter.

Best regards

Dr. Alan A. Waldman
Ms. Jane Campbell

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628

Waldman Biomedical Consultancy, Inc.℠

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October 23, 2002

DUPLICATE

NEW CORRESP
NC

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Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852

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HFD-150 / CDER

Attn: Mr. Sean Bradley

RE: Response to NDA 21-388 Information Request
FDA Questions, 021017, Regarding Literature Searches

Dear Mr. Bradley,

As requested in your FAX dated 10/17/02 and clarified in your FAX dated 10/18/02, we are hereby responding to the questions raised regarding how the literature searches used to support NDA 21-388 for Bryan Corporation's Sterile Talc Powder were conducted.

As directed, the original signed copy, along with one review copy, is being provided to your attention.

Please note that a FAX of this submission was sent yesterday.

If the Agency would like additional copies or would like to discuss this matter further with us, please don't hesitate to contact us at the contact points in the letterhead.

Best regards,

Yours truly,

Alan A. Waldman

Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To:	Jane Campbell	**From:**	Sean Bradley, CSO
Fax:	845-469-4212	**Fax:**	310-827-4590
Phone:	845-469-4289	**Phone:**	301-594-5770
Pages, including cover sheet:	1	**Date:**	October 18, 2002
Re:	NDA 21-388-Information Request		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

Please review the following comments regarding your questions about our request for clarification on the methodology of our literature search:

1. A simple listing of all databases and search terms will be satisfactory.

2. We requested that you "state the criteria for selecting or rejecting individual papers in the review". We do not require the number or titles of papers rejected. Please tell us your methodology, e.g. randomized trials, English/German, endpoints, cancer or other diagnoses, etc.

3. The information must be officially and formally submitted to the NDA, but you may choose to send us a duplicate fax, as well, to be sure that we have sufficient time to review before the 45-day date.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.PL
/S/
Regulatory Project Manager

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Jane Campbell	**From:** Sean Bradley, CSO
Fax: 845-469-4212	**Fax:** 310-827-4590
Phone: 845-469-4289	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** October 17, 2002
Re: NDA 21-388-Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your September 20, 2002 New Drug Application (NDA) submitted to the Agency for Sterile Talc Powder.

During our initial review of your NDA for file-ability, we note that you have not provided the complete methodology for your literature review (page 6).

Please provide us with the following information as soon as possible:

1. List *all* databases which you searched.
2. Provide the **search terms** that you employed.
3. State the criteria for selecting or rejecting individual papers for inclusion in the review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Thank you for your prompt attention to this matter.

Sean Bradley R.Ph
Regulatory Project Manager
/S/

Waldman Biomedical Consultancy, Inc.℠
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October 5, 2002

Dr. Richard Pazdur, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
Office of the Director
1451 Rockville Pike
Rockville, MD 20852

Attn: Mr. Sean Bradley

Re Additional copies of
Original New Drug Application - 21-388
Sterile Talc Powder

Dear Dr. Pazdur,

As requested, on behalf of Bryan Corporation of Woburn, Massachusetts we are hereby submitting ten additional copies of Volume 1, 2 additional copies of Volumes 2 and 3 and an electronic version of the labeling included in the original NDA for Bryan Corporation's Sterile Talc Powder, N 21-388. Six complete review copies and a seventh copy for archiving were provided to the Agency on September 20, 2002 along with a field copy of the Quality Sections of this application which was sent to the FDA district office for New England.

If additional copies are needed, or if there are any questions regarding this matter, please don't hesitate to contact either Dr. Alan Waldman, President of Waldman Biomedical Consultancy (WBC) or Ms. Jane Campbell, Senior Consultant for Regulatory Affairs for WBC us at the address noted in the letterhead.

Best regards,

Yours truly,

Dr. Alan A. Waldman, Ph.D.
Acting as Agent for
Bryan Corporation

Attachments

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628

Waldman Biomedical Consultancy, Inc.
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September 20, 2002

Dr. Richard Pazdur, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
Office of the Director
1451 Rockville Pike
Rockville, MD 20852

Attn: Mr. Sean Bradley

Re Original New Drug Application - 21-388
Sterile Talc Powder
Archival Copy

Dear Dr. Pazdur,

As required, on behalf of Bryan Corporation of Woburn, Massachusetts we are hereby submitting seven copies of an original NDA for Bryan Corporation's Sterile Talc Powder. Six copies are for review and the seventh copy for archiving. Additional copies will be provided upon request. A field copy of the Quality Sections of this application has been provided to the FDA district office for New England.

Sterile Talc Powder is a non-aerosol version of Bryan Corporation's Sclerosol® Sterile Aerosol Talc. Sterile Talc Powder is supplied in a single use glass bottle containing — g of the same asbestos-free talc that is used for Sclerosol Aerosol Talc. The talc-filled bottle is sterilized by gamma radiation. Sterile Talc Powder is indicated for

Sterile Talc Powder is mixed with sterile saline to make a slurry. The usual dosage is a single — g dose delivered intrapleurally through a chest tube. The dose is to be individualized to each patient's needs.

As discussed in various telephone conversations between agents for Bryan Corporation and the Agency, this New Drug Application is based on published literature references and does not contain a clinical section that is based on IND supported clinical studies conducted by the sponsor. This is supported by a FAX from the Agency dated 3/28/2001 which states that it is acceptable to submit a literature based NDA for this product

Talc has been used to control pleural effusions for over sixty years, the first use having been reported by Bethune in 1935. The only intrapleural talc that is currently approved for marketing in the United States for this indication is Bryan Corporation's

Sclerosol® Aerosol Talc. No other government regulatory agency regulates this use of talc as a prescription drug.

[redacted] has acted as a medical advisor to Bryan Corporation [redacted] Dr. [redacted] is a specialist in pulmonary medicine with extensive experience in the management of MPE.

In a letter dated February 11, 2002, from the Office of the Chief Mediator and Ombudsman, we were notified that Bryan's request that the prescription drug user fee for this application be waived by the agency has been granted. A copy of this letter is attached.

Bryan Corporation also submitted a request for Orphan Designation for this drug based on the administration of this drug through a chest tube as a slurry, thus eliminating the need for open chest surgery as is required for use of the aerosol version of this drug. We were notified by Lt. Commander Fritsch of the Office of Orphan Products Development that the original orphan-drug designation which was granted to Bryan Corporation's Sclerosol Aerosol Sterile Talc Powder on September 18, 1995 can be extended to cover the non-aerosol version of this drug, Sterile Talc Powder.

If additional information is needed, or if there are any questions regarding this matter, please don't hesitate to contact either Dr. Alan Waldman, President of Waldman Biomedical Consultancy (WBC) or Ms. Jane Campbell, Senior Consultant for Regulatory Affairs for WBC us at the address noted in the letterhead.

Best regards,

Yours truly,

Dr. Alan A. Waldman, Ph.D.
Acting as Agent for
Bryan Corporation

Attachments

ORIG AMENDMENT

Waldman Biomedical Consultancy, Inc.

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February 25, 2002

DUPLICATE
N-000 (BC)

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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncological Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852

RECEIVED
FEB 27 2003
HFD-150 / CDER

Attn: Mr. Sean Bradley

RE: Response to NDA 21-388 Information Request
FDA Request, 030213, and Teleconference, 030221,
Regarding — Used for Sterile Talc Powder

Dear Mr. Bradley,

As requested in your FAX dated 02/13/02, and during the teleconference of 02/21/03, we are hereby responding to the request for information concerning the — used for Sterile Talc Powder, and concerning the — of same during radiation-based sterilization of the sterile talc powder.

The original signed copy, along with two review copies, is being provided to your attention.

If the Agency would like additional copies or would like to discuss this matter further with us, please don't hesitate to contact us at the contact points in the letterhead.

Best regards.

Yours truly,

Alan A. Waldman, Ph.D.
President
Waldman Biomedical Consultancy, Inc.
Agent for Bryan Corporation

P.O. Box 575 • Oceanside, New York 11572 • 516-763-1158 • FAX 516-536-7628
Web Site http://www.waldmanbiomed.com • e-Mail consultancy@waldmanbiomed.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

February 11, 2002

Mr. Frank Abrano
President
Bryan Corporation
Four Plympton Street
Woburn, MA 01801

RE: Bryan Corporation, Sterile Talc Powder (talc), Application Fees, Waiver Request 2001.037

Dear Mr. Abrano:

This responds to the June 14, 2001, and November 1, 2001, letters from Dr. Alan Waldman of Waldman Biomedical Consultancy, Inc. (Waldman), to the Office of the Chief Mediator and Ombudsman, your letter of July 18, 2001, and the January 16, 2002, letter from Jane B. Campbell of Waldman, requesting a waiver of the applicable human drug application fee under four waiver provisions of the Federal Food, Drug, and Cosmetic Act (the Act) [1] (Waiver Request 2001.037). Because the responsibility for evaluation of certain waivers resides with the Associate Director for Policy, Center for Drug Evaluation and Research (CDER), your letters were transferred to me for response.[2]

Dr. Waldman's June 14, 2001, letter requested a waiver or reduction of applicable fees under the fees-exceed-the-cost waiver and small business exception provisions of the Act. In your July 18, 2001, letter, you also requested consideration under the public health and barrier-to-innovation provisions. In Dr. Waldman's November 1, 2001, letter, the initial requests for a waiver under the fees-exceed-the-cost and small business exception provisions (sections 736(d)(1)(C) and 736(d)(1)(E)) were withdrawn. We acknowledge the withdrawal of your request for a waiver under the fees-exceed-the-cost and small business exception provisions of the Act.

For the reasons described below, the Food and Drug Administration (FDA) grants the Bryan Corporation's (Bryan's) request for a waiver of the applicable human drug application fee under the barrier-to-innovation waiver provision of the Act (section 736(d)(1)(B)). Because the waiver is granted under the barrier-to-innovation provision, it is not necessary to address the public health waiver provision (section 736(d)(1)(A)).

I. Bryan's Waiver Request

According to your waiver requests, you believe that a barrier-to-innovation waiver should be granted for the following reasons:

[1] 21 U.S.C. 379h(d)(1).

[2] *Note: Future waiver requests should be forwarded to the User Fee Waiver Office (HFD-5) rather than to the Office of the Chief Mediator and Ombudsman.*

- You claim that talc as slurry is an innovative alternative to Sclerosol Aerosol Talc, because it provides a less invasive way to administer talc for pleurodesis. The alternative product, Sclerosol Aerosol Talc, is the only sterile talc that is FDA approved for intrapleural administration through a delivery tube during open chest surgical procedures such as thoracoscopy or open thoracotomy. You note that this procedure is invasive and quite expensive.
- You claim that use of the talc slurry will markedly improve the quality of life for those individuals who receive this treatment.
- You assert that studies comparing the talc as a slurry to aerosolized talc indicate that talc as a slurry is as effective as aerosolized talc and much easier to apply.
- You assert that use of this product is far less traumatic for the patient, easier for the physician to administer, and involves less time than use of the aerosolized talc solution.
- You claim imposition of user fees would inflict a financial burden on the resources of the company.
- You also claim that imposition of user fees may prevent Bryan from being able to support its efforts to bring this innovative drug to the marketplace.
- You claim that with average revenues of —— over the last two years, Bryan meets the description of a Type 4 "small company."
- You also note that Bryan had revenue of —— in the year from July 1, 2000, to June —— and that gross revenues from July 1, 2001, through December 31, 2001, were ——

II. Criteria for a Barrier-to-Innovation Waiver

Under the Act, a waiver or reduction of fees may be granted if the assessment of the fee would present a significant barrier to innovation because of limited resources available to the applicant or other circumstances (section 736(d)(1)(B)). As FDA has interpreted this provision, a waiver or reduction may be appropriate when: (1) the product for which the waiver is being requested is innovative or the entity requesting the waiver is otherwise pursuing innovative drug products or technology, and (2) the fee would be a significant barrier to the entity's ability to develop, manufacture, or market innovative products or technology. To qualify for a waiver, you must meet both criteria under the waiver provision.

Not all products that have been approved for marketing in the United States are necessarily "innovative" within the meaning of section 736(d)(1)(B). In evaluating whether a product is innovative, FDA considers, among other factors, whether a drug product is a new molecular entity, has been designated as a priority drug,[3] or has been granted fast track status.[4] We will also consider the existence of treatment alternatives. The existence of treatment alternatives will weigh against deciding that a product is innovative.

[3] Further information regarding priority drugs can be found in CDER's Manual of Policies and Procedures (MAPP) 6020.3, *Priority Review Policy*, available on the Internet at www.fda.gov/cder.

[4] Further information regarding fast track status can be found in CDER's guidance for industry on *Fast Track Drug Development Programs – Designation, Development, and Application Review*, available on the Internet at www.fda.gov/cder.

III. Evaluation of Bryan's Waiver Request

A. Is the product innovative?

FDA's *Attachment G — Draft Interim Guidance Document for Waivers of and Reductions in User Fees*, July 1993 (waiver guidance),[5] allows for a fee waiver if the product is innovative or if the fee is a barrier to the company's ability to continue to pursue innovative technology. Therefore, to be considered for the barrier-to-innovation waiver, the applicant needs to show that the product is innovative or that innovative products or technology are continuing to be pursued by the applicant.

Our records show that a new application for a non-aerosol slurry version of sterile talc powder would not be considered a new molecular entity. Also, the FDA Division of Oncologic Drug Products (DODP) noted that at this time, without the actual application available for a priority determination, the non-aerosol slurry version of sterile talc powder application would probably not qualify for an accelerated regulatory path or for priority review. In addition, there are other treatment alternatives for malignant pleural effusions that weigh against determination that this product is innovative (e.g., bleomycin, doxycycline, nitrogen mustard, Sclerosol). However, a non-aerosol slurry version of sterile talc powder would offer the benefit of a less-invasive dosage form over the current alternatives.

The information provided in your June 14 and July 20, 2001, letters, your website (www.bryancorp.com), and current FDA records indicate that Bryan Corporation is actively involved in the development, manufacture, and marketing of aerosolized sterile talc for malignant pleural effusions. This new dosage form, sterile talc powder for reconstitution with normal saline and administration intrapleurally as a slurry, is a pharmaceutic adaptation of the NDA 20-587, Sclerosol (sterile talc powder aerosol) product, a new molecular entity that was granted priority review. This adaptation of the talc aerosol product allows a less invasive procedure for instillation of the product.

Therefore, considering all the factors noted above, FDA believes that you have met the first criterion in pursuing the development and manufacture of innovative products for the purpose of a waiver of the application user fee.[6]

FDA's conclusion for user fee waiver purposes that a product is innovative or that a firm is engaged in the research, development, or marketing of an innovative product should not be construed as an opinion on the approvability of the new drug application.

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[5] Available online at www.fda.gov/cder/pdufa/default.htm.

[6] The determination of "innovative" for user fee waiver purposes applies to this application fee waiver evaluation only and is based on current information. FDA will reevaluate the waiver determination for user fee purposes in response to future waiver requests. In its reevaluation, the Agency will consider, for example, (1) the availability of multiple talc products, (2) the information about the product garnered through the application review process, (3) whether other effective treatments are available, and (4) any other relevant information.

B. Would the fee be a significant barrier to Bryan's ability to develop, manufacture, or market the innovative product?

In evaluating whether the fees imposed are a significant barrier to Bryan's ability to develop, manufacture, or market innovative products or technology, the Agency considers the relationship between the annualized cost of user fees and the gross annual revenues of the entity requesting the waiver and its affiliates.[7] This consideration is discussed in the waiver guidance.

According to your waiver request, Bryan had a gross revenue of — for the year ending June 30, 2001, and gross revenues of — from July 1, 2001, through December 31, 2001. FDA classifies pharmaceutical companies based on gross annual revenues. As discussed in the waiver guidance, Bryan would be classified as a Type 4 pharmaceutical firm (a small company including affiliates with revenues between $1 and $9.99 million). FDA believes that an entity with less than $10 million in annual gross revenues is less likely to be able to develop, manufacture, or market innovative products or technology because of user fees.

In light of these revenue figures and the waiver guidance, FDA concludes that the fees would be a significant barrier to Bryan's ability to develop, manufacture, or market innovative products or technology for user fee waiver purposes. Consequently, your request for a waiver of the application fee for sterile talc powder (NDA 21-388) is granted under the barrier-to-innovation waiver provided FDA receives the marketing application no later than one year after the date of this letter.

IV. Disclosure of Public Information

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If you have any questions about this matter, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

/S/

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc. Jane Campbell
Waldman Biomedical Consultancy, Inc.
P.O. Box 575
Oceanside, NY 11572

[7] Section 103(h) of the Food and Drug Administration Modernization Act reaffirms that the "person" subject to fees "shall continue to include an affiliate thereof."

MEETING MINUTES

MEETING DATE: March 29, 2001 **TIME:** 1:00 PM, EST

LOCATION: Conference Room B

Request Submission Date: January 31, 2001
Briefing Document Submission Date: March 19, 2001

DRUG: Sterile Talc Powder

SPONSOR/APPLICANT: Bryan Corporation

TYPE of MEETING: pre-NDA

PARTICIPANTS

FDA

Richard Pazdur, M.D.	Division Director
Alison Martin, M.D.	Medical Team Leader
Nancy Scher, M.D.	Medical Officer
Eric Duffy, Ph.D.	Chemistry Team Leader
Josephine Jee, Ph.D.	Chemisty Reviewer
Sean Bradley, R.Ph.	Consumer Safety Officer

WALDMAN BIOMEDICAL (CONSULTANTS FOR BRYAN CORP.)

Alan A. Waldman, Ph.D	President, Waldman Biomedical Consultancy
Jane B. Cambell, RAC	Senior Consultant, Regulatory Affairs, Waldman Biomedical Consultancy

MEETING OBJECTIVES: To discuss Bryan's plans for submitting a literature based NDA for Sterile Talc Powder

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Are the proposed plans for the submission of a literature-based NDA for Sterile Talc Powder proper?

   FDA: It is acceptable to submit a literature-based NDA. However, we do not have the precise plan. We can provide guidance.

2. Are there any specific manufacturing issues that concern the Agency and will have to be included in the CMC section of the literature-based NDA?

   FDA: Provide the exact composition of the drug product.

   Provide detailed information on the container system.

   Will the market container be for single use?

   Indicate whether the entire product (talc in the market container) is gamma sterilized.

   Describe the entire manufacturing and sterilization process.

   Describe how slurry density will be maintained throughout administration.

3. Are there any pre-clinical issues of concern to the Agency related to talc?

   FDA: The Bryan/Waldman corp. will have to do a request for a biowaiver with justification for the request. This is considered a new formulation and will require new paperwork.

4. Do the planned literature search activities meet the Agency's expectations?

   FDA: Please submit your detailed plan for the methodology of the literature search.

5. Are the plans for presenting the results of the literature search acceptable to the Agency?

   FDA: Please submit your detailed plan.

6. How long is the review of this type of submission expected to take?

   FDA: We expect this to be a standard NDA review. A standard review is 10 months and is based on the presentation of your NDA material that is submitted for review.

Additional Questions/Comments:

Waldman: We will base the NDA for Sterile Talc Powder on the format of the Sclerosol NDA. The talc product is the same the only difference is the aerosol used in the Sclerosol formulation. We will supply an outline of our planned NDA submission for your review.

ACTION ITEMS:

Waldman Biomedical-

1. Will submit a detailed plan for the methodology of the comprehensive literature search, which will be the basis of the NDA. As part of the NDA submission, the sponsor will identify adequate and well-controlled trials from the literature which demonstrate efficacy of talc slurry. Waldman will provide analysis of these studies, with particular attention to trial design.
2. Will request a copy of the original medical officer review for Sclerosol (NDA 20-587) as well as a copy of the ODAC meeting minutes form the Freedom of Information Office.
3. Will submit a methods of validation package to the FDA for review.

The meeting concluded at 14:12 PM, EST. There were no unresolved issues or discussion points.

/S/

Minutes prepared by: _____
Sean Bradley, R.Ph., Project Manager

/S/

Concurrence Chair: _____
Nancy Scher, M.D., Medical Officer