

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-388**

**Medical Review(s)/Statistical Review(s)**

# **NDA 21-388: Sterile Talc Powder**

**Applicant: Bryan Corporation**

## **FDA Medical and Statistical Review**

**Medical Reviewer: Nancy S. Scher, M.D.**

**Statistical Reviewer: Peiling Yang, Ph.D.**

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## The Executive Summary of the Primary Clinical Review

### 1 Recommendations

#### 1.1 Recommendations on Approvability

Although Sterile Talc Powder is safe and effective for the treatment of malignant pleural effusion (MPE), Bryan Corporation has failed to validate its sterilization procedure for the product. From the clinical perspective, we recommend approval of Sterile Talc Powder, as a 505(b)(2) application, based on the demonstration of efficacy and safety from the medical literature. The 5 randomized trials from the literature are adequate and well controlled. The 13 single arm trials from the literature are supportive. The data from the literature demonstrate efficacy and safety for talc instilled as a slurry into the pleural space via chest tube as a sclerosing agent to decrease the recurrence of MPE in symptomatic patients. The product cannot be approved until the applicant validates the sterilization procedure.

#### 1.2 Recommendations on Postmarketing Studies and/or Risk Management Steps as Appropriate.

There will not be a request for postmarketing commitment studies.

The "Precautions" section of the label includes a statement about reports of Acute Respiratory Distress Syndrome (ARDS) in 3 patients from the literature who received a 10 gram (gm) dose of talc. The Agency's draft label for the product recommends a talc dose of 5 gm.

### 2 Summary of Clinical Findings

#### 2.1 Brief Overview of Clinical Program

Sterile Talc Powder, administered intrapleurally via chest tube, is indicated as a sclerosing agent to decrease recurrence of malignant pleural effusion in symptomatic patients. As a 505(b)(2) application, the New Drug Application (NDA) relies on existing trials in the medical literature for evidence of clinical efficacy and safety. Bryan Corporation did not conduct any clinical trials in support of this application. The same sterile talc substance, packaged as an aerosol, was previously submitted by Bryan Corporation under section 505(b)(2) and approved by the Food and Drug Administration (FDA) on December 24, 1997 (NDA 20587), relying on the medical literature for evidence of clinical efficacy and safety. The indication for Sclerosol<sup>®</sup> Intrapleural Aerosol was also "to prevent recurrence of malignant pleural effusions in symptomatic patients". Whereas Sclerosol<sup>®</sup> was approved for administration by aerosol during thoracoscopy or open thoracotomy, Sterile Talc Powder is mixed with normal saline solution to form a slurry and is administered intrapleurally via chest tube.

The applicant has provided evidence of efficacy and safety for Sterile Talc Powder by identifying and analyzing 5 adequate and well-controlled trials from the literature that

support the proposed indication. The applicant and the reviewer identified additional single arm trials from the literature that provide support to the data from the randomized trials. There were 89 patients evaluable for efficacy from the randomized trials and 346 patients from the single arm trials from the literature, for a total of 435 patients evaluable for efficacy. The safety database consists of the 89 patients in the randomized trials and 366 patients from the single arm trials, for a total of 455 patients.

## 2.2 Efficacy

The applicant has provided evidence of efficacy for Sterile Talc Powder by identifying and analyzing 5 adequate and well-controlled trials from the literature that support the proposed indication. The studies provide Level I evidence of efficacy of talc slurry in the therapy of MPE. The studies are randomized and controlled trials using a prospectively defined objective measure of "success." Success is defined as lack of recurrence of fluid (or most fluid), as assessed by chest x-ray. In the majority of these studies, response is assessed at a standardized time and all patients are accounted for. (See section 6.3.1 for detailed analysis of the 5 trials.) For the 89 evaluable patients studied in the 5 randomized controlled trials in which talc slurry was used as a sclerosing agent, there was an 89% (79/89) response to treatment (range 79-100%). The dose of talc was 5 gm in 4 studies (80 patients) and 10 gm in 1 study (9 patients). In spite of design and treatment differences among the trials, talc consistently demonstrates efficacy in decreasing recurrence of MPE in each of the 5 randomized controlled trials.

Thirteen additional single arm trials and retrospective series identified by the applicant and the reviewer from the literature are supportive of efficacy, as well. The range of success for the 346 evaluable patients in the single arm trials was from 75-100%. In these studies, 213 patients were treated with talc 5 gm and 105 patients were treated with a 10 gm dose. The dose range was 2-10 gm. (See table 16.) Again, in spite of the many differences in details of design and execution among the studies, the efficacy of talc as a sclerosing agent was consistently demonstrated across the studies.

The two drugs currently approved, as sclerosing agents for intrapleural instillation through a chest tube are mechlorethamine (nitrogen mustard) and bleomycin. Mechlorethamine is rarely used for this purpose today because of severe pain associated with administration. Bleomycin was approved on the basis of superiority in a randomized trial compared with tetracycline, with a 30 day recurrence rate of 36 % (10/8) for bleomycin vs. 67% (18/27) for tetracycline. Bleomycin can cause fever and nausea. When given parenterally, bleomycin causes pulmonary toxicity. Although this has not been documented when used intrapleurally, it is of theoretical concern in this patient population. Due to systemic absorption of bleomycin administered intrapleurally, caution must be used in patients with renal dysfunction, who may experience systemic toxicity (Siegel and Schiffman, 1990). Finally, bleomycin is very costly.

USP (United States Pharmacopeia) grade talc has been used for many years as a sclerosing agent, introduced as aqueous slurry into the pleural space through a chest tube (Chambers, 1958) or insufflated as a powder directly onto the pleural surface. A regulated product

meeting standards of purity and sterility would be preferable to USP grade talc, which is unregulated as far as sterility and asbestos content, although proposals have been made to require asbestos testing for 2004. The only licensed formulation of talc (Sclerosol Intrapleural Aerosol, Bryan Corporation) is packaged with a chlorofluorocarbon (CFC) propellant for direct insufflation onto the open pleural surface intraoperatively or during thoracoscopy. In addition to the disadvantages of requiring an anesthetic and being more invasive to the patient when talc is administered in this way, Sclerosol will soon be discontinued because of the restriction of CFC use by international treaty.

### 2.3 Safety

The 5 randomized trials and the 13 single arm trials from the literature collectively provide safety data for the use of intrapleural talc slurry via chest tube to prevent recurrence of symptomatic MPE in approximately 455 patients. The adverse events reported in the trials were mostly mild and of short duration, often including local pain and low-grade fever associated with the induced inflammatory reaction. There was a low incidence of wound infection, mainly in the series of patients who had large-bore chest tubes rather than small catheters. There were 3 cases of non-fatal ARDS among the patients in 1 study (Kennedy et al, 1994) who received a dose of 10 gms of talc intrapleurally. Among the trials using lower dose talc, there was 1 episode of non-fatal ARDS requiring ventilatory support in a patient who received a second dose of talc 5 gm 48 hours after the first, to treat bilateral pleural effusion. The data from the literature demonstrates talc to be safe when instilled as a slurry into the pleural space via chest tube as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients, but suggests that there is an incidence of serious pulmonary adverse effects. The data overall are inconclusive, but suggest that ARDS may be related to dose.

A dose of talc 5 gm administered intrapleurally as a slurry via chest tube has an acceptable safety profile. Patients in the trials from the literature review generally had a single lifetime exposure to talc intrapleural therapy, although a handful of patients were treated with intrapleural talc for bilateral pleural effusion. In the randomized and single arm trials, 213 patients were treated with talc 5 gm and 105 patients were treated with a 10 gm dose. The range of talc doses used was 2-10 gm. (See table 16.) Since most patients reported in the trials had progressive metastatic cancer, many patients survived just a few months after intrapleural therapy. For this reason, and because the design of several of the trials was to assess efficacy and safety after 1-3 months, limited long-term safety data are available.

### 2.4 Dosing, Regimen, and Administration

The recommended dose of Sterile Talc Powder is 5 gm, dissolved in 50-100 ml sodium chloride. It is administered intrapleurally via chest tube, following adequate drainage of the effusion. Although the optimal dose for effective pleurodesis is unknown, 5 gm was the dose of talc most frequently reported in the published literature (293 treatments from a database of 435). The dose range reported in the published trials was 2-10 gm. (See table 16.)

From the published data, it was not possible to establish a dose-toxicity relationship for talc. Of the 4 patients in the single arm studies who developed respiratory failure requiring mechanical ventilation subsequent to talc pleurodesis, 3 of these patients were treated with talc 10 gm intrapleurally. The fourth patient developed acute respiratory distress one day after receiving a second 5 gm intrapleural dose of talc within 48 hours (bilateral effusion). Rinaldo (1983) reported a series of 3 patients who developed ARDS following talc intrapleural therapy. These patients were also treated with talc 10 gm. However, of the 114 patients in the literature database who were treated with talc 10 gm, the vast majority did not experience serious acute pulmonary toxicity.

There are no recommendations for dose modification for special populations.

## 2.5 Drug-Drug Interactions

Talc is an inert substance. No drug-drug interactions are expected.

## 2.6 Special Populations

The NDA depends on existing trials in the literature to document efficacy and safety for the indication. For the 4 of 5 randomized trials which provided gender data, 54% (43) of the patients in the talc arm were male and 46% (37) were female. For the 10 of 13 single arm trials which provided gender data, 122 of 334 were male (37%) and 212 (63%) were female. If the total numbers of patients who received talc are combined from the controlled and single arm trials, 165 (40%) were male and 249 (60%) were female. The estimated mean and median ages of patients treated with talc in the clinical studies are 60-62 years, with a range of 26-88 years of age. Many of the treated patients were older than age 65. No children were treated in the trials. None of the studies provided information about the racial or ethnic subgroups of participants.

Analysis of efficacy and safety data by demographic parameters is limited by the amount of demographic data provided in the clinical trials in the published literature. In the trials, Kennedy et al (1994) reported the only data on response by age. They found the average age of responders to be 54.8 $\pm$ 2.0 years and non-responders, 54.8 $\pm$ 5.76 years. Since the number of patients in the literature who failed to respond or had life-threatening toxicity was small across the trials, it would not be possible to identify differences in response or toxicity by gender or age.

There are no issues with the elderly or patients with renal or hepatic impairment because talc is not metabolized.

Pediatric studies will not be required.

This drug is not likely to be used in pregnant women, but since it is an inert substance that is administered intrapleurally, it could be used if a physician determined the benefit outweighs the risk.

**Clinical Review****1 Introduction and Background****1.1 Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indications(s), Dose, Regimens, Age Groups**

1.1.1 Established Name: Talc (hydrated magnesium silicate)

1.1.2 Proposed Trade Name: Sterile Talc Powder

1.1.3 Drug Class: Sclerosing agent

1.1.4 Applicant: Bryan Corporation  
4 Plympton Street  
Woburn, MA 01801

1.1.5 Applicant's Proposed Indication:

[

]

1.1.6 Dosage and Administration

Proposed label: [

]

[

]

Prepare the talc slurry using aseptic technique in [

1. Remove talc container from packaging. Remove protective flip-off seal. [

]

1. [

]

2. [

]

3. [

]

4. [ ]

5. [ ]

6. [ ]

[ ]

*Reviewer comment: No guidance is given as to how the choice of dose is made with the recommendation of the "usual dose" — grams "individualized to each patient's needs".*

**1.1.7 How Supplied**

"Sterile Talc Powder is supplied in a 100 ml glass bottle containing — of talc. The sterile bottle is closed with a gray stopper and covered with a flip-off seal."

**1.2 State of Armamentarium for Indication(s)**

Sterile Talc Powder, administered intrapleurally by chest tube as a slurry, is indicated as a sclerosing agent to decrease the recurrence of malignant pleural effusion (MPE) in symptomatic patients. Patients with chemotherapy-insensitive or resistant cancer may require mechanical sclerosis of the pleural surfaces to control symptoms of recurrent pleural effusion. Many of these patients have lung or breast cancer.

For some patients, intermittent thoracentesis may be adequate to control symptoms of dyspnea, cough and chest pain associated with recurrent pleural effusion. Chronic indwelling pleural catheters may be used in selected cases to permit continuous removal of fluid in some symptomatic patients. Sorensen et al demonstrated (1984) that mechanical sclerosis can be achieved without intrapleural instillation of a drug in some patients with MPE, following complete drainage of pleural fluid through a large bore chest tube left in the pleural space for several days, associated with the irritative effect of such a tube. However, to maximize the probability of successful pleurodesis, the majority of patients will be treated intrapleurally with a sclerosing agent after drainage of effusion and re-expansion of the lung.

Physicians have used several different products over the years as sclerosing agents to control MPE. Quinidine hydrochloride was employed at one time, but it is no longer marketed. Tetracycline hydrochloride intravenous solution was commonly used for its sclerosing properties, but this formulation of the antibiotic is no longer on the market. Doxycycline has been used more recently with some success, but this antibiotic formulation may require repeated instillation and few clinical studies have been done. The two drugs currently approved, as sclerosing agents for intrapleural instillation through a chest tube are mechlorethamine (nitrogen mustard) and bleomycin. Mechlorethamine is rarely used for this purpose today because of severe pain associated with administration. Bleomycin was approved on the basis of superiority in a randomized trial compared with tetracycline, with a 30 day recurrence rate of 36 % (10/8) for bleomycin vs. 67% (18/27) for tetracycline. Bleomycin can cause fever and nausea. When given parenterally, bleomycin causes pulmonary toxicity. Although this has not been documented when used intrapleurally, it is of theoretical concern in this patient population. Due to systemic absorption of bleomycin administered intrapleurally, caution must be used in patients with renal dysfunction, who may experience systemic toxicity (Siegel and Schiffman, 1990). Finally, bleomycin is very costly.

Pharmacy compounded talc (USP grade) has been used for many years as a sclerosing agent, introduced as aqueous slurry into the pleural space through a chest tube (Chambers, 1958) or insufflated as a powder directly onto the pleural surface. Although widely used for many years, USP grade talc is unregulated as far as asbestos content and sterility. An FDA regulated product meeting standards of purity and sterility would be preferable. The only licensed formulation of talc (Sclerosol Intrapleural Aerosol, Bryan Corporation) is packaged with a propellant (dichlorodifluoromethane, CFC-12) for direct insufflation onto the open pleural surface intraoperatively or during thoracoscopy. In addition to the disadvantages of requiring an anesthetic and being more invasive to the patient when talc is administered in this way, Sclerosol will soon be discontinued because of the restriction of CFC use by international treaty.

FDA approved Bryan Corporation's New Drug Application (NDA) for Sclerosol Intrapleural Aerosol on December 24, 1997, under section 505(b)(2) of the Food, Drug and Cosmetics Act, relying on the medical literature for evidence of clinical efficacy and safety. (NDA 20-587 was initially submitted August 11, 1995, and resubmitted November 13, 1997.) The current NDA 21-388 is also submitted under section 505(b)(2). Bryan Corporation again references the medical literature to demonstrate efficacy and safety of talc slurry as a sclerosing agent to prevent recurrence of MPE in symptomatic patients. Bryan also references the safety of Sclerosol Intrapleural Aerosol in its application. The applicant did not perform any clinical trials in support of this NDA.

### 1.3 Important Milestones in Product Development

#### Sclerosol Intrapleural Aerosol (sterile talc powder)

On December 14, 1995, the Oncology Drug Advisory Committee (ODAC) recommended approval of Bryan Corporation's Sclerosol Intrapleural Talc based on evidence from the medical literature of efficacy and safety. FDA approved Sclerosol for the prevention of recurrence of malignant pleural effusions in symptomatic patients on December 24, 1997, under section 505(b)(2) of the Food, Drug and Cosmetic Act. This approval was based on the analysis of the data from controlled (9) and uncontrolled (24) trials.

#### Sterile Talc Powder

In a pre-NDA teleconference held March 29, 2001, between the Division of Oncology Drug Products (DODP) and Bryan Corporation (BC), the DODP agreed that it was acceptable for BC to submit a literature-based NDA for Sterile Talc Powder. BC agreed to provide evidence of efficacy and safety by analyzing adequate and well-controlled trials from the literature, using an objective measure of response at a standardized time. Additional safety data was to be provided from cross-reference of NDA 20-587 (Sclerosol Intrapleural Talc).

On February 11, 2002, FDA notified BC that the agency would grant a waiver of the prescription drug user fee for the application.

Orphan drug status was granted to BC's Sclerosol Intrapleural Aerosol on 9/18/95 and orphan drug status is being extended to Sterile Talc Powder, as well.

09/20/2002	BC submitted original NDA 21-388 under section 505(b)(2) (FDA receipt date 9/23/02)
11/22/2002	NDA filed as a priority status review
03/21/2003	User fee goal date

### 1.4 Other Relevant Information

Approval for Sterile Talc Powder has not been sought outside of the U.S. (Sclerosol Intracellular Talc is approved only in the U.S., as well.)

### 1.5 Important Issues with Pharmacologically Related Agents

Depending on the source of talc, it may contain asbestos. USP talc does not yet require testing for asbestos, although the proposed revised USP monograph for 2004 will require talc to be asbestos free. Bryan Corporation's licensed product, Sclerosol, is an aerosolized, asbestos-free talc for thoracoscopic use. It is being phased out because of restrictions on CFC propellants by international treaty.

## 2 Significant Findings From Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

### 2.1 Chemistry

The significant outstanding Chemistry, Manufacturing and Control (CMC) concern is the Microbiology issue (see below).

### 2.2 Animal Pharmacology and Toxicology

The applicant did not perform preclinical studies to support this NDA nor the Sclerosol application. Limited nonclinical pharmacology studies are available from the published literature with the slurry preparation. The Pharmacology and Toxicology reviewers stated that "no new safety concerns [are] raised in the nonclinical studies by the change in formulation" and the NDA is approvable from their perspective.

### 2.3 Microbiology

The Microbiology consultants (Dr. V. Pawar and Dr. P. Cooney) have determined that Bryan Corporation has failed to validate its sterilization procedure for the product. To qualify for approval, the applicant must design and implement an acceptable validation program.

## 3 Human Pharmacokinetics and Pharmacodynamics

A waiver of the requirement for evidence of *in vivo* bioavailability was granted since talc is administered directly into the pleural cavity, and measurement of talc blood levels is not feasible. The Clinical Pharmacology and Biopharmaceutics review identified no new risk management recommendations.

## 4 Description of Clinical Data and Sources

### 4.1 Sources of Clinical Data

The clinical data for this review is obtained from the published literature. The applicant provided data from 5 randomized controlled trials and 14 single arm studies from the literature, in which talc slurry was administered by chest tube to treat malignant pleural effusion (MPE). The applicant's analysis and copies of the papers were submitted in paper volumes 1 and 6 (of a total of 7 paper volumes).

### 4.2 Overview of Clinical Trials

The applicant performed no clinical trials to support this NDA. See sections 6.3.1 and 6.3.2, below, for the trials referenced from the published literature.

### 4.3 Postmarketing Experience

Sterile Talc Powder is not marketed in any county. Sterile Talc Powder is the same asbestos-free talc that is used for Bryan's Sclerosol Aerosol Talc.

### 4.4 Literature Review

The applicant searched National Library of Medicine (NLM) Medline, HealthSTAR, and National Cancer Institute (NCI) CancerLit databases directly and indirectly through on-line megasearch agents (MDConsult.com and BioMedNet.com). The applicant supplemented the searches with sections from textbooks and additional references cited in specific articles. The period of the search was from 1958 through September 2002. Searches were performed using the following terms: Talc, Pleurodesis, Talc Pleurodesis, Talc Slurry, Pleural Effusions and Malignant Pleural Effusions.

The applicant obtained abstracts of all articles and chapters, regardless of publication language, if they dealt with (i) animal studies using talc or other sclerosing agents, (ii) treatment of humans with talc in any form for any purpose, or (iii) treatment of MPE in humans with non-talc sclerosing agents. After review of the abstracts, the applicant obtained full articles and chapters for those articles which dealt with (i) safety of talc in animals or humans, (ii) comparison of talc and other sclerosing agents in animals, (iii) treatment of humans with talc as slurry or poudrage, (iv), non-talc sclerosing agents for MPE. The applicant identified 5 randomized clinical trials with a concurrent control and 14 single arm trials with talc slurry used as a sclerosing agent administered through a tube into the pleural space of patients with MPE to serve as the clinical database in support of the NDA. These references were published from 1956-2001. The applicant cites 10 additional references from the literature (volume 6, section 9) to support safety, of which only 1 study (Kennedy 1994) is included in the efficacy database.

In order to assess the completeness of the applicant's submitted database, this reviewer performed an independent literature search. Search terms linked "malignant pleural effusion" and "talc". The following lists the databases searched and the results obtained:

**Table 1: Result of FDA Literature Search (Reviewer Table)**

DATABASE	NUMBER OF CITATIONS
PubMed (1966-present)	139
Embase (1974-present)	232
IPA (International Pharmaceutical Abstracts, 1970-present) and BIOSIS (1969-present)	37
SciSearch (Science Citation Index, 1974-present)	28
Derwent Drug Files (1964-present)	25
CancerLit (1960s-present)	*23
Cochrane-Systematic Reviews	1 (protocol)
Cochrane-Controlled Clinical Trials Register	1

\*Unique references, not included in PubMed search

There was extensive overlap of the databases. In addition, websites for current clinical trials were searched. ClinicalTrials.gov revealed one ongoing study comparing chest tube with talc slurry pleurodesis vs. small catheter drainage only (Cancer and Leukemia Group B).

Abstracts from the references in the databases were obtained and reviewed. In an attempt to add to the clinical database, the reviewer obtained copies of articles in English pertinent to the efficacy and safety of talc for treatment of MPE. The FDA literature search did not provide additional adequate and well-controlled trials in which talc slurry was a comparator. Only a few additional reports of uncontrolled studies and series of cases were identified. These were reviewed but they did not add substantially to the clinical database. See additional discussion Section 6, Integrated Review of Efficacy.

## **5 Clinical Review Methods**

### **5.1 Describe How Review was Conducted**

The clinical data from the published literature were reviewed to establish efficacy and safety of Sterile Talc Powder. See section 4.4 above. Materials related to the Sclerosol NDA were reviewed for regulatory content and efficacy and safety of talc. Postmarketing experience with Sclerosol was reviewed for additional safety data.

### **5.2 Overview of Materials Consulted in Review**

The medical officer reviewed the following materials:

- The regulatory history of the application
- Medical Officer Review of NDA 20-587 (Sclerosol Intrapleural Aerosol)
- Oncology Drugs Advisory Committee minutes 12/14/95 (Sclerosol)
- Correspondence between the applicant and FDA in Division Files
- Paper submissions of the NDA
- Relevant published literature
- Electronic labeling proposal
- Adverse Event Reporting System (AERS) search for Sclerosol and talc

### **5.3 Overview of Methods Used to Evaluate Data Quality and Integrity**

The medical reviewer performed an independent literature search to verify that all published data relevant to efficacy and safety of Sterile Talc Powder for therapy of malignant pleural effusion were included in the analysis. (See section 4.4 for description of methodology.) Since this NDA is literature based, Division of Scientific Investigation did not perform any inspections.

### **5.4 Were Trials Conducted in Accordance with Accepted Ethical Standards**

Bryan Corporation did not conduct any clinical trials to support this NDA. The investigators for each of the published randomized clinical trials stated that Review Board approval and patient Informed Consent were obtained.

### **5.5 Evaluation of Financial Disclosure**

Financial disclosure by clinical investigators is not applicable to this NDA.

## 6 Integrated Review of Efficacy

### 6.1 Brief Statement of Conclusions

The NDA is submitted under section 505(b)(2) of the Food, Drugs and Cosmetics Act, relying on the medical literature for evidence of clinical efficacy and safety. Bryan Corporation did not conduct any clinical trials in support of this application. The same sterile talc substance, packaged as an aerosol, was previously submitted by Bryan Corporation under section 505(b)(2) and approved by the FDA on December 24, 1997 (NDA 20587), relying on the medical literature for evidence of clinical efficacy and safety. The indication for Sclerosol® Intrapleural Aerosol was also "to prevent recurrence of malignant pleural effusions in symptomatic patients". Whereas Sclerosol® was approved for administration by aerosol during thoracoscopy or open thoracotomy, Sterile Talc Powder is mixed with normal saline solution to form a slurry and is administered intrapleurally via chest tube.

The applicant has provided evidence of efficacy for Sterile Talc Powder by identifying and analyzing 5 adequate and well-controlled trials from the literature that support the proposed indication. These trials are listed in Table 2. The studies provide Level I evidence of efficacy of talc slurry in the therapy of MPE. The studies are randomized and controlled trials using a prospectively defined objective measure of "success." In the majority of these studies, response is also assessed at a standardized time and all patients are accounted for. (See section 6.3.1 for detailed analysis of the 5 trials.) For the 89 evaluable patients studied in the 5 randomized controlled trials in which talc slurry was used as a sclerosing agent, there was an 89% (79/89) response to treatment (range 79-100%). The dose of talc was 5 gm in 4 studies (80 patients) and 10 gm in 1 study (9 patients). In spite of design and treatment differences among the trials, talc consistently demonstrates efficacy in decreasing recurrence of MPE in each of the 5 randomized controlled trials. Additional single arm trials and retrospective series identified by the applicant and the reviewer from the literature are supportive of efficacy, as well.

### 6.2 General Approach to Review of the Efficacy of the Drug

The efficacy data base consists of data from the clinical trials from the literature identified by the applicant, supplemented by additional studies identified by the medical reviewer from the FDA literature review. (See section 4.4 for description of methodology.)

The medical reviewer read the articles referenced by the applicant in volume 6 of the paper submission as the efficacy and safety database for the NDA and reviewed the abstracts of articles identified in the FDA literature search. The reviewer selected and read all articles, which seemed pertinent to the efficacy and safety of talc in the treatment of MPE in an attempt to add to the clinical database.

Particular emphasis was placed on the data from a core of articles which contain adequate and well-controlled trials, with sufficient description of methodology and data to permit analysis (level I evidence). The best studies would account for all patients and provide objective measures of response at a standardized time. Nonrandomized case-control or cohort studies would provide the next lower level of evidence (level II), but such studies

were not identified in the talc literature. The lowest level of evidence ((level III) is provided by uncontrolled or retrospective studies, which were identified in the literature and reviewed.

### 6.3 Detailed Review of Trials by Indication

#### 6.3.1 Randomized Controlled Trials of Talc Slurry

The following reviewer table summarizes the 5 randomized controlled trials of talc slurry administered intrapleurally by chest tube to reduce recurrence of MPE in symptomatic patients with a variety of solid tumors.

**Table 2: Randomized Controlled Trials of Talc Slurry as Sclerosing Agent (Reviewer Table)**

REFERENCE	TREATMENT	RESPONSE RATE EVALUABLE PTS* p value*	RESPONSE RATE ALL PTS p value*	MINIMUM DURATION OF RESPONSE
Sorensen et al. Eur J Respir Dis. 1984;65:131-5	Talc Slurry 10g /250 ml NS vs. Chest Tube drainage	100% (9/9) vs. 58% (7/12) p = 0.04	64% (9/14) vs. 41% (7/17) p = 0.29	3 months  ( Median duration = 10 months)
Noppen et al. Acta Clin Belg 1997; 52:258-62	Talc Slurry 5g /50 ml NS vs. Bleomycin 1mg/kg /50 ml NS	79% (11/14) vs. 75% (9/12) p = 1.00	79% (11/14) vs. 75% (9/12) p = 1.00	Not given
Zimmer PW et al. Chest 1997; 112(2):430-434	Talc Slurry 5g /50 ml NS <sup>c</sup> vs. Bleomycin 60U /50 ml NS <sup>c</sup>	90% (17/19) <sup>b</sup> vs. 79% (11/14) <sup>b</sup> p = 0.63	Not given	Not given
Ong KC et al. Respirology 2000; (5):99-103	Talc Slurry 5g /150 ml NS <sup>d</sup> vs. Bleomycin 1 U/kg /150 ml NS <sup>d</sup>	89% (16/18) vs. 70% (14/20) p = 0.24	64% (16/25) vs. 56% (14/25) p = 0.77	1 month
Yim AP et al. Ann Thorac Surg 1996; 62:1655-8	Talc Slurry 5g /50ml NS, lidocaine 2% 10ml vs. Talc Insufflation 5g powder	90% (26/29) vs. 96% (27/28) p = 0.61	90% (26/29) vs. 96% (27/28) p = 0.61	Not given

\*Two-sided p-value based on Fisher's exact test

<sup>a</sup>Patients were evaluable if chest x-rays were done to assess response per protocol. Sorensen study, patients also excluded if incomplete lung re-expansion post drainage.

<sup>b</sup>Data per procedure (33 procedures per 29 evaluable patients, 3 patients with bilateral effusions)

<sup>c</sup>Plus lidocaine 1% 20ml

<sup>d</sup>Plus lidocaine 1% 10ml

In this section, some of the similarities and differences between the 5 randomized controlled trials are summarized. For all of these trials, the patients in one arm were treated with intrapleural talc slurry, 5 gm in all studies except the Sorensen et al study, in which the dose was 10 gm of talc slurry. The volume of saline in which the talc was suspended varied in the studies from 50 to 250 ml, and, in some cases, 10 to 20 ml of lidocaine (1 or 2%) was added. The comparator arms were as follows:

- In the Sorensen study, the comparator was chest tube drainage only, without the addition of a sclerosing agent.
- In the Yim et al study, the comparator was video-assisted thoracoscopic (VAT) talc powder insufflation using the same 5 gm dose for both arms.
- For the 3 remaining controlled trials, the comparator sclerosing agent was Bleomycin, 1 U/kg for the Noppen et al and Ong et al studies, and 60U for the Zimmer et al study.

The applicant states that there were 89 evaluable patients treated with talc slurry, of whom 79 (89%) responded to treatment in the 5 randomized trials:

*Reviewer comment: Excluding the Zimmer study in which efficacy was reported in terms of procedures, not patients, there were 70 evaluable patients treated with slurry, of whom 62 responded, for a response in 89% of these patients. In the Zimmer study, there were 29 evaluable patients in both arms of the trial, including 3 patients with bilateral effusion, and a total of 33 procedures were performed. One of the three evaluable patients with bilateral effusions received Bleomycin bilaterally and the other 2 patients received different agents on each side. The Zimmer data is presented as response rate per procedure, with 17 successful of 19 pleurodeses attempted with talc, also an 89% success rate per talc procedure performed.*

The studies had different definitions of "success" of the procedure and schedules for efficacy evaluation, as follows:

- The Sorenson study required chest x-rays at 1 month and then every 3 months, with success defined as no "reaccumulation of pleural fluid... within 3 months." The Ong study also defined response (lack of recurrence on x-ray) at a standardized time, in this case, 1 month after pleurodesis.
- Noppen defined therapeutic failure as reaccumulation of  $\geq 50\%$  the initial volume of fluid seen on chest x-ray assessed every 2 months or the requirement for repeat thoracentesis.
- Zimmer defined success as a score of 1 (no effusion) or 2 ( $< 10\%$  of presclerosis volume) on a scale of 4, based on chest x-ray obtained at follow-up, which ranged from 2 weeks to 8 months with a mean of 1.7 months.
- Yim similarly defined "success" as the absence of recurrence of effusion during the period of follow-up. Patients were "seen in the clinic at 6-week intervals for the first 4½ months and then every 3 months" for "radiologic evidence of fluid reaccumulation", with a mean follow-up of 10 months for the survivors (range, 4-16 months). Radiologic recurrence was documented in 3 talc slurry patients (at 6, 12, and 14 months) and at 11 months in 1 VAT patient.

*Reviewer comment: Since many of the patients in these studies had advanced cancer with short survivals, an early evaluation for lack of recurrence, such as at 1 month, would minimize the number of patients who are inevaluable for recurrence due to death or other reason for loss to follow-up. However, the studies that define "success" as lack of recurrence of effusion during the period of follow-up, show a very high percentage of evaluable patients remaining effusion-free long-term, most for the duration of survival or follow-up.*

#### 6.3.1.1 Individual Summaries of Randomized Trials

**Article:** Sorensen PG, Svendsen TL, Enk B. Treatment of Malignant Pleural Effusion with Drainage, with and without Instillation of Talc. *Eur J Respir Dis.* 1984; 65: 131-135.

**Objective:** To compare the efficacy of sclerosis with talc slurry following chest tube drainage of MPE compared with drainage alone.

**Study Design:** Prospective, randomized controlled trial

**Study Dates:** Not stated; submitted for publication 11/18/82

**Patient Population:** Histologically documented malignant pleural effusion causing respiratory distress; no previous sclerosis; cancer resistant to conventional therapy; patients excluded if lung not fully expanded within 72 hours of chest tube drainage by suction (following thoracoscopy)

**Treatment Plan:** All patients had thoracoscopy, pleural biopsy and drainage for  $\leq 72$  hours until dry; patients were excluded from study if lung not fully expanded. Patients randomized to talc were given 10 gm sterile talc suspended in saline 250 ml intrapleurally by chest tube. (The source and characteristics of the talc were not otherwise specified.) The chest tube was clamped for 2 hours "during which the patient changed position several times, ending in the Trendelenburg position, in order to distribute the suspension of talc over the surface of the pleura." After 72 hours of suction, the chest tube was removed. For patients randomized to drainage only, constant suction was applied for 72 hours after re-expansion of the lung, when the tube was removed.

**Efficacy Monitoring:** Chest x-rays were done at 1 month and then every 3 months following pleurodesis. Patients were not evaluated for efficacy if their lungs did not expand by 72 hours.

**Definition of "Success":** No radiographic recurrence within 3 months. Failure to be confirmed by thoracentesis.

**Statistical Plan:** The trial was designed to have 50% power to conclude superiority of talc provided that talc did in fact improve success by at least 40%.

**Results:****Table 3: Sorensen et al, Demographics, Tumor Type and Evaluability (Reviewer Table)**

Treatment	Age, median (range)	No. M/F (total pts)	# Evaluable / # Entered	Tumor Type incidence not provided by arm
CT + T	62 (39-79) both groups combined	(14)	9/14	7 ovarian, 3 breast, 3 lung, 2 GI, 3 cervical, 1 hypernephroma, 6 mesothelioma, 1 prostate, 5 adenocarcinoma of unknown primary.
CT		(17)	12/17	

CT = chest tube drainage; T = talc

**Source: Original Sclerosol NDA review, 1996**

Ten patients (5 per arm) were considered to be inevaluable. Of these, 7 patients (2 chest tube plus talc/ 5 chest tube only) died of cancer within 3 months and, as such, were unavailable for assessment at the predefined time. Two patients were excluded for failure of initial lung re-expansion; and 1 patient developed empyema (chest tube plus talc). It is unclear whether the 7 patients that died were assessed by chest X-ray as planned at 1 month. Gender and performance status of the patients was not provided.

**Table 4: Sorensen et al, Response (Reviewer Table)**

Treatment	# Evaluable / # Entered	Success (definition provided Y/N)	Duration, median (range)	Symptom (sx) Relief
CT + T	9/14	9/9 (Y)	10 mo. (3-24 mo.)	9/9 "partial or complete resolution of dyspnea"
CT	12/17	7/12 (Y)	10 mo. (4-17 mo.)	6/7 "subjective improvement"

CT = chest tube drainage; T = talc

**Source: Original Sclerosol NDA Review, 1996**

All 9 evaluable patients treated with chest tube drainage plus talc had a complete response until death (median 10 months, range 3-24 months). Chest X-rays revealed "pleural thickening and diaphragmatic adhesions". The author states that these 9 patients "obtained subjective improvement with partial or complete resolution of dyspnea." None of the patients reported chronic chest discomfort post procedure.

**Conclusions and Comments:** The authors state that chest tube plus talc is superior to chest tube alone for treatment of MPE. "If re-expansion of the lung is possible..., pleurodesis can be obtained in 60% of the treated patients with pleural drainage alone. The addition of talc instillation into the pleural cavity produced a statistically significant improvement in the treatment..."

*Reviewer comment: The study provides Level 1 evidence of efficacy of talc slurry in the therapy of MPE. The study is randomized and controlled, all patients accounted for, and*

*a prospective, objective definition of "success" is provided.. Although the trial was only powered to have a 50% chance to detect talc superiority, the benefit is statistically significant when analysis is performed on evaluable patients but not on the intent to treat population. Several patients in both groups are not evaluable because of early death due to cancer, in this population of patients with advanced disease and very limited treatment options. Additional patients were inevaluable because they were randomized and then withdrawn because of inadequate re-expansion of the lung after the initial period of chest tube drainage. A better design, which would have left fewer patients inevaluable, would have been to randomize patients after establishing that inclusion criteria were met, i.e. adequate re-expansion of lung post initial period of drainage.*

**Article:** Noppen M, Degreve J, Mignolet M, and Vincken W. A Prospective, Randomized Study Comparing the Efficacy of Talc Slurry and Bleomycin in the Treatment of Malignant Pleural Effusions. *Acta Clin Belg* 1997; 52: 258-62.

**Objective:** To compare the efficacy of talc slurry with Bleomycin administered by tube thoracostomy for MPE.

**Study Design:** Prospective, randomized controlled trial

**Study Dates:** Not stated

**Patient Population:** Consecutive patients with proven (positive pleural fluid cytology or pleural biopsy) MPE, recurrent after at least 2 thoracenteses; no previous sclerosis; symptomatic; Karnofsky performance status (KPS)  $\leq$  50 and expected survival  $\leq$  1 year.

**Treatment Plan:** The pleural space was emptied (confirmed by chest x-ray) by continuous suction through a 14 F chest tube, until drainage was  $<$  150 ml/24 hours. Lidocaine 2% 20 ml was injected through the chest tube, which was then flushed with sterile saline 10ml, and the tube was clamped for 10 minutes. The clamp was released, bleomycin or talc slurry injected, followed by 10 ml saline. The tube was clamped for 30 minutes, then unclamped, applying suction for at least 24 hours and until drainage was  $<$  150 ml/day. The doses were talc, 5 g in 50 ml saline, and bleomycin, 1 mg/kg in 50 ml saline. The talc was sterile, asbestos-free, pharmacopoeia grade.

*Reviewer comment: Unlike the other studies, there is no statement that patients were instructed to change position immediately post procedure to facilitate dispersion of talc through the pleural space.*

**Efficacy Monitoring:** Chest x-rays were obtained at 2 months post-procedure and every 2 months until death. The immediate post pleurodesis chest x-ray was used as a baseline.

**Definition of "Success":** Success defined as lack of reaccumulation of fluid on chest x-ray obtained every 2 months. Failure defined as reaccumulation of  $>$  50% of pre-treatment volume, or requirement for repeat thoracentesis.

**Statistical Plan:** Data were expressed as mean +/- SD (standard deviation of the sample). Patient characteristics, survival and recurrence rates between groups were compared using either the Mann Whitney rank sum test or Fisher exact test.

**Results:**

**Table 5: Noppen et al, Demographics, Tumor Type and Evaluability (Reviewer Table)**

Treatment	Age, Mean (+/- S.D.*)	Male/Female	# Evaluable/ # Entered	Tumor Type
Talc slurry	60.9 (13.9)	8/6	14/14	4 breast, 5 lung, 2 gastric, 2 mesothelioma, 1 melanoma
Bleomycin	60.6 (19.7)	3/9	12/12	5 breast, 4 lung, 1 NHL, 1 unknown primary, 1 endometrium

\*Standard deviation of the sample

The age of the patients and predominance of non-small cell lung cancer (NSCLC) and breast cancer were similar for both treatment groups.

**Table 6: Noppen et al, Response (Reviewer Table)**

Treatment	# Evaluable / # Entered	Success (definition provided Y/N)	Duration	Recurrence
Talc slurry	14/14	11/14 (Y)	Not given	3/14
Bleomycin	12/12	9/12 (Y)	Not given	3/12

All patients were available for evaluation and were accounted for. Response was assessed by chest x-ray every 2 months. The response rates in the groups were 79% for the talc slurry patients and 75% for the Bleomycin patients ( $p = 1.000$ ). The duration of response was not provided. The incidence of recurrence was slightly higher for the Bleomycin patients (3/12 = 25%) compared with the talc patients (3/14 = 21.4%), but not significantly so.

**Conclusion and Comments:**

The authors conclude that talc slurry is as effective as bleomycin in achieving pleurodesis.

*Reviewer comment: Although the differences are not statistically significant, the study provides Level I evidence of efficacy of talc slurry for treatment of MPE. The study is randomized and controlled, all patients accounted for, and a prospective, objective definition of "success" is provided. Although patients were required to be symptomatic, the author does not provide information regarding symptomatic improvement as an outcome. The author points out that their study intentionally selected very sick patients ( $KPS \leq 50$ ), who*

*were followed to death, so that "our results of a 78.6% successful and permanent pleurodesis are comparable with the literature data". In view of the much greater expense of Bleomycin compared to talc, comparable outcome could be viewed as a benefit of talc over Bleomycin.*

**Article:** Zimmer PW, Hill M, Casey K, Harvey E, Low DE. Prospective Randomized Trial of Talc Slurry vs. Bleomycin in Pleurodesis for Symptomatic Malignant Pleural Effusions. August 1997; Chest 112: 430-434.

**Objective:** To compare talc slurry and bleomycin for effectiveness, safety, and cost.

**Study Design:** Prospective, randomized controlled trial

**Study Dates:** July 1992-March 1995

**Patient Population:** Patients had symptomatic malignant pleural effusion, documented by pleural fluid cytology in 33 patients and thorascopic or open biopsy in 2 patients. Patients had life expectancy > 1 month. Patients were excluded if they had significantly loculated effusions or trapped lung after drainage.

**Treatment Plan:** Patients were randomized following determination of satisfactory lung re-expansion after drainage of pleural by suction through a 28F tube for 12-24 hours. The sclerosing agent was injected into the chest tube, and then the tube was flushed with 25 ml of sterile normal saline. The tube was clamped for 2 hours and "the patient placed in Trendelenburg and reverse Trendelenburg positions while in the prone, supine, and left and right decubitus positions for 10 to 15-minute intervals." The tube was returned to suction, usually for 48 hours, until lung expansion was documented on chest x-ray. The sclerosing agents were prepared with 20 ml of 1% lidocaine, and either 60 U of bleomycin or 5 g of talc, diluted to a total of 50 ml with normal saline solution. The talc was pharmaceutical grade, USP-certified, and asbestos-free, provided by Spectrum Chemical Manufacturing Corporation, Gardena, CA. The investigators steam sterilized the talc 6 hours at 270 degrees.

**Efficacy Monitoring:** Chest x-rays were obtained at follow-up, which ranged from 2 weeks to 8 months with a mean time of follow-up of 1.7 months.

**Definition of "Success":** Zimmer defined success as a score of 1 (no effusion) or 2 (< 10% of presclerosis volume) on a scale of 4, based on chest x-ray obtained at follow-up, which ranged from 2 weeks to 8 months with a mean of 1.7 months.

**Statistical Plan:** Radiograph scores were compared using the chi-square test.

## Results:

Table 7: Zimmer et al, Demographics, Tumor Type and Evaluability (Reviewer Table)

Treatment	Age, Mean (+/-SEM*)	Male/Female	# Evaluable/ # Entered	Tumor Type
Talc slurry	65 (3.5)	7/12	19/?**	5 lung, 5 breast, 3 ovarian, 6 other
Bleomycin	68 (4.4)	4/10	14/?**	8 lung, 0 breast, 2 ovarian, 4 other

\*Standard error of the mean

\*\*Data presented per procedure (33 procedures per 29 evaluable patients, 3 patients with bilateral effusions). Six patients who underwent 7 procedures were unavailable for follow-up, including 1 patient with bilateral effusions treated with different agents, dying in hospital of disease. Treatment group not provided for inevaluable patients with unilateral effusions.

The mean age is similar for the groups. There is a male predominance in the talc group of 58%, compared with only 40% male in the bleomycin group. The talc group includes more patients with breast cancer than the bleomycin group.

*Reviewer comment: Although breast cancer is often chemosensitive, we are not told if any patients in either group were eligible for chemotherapy or hormonal therapy, which could impact effusion recurrence.*

Table 8: Zimmer et al, Response (Reviewer Table)

Treatment	# Evaluable/ # Entered	Success (definition provided Y/N)	Duration	Recurrence
Talc slurry	19/?*	17/19 (Y)	Not given	2/19
Bleomycin	14/?*	11/14 (Y)	Not given	3/14

\*See footnote Table 7, above

The response rates per procedure (for evaluable patients) were 90% (17/19) for talc slurry and 79% (11/14) for bleomycin, not statistically different.

**Conclusions and Comments:** The authors conclude "we found both bleomycin and talc slurry to be highly effective at controlling malignant effusions and decreasing the associated symptoms of dyspnea and pain." They cite the striking difference in cost of the 2 agents in their institution, \$12.36 for talc and \$955.83 for bleomycin, and recommend routine use of talc slurry because it is effective, safe, and much more cost-effective than bleomycin.

*Reviewer comment: Although the differences are not statistically significant, the study provides Level I evidence of efficacy of talc slurry in the therapy of MPE. The study is randomized and controlled and a prospective definition of "success" is provided. Thirty-five patients were prospectively randomized for pleurodesis with talc slurry or bleomycin, and had 40 procedures (4 bilateral effusions and 1 re-treatment). Only 29 patients who underwent 33 treatments were available for follow-up (see table 7 and accompanying*

*footnote). Patients were inevaluable because of failure to return for follow-up x-rays. The study suffers from the inability to account for all patients, and we do not know into which treatment groups the lost patients fall. Even those patients who were available for follow-up did not have evaluation at a standardized time, with the time of the follow-up x-ray ranging from ½ month-8 months. The study included 3 (evaluable) patients with bilateral effusions, 2 of whom had different therapies, necessitating analysis by procedure instead of by patient. It would have been appropriate to exclude from the study patients who required treatment of bilateral effusions. The strength of the study would have been improved by assessing response at a standard time (eg. 1-3 months) and trying to obtain data on durability of response.*

**Article:** Ong KC, Indumathi V, Raghuram J, and Ong YY. A Comparative Study of Pleurodesis using Talc Slurry and Bleomycin in the Management of Malignant Pleural Effusions. *Respirology* 2000; 5: 99-103.

**Objective:** To compare the efficacy of talc and bleomycin for pleurodesis of MPE.

**Study Design:** Prospective, randomized controlled trial

**Study Dates:** April 1994-April 1999

**Patient Population:** Proof of malignant effusion fluid cytology or pleural biopsy was required. Patients were excluded if they had trapped lung, loculated effusion, recurrent effusion, or life expectancy < 1 month. If pleural drainage > 100 ml/day continued for 10 days, patients were excluded. All patients had unilateral effusions and were symptomatic (e.g. pain, dyspnea).

**Treatment Plan:** Patients were randomized following determination of satisfactory lung re-expansion after drainage of pleural fluid by suction through a 20-28 F thoracostomy tube until daily flow was < 100 ml for 2 days. The sclerosing agent was injected into the tube, which was then flushed with 100 ml of sterile normal saline. The tube was clamped for 6 hours and "the patient placed in the prone, supine and left and right decubitus positions at 30 minute intervals." The tube was returned to suction and removed when drainage was < 200 ml per day. The sclerosing agents were prepared with 10 ml of 1% lidocaine and either 1 U/kg of bleomycin or 5 g of talc, diluted to a total volume of 50 ml with normal saline. The talc was pharmaceutical grade, USP-certified, asbestos-free and sterilized (Merck, Germany).

**Efficacy Monitoring:** Chest x-rays were obtained immediately after chest tube removal and 1 month later. A single, blinded investigator scored all follow-up chest x-rays.

**Definition of "Success":** Success was defined by the absence of pleural effusion on the 1 month chest x-ray. The 1 month follow-up chest radiographs were scored as follows: (i) 0: No recurrence as compared with immediate post-pleurodesis films; (ii) 1: Minimal effusion (recurrence < 33% of hemithorax); (iii) 2: Moderate effusion (34-67%); (iv) 3: massive effusion (68-100% of hemithorax).

**Statistical Plan:** Comparisons between groups were done with unpaired 2-tailed Student's t-test for normally distributed continuous variables and Mann-Whitney U-test for non-normally distributed continuous variables. Chi-squared analysis was used for comparison of proportions.

**Results:**

**Table 9: Ong et al, Demographics, Tumor Type and Evaluability (Reviewer Table)**

Treatment	Age, Mean (+/-S.D.*)	Male/Female	# Evaluable/ # Entered	Tumor Type of Evaluable Pts
Talc slurry	59.8 (13.2)	9/9	18/25	10 lung, 3 breast, 3 GI, 2 others
Bleomycin	66.3 (11.7)	8/12	20/25	9 lung, 7 breast, 1 GI, 3 others

\*Standard deviation of the sample

Of the 50 patients randomized, 38 were available for 1 month radiographic evaluation, 18 in the talc group and 20 in the bleomycin group. In the talc group, 4 patients had died and 3 others were not available for x-ray. In the bleomycin group, 4 patients had died by 1 month and 1 additional patient was unavailable. The patients were similar in demographic distribution and tumor types among the groups, except there were more breast cancer patients in the bleomycin group. The authors do not discuss whether patients in this study were permitted or excluded from systemic chemotherapy or hormonal therapy. In the bleomycin group, there were 17 patients with adenocarcinoma, compared with 11 such patients in the talc group. The authors compared the baseline size of pleural effusions for patients in the 2 groups and determined that the size distribution was similar. The authors' statistical analysis showed no significant differences in any baseline or tumor characteristics.

**Table 10: Ong et al, Response (Reviewer Table)**

Treatment	# Evaluable/ # Entered	Success (definition provided Y/N)	Duration (Minimum)
Talc slurry	18/25	16/18 (Y)	1 month
Bleomycin	20/25	14/20 (Y)	1 month

Success was defined as "the absence of recurrent pleural effusion on the chest radiograph 1 month after pleurodesis was achieved." The per cent response was 89% (16/18) for the talc slurry patients and 70% (14/20) for the bleomycin patients but the differences were not statistically significant (see Table 2). In an intent to treat analysis, the response rate for the talc patients was 64% (16/25) and 56% (14/25) for the bleomycin patients. No additional relapse information was provided. The difference in median survival time was not statistically significant ( $p = 0.625$ ) between the talc and bleomycin groups, 4 months and 5 months, respectively.

**Conclusions and Comments:** The authors conclude, "intrapleural instillation of talc slurry for pleurodesis of malignant effusions is as effective as the instillation of bleomycin in preventing recurrences after 1 month of treatment." The authors' cost analysis was in favor of talc with a cost of \$1 for 5 gm vs. \$66.27 per 15 U of bleomycin, in their setting, estimating a cost difference per treatment of \$308.26 for a 70 kg patient. They recommend bedside instillation of talc slurry for appropriately selected patients. They state, "Patients with multiloculated pleural effusions, or those who require diagnostic examination, however, may benefit more from the use of thoracoscopy and talc poudrage."

*Reviewer comments: This study is a well-designed and executed, randomized controlled trial that compares talc slurry with bleomycin, a drug previously approved for the indication. Although the differences are not statistically significant, it provides Level I evidence of short-term efficacy of talc slurry in treatment of MPE. All patients are accounted for, a prospective, objective definition of "success" is provided, and the objective evaluation of response is enhanced by having a single, blinded investigator score all the of the follow-up x-rays. Although the study does not provide information about duration of treatment success, the 1-month evaluation time minimizes subject drop-out and inevaluability in a population of patients with short expectation of survival.*

**Article:** Yim AP, Chan AT, Lee TW, Wan IY, and Ho JK. Thorascopic Talc Insufflation versus Talc Slurry for Symptomatic Malignant Pleural Effusion. *Ann Thorac Surg* 1996; 62:1655-8.

**Objective:** To compare the efficacy of video assisted thoracoscopic (VAT) talc insufflation with bedside talc slurry in the treatment of MPE.

**Study Design:** Prospective, randomized controlled trial

**Study Dates:** September 1993-November 1995

**Patient Population:** Patients had symptomatic MPE. Patients were excluded if dyspnea was believed to be due to tumor replacement of lung tissue and if symptoms did not improve after large-volume thoracentesis. KPS was required to be > 30% and pulmonary function to be adequate (forced expiratory volume < 0.5 L in 1 second). Patients were excluded for trapped lung or for chemotherapy or radiation therapy within 6 month of diagnosis of the MPE. The investigators do not comment on need for cytologic or histologic proof of malignancy.

**Treatment Plan:** Eligible patients were randomized to receive VAT talc insufflation under general anesthesia or bedside treatment with talc slurry through an indwelling thoracostomy tube. Any residual fluid was removed from the VAT patients, loculations were broken down and fibrinous adhesions were taken down. Talc 5 gm was insufflated to evenly cover the visceral and parietal surfaces. An atomizer was used with some study

patients, but later the technique was changed to employ a mucus extractor attached to a 50 ml syringe. A 28 F chest tube was left to suction until output was < 50 ml in 24 hours. Slurry was prepared by mixing 5 gm purified talc with normal saline solution 50 ml and 2% lidocaine 10 ml for instillation through the chest tube. The drain was clamped for 2 hours and the patient turned in different positions. The tube was returned to suction until the output was < 50 ml in 24 hours. Purified talc was obtained from Halewood Chemicals, UK, and sterilized by dry heat.

**Efficacy Monitoring:** Patients were seen in the clinic at 6-week intervals for the first 4½ months and then every 3 months, at which time x-rays were obtained for evidence of fluid reaccumulation.

**Definition of "Success":** Success was defined as the absence of recurrence of effusion during the entire period of follow-up.

**Statistical Plan:** "Differences between the two groups were analyzed using Mann-Whitney U tests."

**Results:**

**Table 11: Yim et al, Demographics, Tumor Type and Evaluability (Reviewer Table)**

Treatment	Age, Mean (+/-S.D.*)	Male/Female	# Evaluable/ # Entered	Tumor Type of Evaluable Pts
Talc slurry	65 (12.3)	10/19	29/29	15 lung, 9 breast, 4 GI, 1 other
Talc insufflation	60 (9.4)	10/18	28/28	18 lung, 6 breast, 2 GI, 2 others

\*Standard deviation of the sample

The baseline characteristics of the patients in both treatment groups were similar. The baseline performance status of the patients in this study was superior to patients in some of the other studies by design (see "patient population" prior page), to permit randomization to a procedure in one arm that required general anesthesia.

**Table 12: Yim et al, Response (Reviewer Table)**

Treatment	# Evaluable/ # Entered	Success (definition provided Y/N)	Duration	Recurrence
Talc slurry	29/29	26/29 (Y)	Not given	3/29
Talc insufflation	28/28	27/28 (Y)	Not given	1/28

The success rate (absence of recurrence during follow-up) was 90% for the slurry group and 96% for the insufflation patients, not significantly different. Radiologic recurrence was documented in 3 talc slurry patients (at 6, 12, and 14 months) and at 11 months in 1

VAT patient. No mean or median duration of success was provided. The mean follow-up time was 10 months for the survivors (range, 4-16 months). Fifteen of the talc slurry patients and 19 of the VAT talc insufflation patients died during follow-up without evidence of recurrence.

**Conclusion and comments:** The authors conclude that there is no statistically significant difference between the treatment arms regarding "hospital stay, analgesic requirement, complications, or procedure failures." Of the 4 patients with recurrence, only 1 was symptomatic enough to require further treatment. They recommend talc slurry as the procedure of choice for patients with symptomatic MPE without trapped lung, since slurry is as effective as insufflation, but less invasive and requires fewer resources. The authors recommend consideration of pleuroperitoneal shunt for patients with severely trapped lung who can comply. For patients with less than 25% fixed pneumothorax (minor trapped lung), they suggest consideration of thoroscopic talc pleurodesis.

*Reviewer comment: Although the differences are not statistically significant, the study provides level I evidence of efficacy for talc slurry in the treatment of MPE. The lesser degree of invasiveness and cost for the bedside slurry procedure does make it preferable for properly selected patients. The study is well-designed, randomized and controlled, a prospective definition of "success" was provided, and all patients are accounted for. We are given evidence of durability of response for the patients who recurred (after 6-14 months) but no mean (or median) duration of response for the entire study population.*

#### 6.3.2 Single Arm Trials of Talc Slurry

The following table summarizes the 14 individual clinical studies identified by the applicant from the literature, in which talc slurry was used as a sclerosing agent to prevent recurrence of malignant pleural effusion.

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Table 13: Single Arm Trials Using Talc Slurry (Applicant Table)

REFERENCE	TREATMENT	RESPONSE RATE
Chambers, West J Surg Obstet, Gynecol 1958; 66:26.	Palliative treatment of neoplastic pleural effusions with intercostal intubation and talc instillation	85% (17/20)
Adler and Sayek, Ann Thorac Surg 1976; 22(1): 8-15	Treatment of malignant pleural effusion: a method using tube thoracostomy and talc.	93% (41/44)
Bloomberg, NY State J Med 1970; 70: 1974-7	Thoracoscopy in diagnosis of pleural effusions.	100% (12/12)
Webb <i>et al</i> , J Thorac Cardiovasc Surg 1992; 103(5): 881-5; discussion 885-6.	Iodized talc pleurodesis for the treatment of pleural effusions	100% (28/28)
Kennedy <i>et al</i> , Chest 1994; 106, 342-6	Pleurodesis using talc slurry.	81% (38/47)
Miller <i>et al</i> , Chest 1994; 105(6): 1906- 1907.	Talc slurry for pleurodesis	100% (8/8)
Turler <i>et al</i> , Support Cancer Care 1997; 5: 61-3	Palliative iodized talc pleurodesis with instillation via tube thoracostomy.	92% (36/39)
Jacobi <i>et al</i> , Langenbecks Arch Surg 1998; 383(2): 156-9.	Talc pleurodesis in recurrent pleural effusions.	94% (31/33)
Thompson <i>et al</i> , Ann Pharmacother 1998; 32: 739-42	Pleurodesis with iodized talc for malignant effusions using pigtail catheters.	82% (14/17)
Bloom <i>et al</i> , Cardiovasc Intervent Radiol 1999; 22: 433-6.	Talc pleurodesis through small-bore percutaneous tubes	75% (6/8)
Marom <i>et al</i> , Radiology 1999; 210: 277- 81	MPE: treatment with small-bore catheter thoracostomy and talc pleurodesis	84% (27/32)
Saffran <i>et al</i> , Chest 2000; 118(2): 417-21	Outpatient pleurodesis of malignant pleural effusions using a small-bore pigtail catheter.	75% (6/8)
Sahin <i>et al</i> , Respiration 2001; 68(5): 501-5	The value of small-bore catheter thoracostomy in the treatment of malignant pleural effusions.	84% (16/19)
Prevost <i>et al</i> , Oncol Rep. 2001; 8(6): 1327-31	Long-term effect and tolerance of talc slurry for control of malignant pleural effusions.	81% (22/27)

The following articles do not provide an adequate description of methodology and data to permit analysis, do not add significant support to the efficacy of the indication, and are excluded from consideration below: Chambers (1958), Adler and Sayek (1976),

One additional single arm trial from the literature, identified by the reviewer, seems adequate to support the indication: Marom et al. American Journal of Roentgenology 2002;179:105-108. This series of patients with gynecologic cancers does not seem to include the patients reported by Marom in 1999. The following 2 reviewer tables summarize data from the 13 supportive single arm trials.

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ON ORIGINAL**

Table 14: Single Arm Trials of Talc Slurry: Treatment, Demographics (Reviewer Table)

Reference	Design	Treatment	Age, Mean (Range)	M/F
Adler et al, 1976	Retrospective	Talc 10 gm <sup>a</sup> /250 ml NS	(17-81)	Not given
Webb et al, 1992	Prospective	Talc 5 gm + 3 gm thymol iodide/50 ml NS + lidocaine 1% 20 ml	50 (26-88)	Not given
Kennedy et al, 1994	Retrospective	Talc 10gm / 150-250 ml NS	54.4 (32-84)	40/56 pts (56/73 procedures)
Miller et al, 1994	Retrospective	Talc 2 gm / 50 ml NS	Not given	Not given
Turler et al, 1997	Prospective	Talc 5gm + 3gm thymol iodide/80 ml NS + lidocaine 1% 0.5 ml/kg	63.8 (35-84)	17/26
Jacobi et al, 1998	Prospective	Talc 5gm + 3gm thymol iodide/30 ml NS + lidocaine 1% 0.5ml/kg	60.1 <sup>b</sup> (34-81)	24/26 <sup>b</sup>
Thompson et al, 1998 <sup>c</sup>	Prospective	Talc 5 gm + 3 gm thymol iodine/100ml NS + lidocaine 2% 20 ml	66 (42-78)	4/11
Bloom et al, 1999 <sup>k</sup>	Retrospective	Talc 5 gm/100 ml NS +/- lidocaine 1% 20 ml	(22-81)	1/7
Marom et al, 1999 <sup>d</sup>	Prospective	Talc 5 or 10 gm <sup>e</sup> /100 ml NS + lidocaine 1% 10 ml	64 (26-82) <sup>f</sup>	16/16 <sup>f</sup>
Saffran et al, 2000 <sup>g</sup>	Prospective	"Talc slurry" 4 gm +lidocaine 1% 50 ml	55 (41-79)	0/10
Sahin et al, 2001 <sup>h</sup>	Prospective	Talc 5 gm /50 ml NS+ lidocaine 2% 5 ml	56.4 (43-66)	11/13
Prevost et al, 2001	Prospective	Talc 4 gm/30 ml NS+ lidocaine 2% 10 ml on 2 successive days	62.4	9/22
Marom et al, 2002 <sup>i</sup>	Retrospective	Talc 5 or 10 <sup>j</sup> gm/ 100 ml NS +lidocaine 1% 10ml	63	0/25

<sup>a</sup>Dose reduced 1/2 to 2/3s if pt "small or frail"

<sup>b</sup>Demographic data includes 14 patients with benign disease, 36 malignant

<sup>c</sup> Small-bore pigtail catheter; 15 patients, 17 procedures; 5 treated previously; 11 loculated

<sup>d</sup> Small-bore pigtail catheter

<sup>e</sup> 23/60 patients received talc 10 gm; 37 patients 5 gm; 11/32 evaluable patients received 10 gm, 21/32 received 5 gm; evaluable patients are alive at 30 days and had for x-ray

<sup>f</sup> Demographic data for evaluable patients (32/60); alive at 1 month and had x-ray

<sup>g</sup> Small-bore pigtail catheter to gravity-drainage; outpatient feasibility study

<sup>h</sup> Small-bore catheter

<sup>i</sup> Small-bore pigtail catheter

<sup>j</sup> 3/25 patients received 10 gm; 22/25 patients received 5 gm

<sup>k</sup> Small-bore pigtail catheter

*Reviewer comment: In this section, I shall review some of the differences and similarities among the single arm trials and provide an overview of how the trials support the indication for Sterile Talc Powder. ( Please refer to table 14, above, and table 15, below, for details. ) The 13 referenced trials were published from 1976 through 2002, almost all of them performed in the 1990's. Some of the trials are retrospective and 8 of the 13 are prospective. There are variations among the trials regarding the following details:*

- *The source and dose of talc (2-10 gm)*
- *Iodination of talc (4 trials)*
- *The volume of solution in which the talc is suspended (50-250ml)*
- *The use of large or small-bore chest tubes*
- *The maximum allowable residual daily pleural drainage before talc pleurodesis (usually 50-150 ml)*
- *The management of the patients immediately following administration (eg. re-positioning to disperse talc over 1-3 hours)*
- *Inclusion and exclusion criteria*
- *Definition of clinical "success"*
- *Time of measurement of response*
- *Short or extended follow-up.*

*The most frequently studied dose of talc was 5 gm. This dose was used exclusively in 6 trials and predominantly in 2 others (both Marom trials), for a total of 213 patients. A 10 gm dose was used exclusively in 2 trials (Adler et al, 1976, and Kennedy et al, 1994) and in a minority of patients treated early in both Marom et al trials, for a total of 105 patients treated with 10 gm across the trials. (Marom et al said they decreased the dose mid-trials because 10 gm was more painful than the 5 gm dose and not superior from the literature.) In one trial each patients were treated with 2 gm (Miller et al, 8 patients), 4 gm (Saffran et al, 10 patients), and 4 gm on each of 2 successive days (Prevost et al, 30 patients).*

*Four of the 13 single arm (and none of the 5 randomized) trials added thymol iodide 3 gm to the dose of intrapleural talc, which was 5 gm in these studies. The contribution of the iodide to the success of the therapy is unclear, although one investigator stated that it was believed to decrease bacterial contamination and also permitted radiographic visualization of the pleural surface. Six of the studies used small-bore catheters rather than standard chest tubes, to increase patient comfort, without apparent decrease in efficacy in most of the trials.*

*The following reviewer table summarizes the tumor types of the subjects in each of the 13 trials and result of the trials.*

Table 15: Single Arm Trials of Talc Slurry: Tumor Type and Results (Reviewer Table)

Reference	Tumor Type	Success*	Duration	Recurrence
Adler et al, 1976	20 breast, 7 lung, 7 ovary, 3 lymphoma, 4 other	41/44 procedures (93%) or 38/41 patients	Not given	3/44
Webb et al, 1992	28/34 malignant 18 lung, 2 mesothelioma, 1 each of 8 tumor types	28/28 (100%) at 1 month	1-21 months; 20/28 cancer patients died 1-9 months	0/28
Kennedy et al, 1994	23 breast, 4 lung, 3 endometrium, 4 ovarian, 4 benign	38/47 evaluable procedures <sup>a</sup> (81%)	Mean follow-up 171 days	9/47
Miller et al, 1994	4 lung, 2 breast, 2 other	8/8 (100%)	4 to >27 wks	1/8
Turler et al, 1997	20 lung, 10 breast, 6 mesothelioma, 5 GI, 2 other	40/43 <sup>b</sup> (92%) at 3 , 43/43 <sup>b</sup> at 1 month	No recurrences after 3 mos.	3/43
Jacobi et al, 1998	16 lung, 12 breast, 3 mesothelioma, 3 esophageal, 2 other	31/33 (94%) at 1 month <sup>c</sup>	Mean follow-up 2 to 11 months	2/33 at 1 month
Thompson et al, 1998	5 lung, 5 breast, 2 unknown primary, 3 others	81% at 6 months <sup>d</sup>	No fluid at 9, 10, 15, 20 months	Not given
Bloom et al, 1999	3 breast, 2 lung, 1 ovary, 1 renal, 1 GBM	6/8 (75%) at ½ month	2-30 months	0/8
Marom et al, 1999	17 lung, 7 breast, 2 lymphoma, 6 other	27 <sup>e</sup> /32 (84%) at 1 month	Assessed at 1 month only	Not given
Saffran et al, 2000	6 breast, 1 breast and ovary, 2 lung, 1 leiomyosarcoma	6/8 <sup>f</sup> (75%) 4/8 <sup>f</sup> (50%)	Assessed at 1 month only	Not given
Sabin et al, 2001	11 lung, 6 breast, 5 mesothelioma, 2 other	16/19 <sup>g</sup> (84%) at 1 month 11/14 <sup>b</sup> (79%) at 3 months	Assessed at 1 and 3 months	3/14 at 3 months
Prevost et al, 2001	16 breast, 8 lung, 2 ovary, and 4 other	22/27 <sup>h</sup> (81%)	Assessed at 1-40 months <sup>i</sup>	See below <sup>j</sup>
Marom et al, 2002	15 ovary, 7 uterine, 2 cervix, 1 fallop. tube	11/13 <sup>k</sup> (85%) at 1 month	Assessed at 1 month only	Not given

\*Absence of recurrence, assessed at various times, per study

<sup>a</sup> Success evaluable in 47/73 procedures (64%) for patients available for 1 month x-ray

<sup>b</sup> 43/47 patients evaluable at 1 month due to 4 deaths < 1 month

<sup>c</sup> 33/36 patients evaluable at 1 month with malignant effusion; 3 deaths < 1 month

<sup>d</sup> Kaplan-Meier analysis, probability of control at median follow-up 6 months

<sup>e</sup> 2 patients previously failed bleomycin or tetracycline but responded to talc

<sup>f</sup> 2/10 could not be sclerosed; 6/8 symptoms better at 1 month; 2/6 no x-ray at 1 month

<sup>g</sup> 19/24 patients evaluable 1 month; 2 trapped lung; 2 died and 1 no x-ray at 1 month

<sup>h</sup> 2 more deaths and 3 relapses at 3 months

<sup>i</sup> 27/31 patients evaluable for efficacy; 4 died from cancer after < 1 month

<sup>j</sup> No recurrence requiring thoracentesis for 22/27, 20/20, 9/9 patients at 3, 6, 12 months

<sup>k</sup> 13/25 patients evaluable at 1 month; 11 died < 1 month; 1 lost to follow-up

*Reviewer comment: As expected in studies of MPE, the majority of patients represented in the trials had lung or breast cancer. Since the Marom et al study from 2002 was specifically designed to evaluate patients with MPE due to gynecologic malignancies, the patient population included women with a predominance of ovarian or uterine cancers.*

*There was variability in the exclusion criteria among the trials. Most studies excluded patients who failed to have lung re-expansion following initial drainage of fluid ("trapped lung"), some prior to study entry, and some after study entry, increasing the number of inevaluable patients. Most, but not all studies required that daily pleural drainage decrease to less than 50-150 ml/day before the investigators would attempt talc sclerosis. The requirements for lung expansion and minimal residual fluid prior to sclerosis would be expected to improve the success of the procedure. Some studies excluded patients who were receiving chemotherapy, which could impact outcome; other studies did not even address the issue of concomitant systemic therapy for cancer.*

*Among the 13 studies, the Saffran et al trial was somewhat of an outlier by design. It was a small proof of feasibility of ambulatory (outpatient) pleurodesis with talc and a small-bore catheter. It had the lowest objectively defined response rate. Of 10 patients starting the trial, 2 could not be sclerosed, 6 of 8 were subjectively better by telephone contact at 1 month (75%), but only 4 of 8 patients presented for x-ray documentation of "success". In the context of terminal disease, it was a valid approach to minimize hospital time, focus on subjective improvement and low cost, but the missing data compromises the objective documentation of "success" to prove the efficacy in this small trial was 75% rather than 50% at 1 month.*

*In spite of the many differences in details of design and execution among the studies, the efficacy of talc as a sclerosing agent was consistently demonstrated across the studies and across time. The range of success was from 75-100%. Success was usually defined as lack of recurrence of fluid (or most fluid), as assessed by chest x-ray at a predetermined time. The studies that evaluated success at an early time, such as 1 month, minimized the number of patients inevaluable due to death and other reasons for lost follow-up in this very debilitated population with advanced cancer. This provided for a better-defined endpoint. However, several of the studies that followed patients to death or long-term, were able to demonstrate durability of the response, with many responders remaining effusion-free for the duration of survival or follow-up.*

#### **6.4 Efficacy Conclusions**

The NDA is submitted under section 505(b)(2) of the Food, Drugs and Cosmetics Act, relying on the medical literature for evidence of clinical efficacy and safety. Bryan Corporation did not conduct any clinical trials in support of this application. The same sterile talc substance, packaged as an aerosol, was previously submitted by Bryan Corporation under section 505(b)(2) and approved by the FDA on December 24, 1997 (NDA 20-587), relying on the medical literature for evidence of clinical efficacy and safety. The indication for Sclerosol® Intrapleural Aerosol was also "to prevent recurrence of malignant pleural effusions in symptomatic patients". Whereas Sclerosol® was approved for administration by

aerosol during thoracoscopy or open thoracotomy, Sterile Talc Powder is mixed with normal saline solution to form a slurry and administered intrapleurally via chest tube.

The applicant has provided evidence of efficacy of Sterile Talc Powder by identifying and analyzing a core of 5 adequate and well-controlled trials from the literature that support the proposed indication. They contain sufficient description of methodology and data to permit analysis. These trials are listed in Table 2. The studies provide Level I evidence of efficacy of talc slurry in the therapy of MPE. They are randomized and controlled trials using a prospectively defined objective measure of "success." In the majority of these studies, response is also assessed at a standardized time and all patients are accounted for. (See section 6.3.1 for detailed analysis of the 5 trials.) Additional single arm trials and retrospective series identified by the sponsor and the reviewer from the literature are supportive of efficacy, as well. (See section 6.3.2 and tables 14 and 15 for details.)

There are variations among the 5 randomized trials regarding the dose of talc (5 gm in 4 of the randomized trials), the volume of saline solution in which the talc is suspended, the management of the patients immediately following administration (eg. positioning to disperse talc), inclusion and exclusion criteria, definition of clinical "success", time of measurement of response, choice of comparator, short or extended follow-up. (See overview discussion in section 6.3.1 following table 2 and detailed analysis of individual studies section 6.3.2.) The success with talc slurry is not different from success with the approved drug, bleomycin, in the 3 trials in which bleomycin is the active comparator. In the Yim trial, talc slurry given through a chest tube is not statistically different (for patients without trapped lung) from talc given by insufflation, a procedure considerably more invasive and costly. In the Sorensen trial, the response to talc slurry is statistically significantly superior (evaluable patients) compared with chest tube drainage alone. Several of the studies clearly exclude patients from entry if they have had recent chemotherapy; others make no specific mention of such exclusion, which could confound the results. However, in spite of design differences among the trials, talc slurry consistently demonstrates efficacy in decreasing recurrence of MPE in each of the 5 randomized controlled trials.

For the 89 evaluable patients studied in the 5 randomized controlled trials in which talc slurry was used as a sclerosing agent, there was an 89% (79/89) response to treatment (range 79-100%). The dose of talc was 5 gm in 4 studies (80 patients) and 10 gm in 1 study (9 patients). The studies with an early assessment of response minimized the number of patients who were inevaluable from lack of follow-up due to death and other causes, but did not provide information regarding durability of the response. The studies which followed patients long-term or until death did demonstrate durability of the response with a high percentage of responders remaining effusion-free, most for the duration of survival or follow-up. In Yim et al, the 3 patients who relapsed (of 26 responders) did so at 6, 12, and 14 months. In Sorensen et al, who provided data on median duration of response, it was 10 months, with a range of 3-24 months.

## 7 Integrated Review of Safety

### 7.1 Brief Statement of Findings

The 5 randomized trials and the 13 single arm trials from the literature collectively provide safety data for the use of intrapleural talc slurry via chest tube to prevent recurrence of symptomatic MPE in approximately 455 patients. The adverse events reported in the trials were mostly mild and of short duration, often including local pain and low-grade fever associated with the induced inflammatory reaction. There was a low incidence of wound infection, mainly in the series of patients who had large-bore chest tubes rather than small catheters. There were 3 cases of non-fatal ARDS among the patients in 1 study (Kennedy et al, 1994) who received a dose of 10 gms of talc intrapleurally. Among the trials using lower dose talc, there was 1 episode of non-fatal ARDS requiring ventilatory support in a patient who received a second dose of talc 5 gm 48 hours after the first, to treat bilateral pleural effusion. The data from the literature demonstrates talc to be safe when instilled as a slurry into the pleural space via chest tube as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients, but suggests that there is an incidence of serious pulmonary adverse effects. The data overall are inconclusive, but suggest that ARDS may be related to dose and/or bilateral therapy.

### 7.2 Materials Utilized in the Review

The medical officer reviewed the following materials:

- The regulatory history of the application
- Medical Officer Review of NDA 20-587 (Sclerosol Intrapleural Aerosol)
- Oncology Drugs Advisory Committee minutes 12/14/95 (Sclerosol)
- Correspondence between the applicant and FDA in Division Files
- Paper submissions of the NDA
- Relevant published literature
- Electronic labeling proposal
- Adverse Event Reporting System (AERS) search for Sclerosol and talc

### 7.3 Description of Patient Exposure

Patients in the trials from the literature review generally had a single lifetime exposure to talc intrapleural therapy. A handful of patients in the trials were treated with intrapleural talc therapy for bilateral pleural effusion. Safety data could be evaluated from approximately 89 patients treated with talc in the 5 randomized controlled trials and 366 patients from the single arm trials. The following table lists the number of patients from the trials and the dose of talc received (derived from the database of 435 patients for whom this data was available).

Table 16: Dose of Intrapleural Talc Per Patient (Reviewer Table)

Talc Dose in Gm	Randomized Trials Number of Patients	Single Arm Trials Number of Patients	Total Number of Patients Treated
2		8	8
4		10	10
5	80	213	293
8*		10	10
10	9	105	114
Talc dose unknown	0	20	20
<b>TOTAL PATIENTS</b>	<b>89</b>	<b>366</b>	<b>455</b>

\*Patients treated with 4 gm on each of 2 successive days

For the 4 of 5 randomized trials which gave gender data, 54% (43) of the patients in the talc arm were male and 46% (37) were female. For the 10 of 13 single arm trials which provided gender data, 122 of 334 were male (37%) and 212 (63%) were female. If the total numbers of patients who received talc are combined from the controlled and single arm trials, 165 (40%) were male and 249 (60%) were female. The estimated mean and median ages of patients treated with talc in the clinic studies is 60-62 years. Many of the treated patients were older than age 65. No children were treated in the trial.

#### 7.4 Safety Findings from Clinical Studies

No clinical trials were performed by BC in support of the NDA. See safety findings and analysis from the literature in section 7.6 (Literature Review for Safety).

#### 7.5 Miscellaneous Studies

Not applicable.

#### 7.6 Literature Review for Safety

See section 4.4. The methodologies of the literature search by the applicant and by the medical reviewer to support the application are described in detail in the efficacy section. Table 2 summarizes the randomized trials from the literature that are the subject of this review. Tables 14 and 15 summarize the single arm trials using talc slurry, from which safety data are also derived. Following the presentation of detailed safety data from these sources, I will discuss findings from other pertinent articles from the literature. I will review the data relating to Adult Respiratory Distress Syndrome (ARDS) in patients treated with talc slurry. I will address data that pertains to the question of possible dose-related toxicity.

The common adverse events observed with talc slurry were local pain post therapy and low-grade fever, occurring during the first 1-2 days. There was a low incidence of wound infection, mainly in the series of patients who had large-bore chest tubes rather than small catheters. In the literature, there is also a low incidence of the serious adverse event (SAE) acute respiratory failure, sometimes progressing to ARDS. ARDS was not seen in the randomized trials, but there were a few patients in 2 of the single arm trials who had a clinical course suggestive of ARDS. (See below.)

The following table demonstrates the adverse events reported in the 5 randomized controlled trials. Patients were considered evaluable for safety if they underwent therapy to cause pleural sclerosis.

Table 17: Adverse Events by Trial – Controlled Trials (Reviewer Table)

Author	Therapy	Dose	Patients	Adverse Events	Comment <sup>b</sup>
Sorensen et al, 1984	CT <sup>a</sup> + TS <sup>b</sup>	10 gm	14	Pain 14/14; empyema 1	
	CT only	-	17	Pain 17/17; Staphylococcal sepsis 1	
Noppen et al, 1997	TS	5 gm	14	Fever <sup>c</sup> 5/14	P = .68
	Bleomycin <sup>c</sup>	1 U/kg	12	Fever <sup>c</sup> 3/12	
Zimmer et al, 1997	TS	5 gm	19 <sup>d</sup>	Wound infection 3/19 <sup>d</sup>	P = .24
	Bleomycin	60 U	14 <sup>d</sup>	Wound infection 0/14	
Ong et al, 2000	TS	5 gm	25	Fever 1/25; pain 0	P = .35 (fever)
	Bleomycin	1U/kg	25	Fever 4/25; pain 2	
Yim et al, 1996	TS	5 gm	29	Acute respiratory failure 1/29; wound infection 1	Transient, no need for ventilatory support
	Insufflation	5 gm	28	Reexpansion pulmonary edema <sup>f</sup> 1/28; air leak <sup>g</sup> 1; recurrent tumor at port site 1	

<sup>a</sup> Chest tube drainage

<sup>b</sup> Talc slurry (all patients in all studies had chest tube drainage prior to TS instillation)

<sup>c</sup> All patients in all studies who received bleomycin, had chest tube drainage first

<sup>d</sup> Data presented per procedure rather than per patient

<sup>e</sup> Temperature > 38, responsive to antipyretics; lasting < 2 days

<sup>f</sup> 2 Liters fluid drained thoracoscopically

<sup>g</sup> Extensive lysis of adhesions; leak resolved after 8 days

<sup>h</sup> P-values are 2-sided, based on Fisher's exact test

*Reviewer comment: The adverse events reported in the 5 controlled trials were mostly mild and of short duration. Sorensen reported pain in all patients "for 2-3 days after insertion of the chest drain", with no pain attributable to the talc per se. There were several localized wound infections and 1 case of empyema. The 3 adverse reactions in the Yim study are directly attributable to the procedures related to thoracostomy rather than the talc per se. The single case of acute transient respiratory failure in the TS arm was said to resemble exacerbation of chronic obstructive disease (COPD) in a patient with COPD. It started shortly after instillation of TS and improved after drainage of the TS and treatment for COPD. No cases of ARDS attributable to TS were observed.*

The following table summarizes the adverse events by trial for the single arm trials. Patients were considered evaluable for safety if they had a sclerosing procedure.

Table 18: Adverse Events by Trial – Single Arm Trials (Reviewer Table)

Author	Therapy	Dose	Patients	Adverse Events	Comment
Adler et al, 1976	TS <sup>a</sup>	10 gm	41	"Occasional temperature elevation" day 1; "only mild to moderate discomfort"	
Webb et al, 1992	TS (iodized)	5 gm	28	"Occasional temperature elevation" or "mild to moderate discomfort"	
Kennedy et al, 1994	TS	10 gm	58 <sup>b</sup>	25/73 (34%) increased analgesics post-procedure; 46/73 (63%) fever < 48 hrs; <i>empyema</i> 4/73 (5%); atrial arrhythmia 3/73 (4%); 5/73 <i>respiratory failure</i> 5/58 <sup>c</sup>	More AEs including SAEs than other series.
Miller et al, 1994	TS	2 gm	8	1/8 pneumothorax	
Turler et al, 1997	TS (iodized)	5 gm	47	3/47 fever ≤ 24 hours	
Jacobi et al, 1998	TS (iodized)	5 gm	36	"most patients transient increase body temperature"	
Thompson et al, 1998 <sup>d</sup>	TS (iodized)	5 gm	15 <sup>e</sup>	Dyspnea 15/17 <sup>f</sup> ; fever 17; pain at catheter site 17; pleuritic chest pain 17; tachycardia 17	3 patients decreased O2 saturation
Bloom et al, 1999 <sup>d</sup>	TS	5 gm	8	Fever 2/8; small pneumo-thoraces 4; moderate pain 1	
Marom et al, 1999 <sup>d</sup>	TS	5 or 10 gm	32	Fever 13/32 (41%); Pleuritic chest pain or dyspnea 6 (19%)	
Saffran et al, 2000 <sup>d</sup>	TS	4 gm	8	None stated	
Sahin et al, 2001 <sup>d</sup>	TS	5 gm	22	Fever 7/22 (32%); chest pain 2 (9%); dyspnea 2 (9%); pain at insertion 1 (4%); subcutaneous empyema 1 (4%)	
Prevost et al, 2001	TS	8 gm (4gm x 2)	31	Fever 7 (22%), Moderate pain 12 (39%); nausea 5 (16%)	
Marom et al, 2002 <sup>d</sup>	TS	5 or 10 gm	25	Fever ≤ 24 hours 6/25; pleuritic chest pain or dyspnea ≤ 4 hours 3/25	

<sup>a</sup> Talc slurry subsequent to chest tube drainage of pleural effusion

<sup>b</sup> 75 procedures, 2 unilateral, 12 bilateral

<sup>c</sup> No deaths; 2 required only O2 and steroids; 3 required ventilation ensuing 72 hours; of these, 2 felt unrelated: 1 pneumonia, 1 excess narcotics; 3<sup>rd</sup> patient had bilateral talc, developed fever, bilateral infiltrates, hypoxemia; extubated after 5 days.

<sup>d</sup> Small-bore chest catheters employed in these studies.

<sup>e</sup> 15 patients/17 instillations

<sup>f</sup> Acute respiratory distress 1 patient, requiring ventilator 1 day after 2<sup>nd</sup> talc pleurodesis; ICU for a week

In the majority of patients, the adverse events were mild to moderate and most commonly included pain at the catheter site or pleural surface and low-grade fever lasting 24-48 hours. Six of the single arm trials used small-bore rather than conventional chest tubes, to improve patient comfort. The Kennedy et al study reported a higher incidence of adverse events of different types compared with most of the other trials. There were 4/73 (5%) incidences of empyema, 3 episodes (4%) of atrial arrhythmia, 3 incidences of hypotension responding to crystalloid, and 3 patients (4%) requiring mechanical ventilation for hypoxemic respiratory failure, but no deaths. In the Thompson study, 3 patients developed hypoxia, but only 1

patient required mechanical ventilation for a week. That patient developed acute respiratory distress 1 day after receiving a second 5 gm intrapleural dose of talc (bilateral effusion).

*Reviewer comment: The exact incidence of ARDS developing in patients treated with talc sclerosis therapy is unknown, but probably low. In patients with advanced cancer, pre-existing pulmonary disease and immunocompromise, attribution of the syndrome to therapy with surety is difficult. However, the temporal relationship between treatment and event suggests a true association in at least some patients.*

*The Kennedy study had a 5/73 incidence of hypoxia developing post talc instillation via a chest tube, with no deaths, 2 patients responding to steroids and oxygen, and 3 patients requiring mechanical ventilation. In this study the dose of talc was 10 gm. There was also evidence of a possible dose effect for the patient in the Thompson study who developed ARDS. The dose of talc in the Thompson study was 5 gm but the affected patient had bilateral pleurodesis, with the second treatment 48 hours after the first. She required mechanical ventilation 1 day following the second procedure, 1 week in ICU, but eventually was discharged. A series of cases reported by Rinaldo et al in 1983 also documents ARDS following instillation of intrapleural talc 10 gm in 3 patients. The patients developed fever, dyspnea progressing over 72 hours to respiratory failure, without documented infection. The data are inconclusive, but they may provide a signal for possible dose-related increased risk of serious pulmonary toxicity.*

*However, ARDS is conspicuously absent from the patients in other studies in the database who received 10 gm doses of talc. Across the studies, there were differences in source of talc, sterilization procedures, and other unknown variables that could possibly account for differences in observed toxicities.*

*The etiology of ARDS, observed in a small number of patients treated with talc pleurodesis, is unknown. Bouchama et al (1984) suggest that the mechanism could relate to the well-known effects of intravenous talc, which include pulmonary hypertension. The authors present a patient who developed fever, acute respiratory distress, and bilateral infiltrates 3 hours following talc pleurodesis. The patient underwent pleural biopsy immediately before talc instillation. Bronchopulmonary lavage demonstrated talc fibers in the lung. The authors suggest that local pleural vascular injury may have permitted talc to gain access to the bloodstream, and then to the lungs, causing pulmonary hypertension and the clinical picture of ARDS. If this is correct, biopsy immediately prior to talc instillation should be avoided, as well as higher doses (10 gm).*

#### **7.7 Postmarketing Surveillance - If Applicable.**

The formulation of sterile talc powder that is the subject of the current NDA is not marketed. However the same drug substance has been marketed in an aerosol formulation since approval in December 1997 as Sclerosol Intrapleural Aerosol. As of February 2003, there were 25 AERS postmarketing safety reports for Sclerosol and Talc. These include reports for Sclerosol and reports for compounded talc given as slurry. The largest number of reported events, by system, was 15 "Respiratory" events and 11 "Infections". Among the

serious adverse events associated with death, the most frequently reported events, by preferred term, were: 7 dyspnea; 4 tachycardia; 3 condition aggravated; 3 pyrexia; 3 lobar pneumonia; 3 pneumonia NOS; 3 ARDS; 3 hypoxia; 3 pulmonary fibrosis; 3 respiratory failure. There are 2 cases of SAEs that were reported by Bryan and appear in the MedWatch records in which Sclerosol was improperly applied through a chest tube rather than through a trocar during thoracoscopy. Both patients complained immediately of severe local pain. One patient was successfully resuscitated following transient asystole. The second patient became hypertensive and suffered a non-hemorrhagic parietal infarct. Neither of these SAEs was due to talc powder. Both were felt to be related to improper use of the aerosol preparation.

#### **7.8 Safety Update - If Available.**

Since this NDA is literature-based, no safety update can be required. The applicant entitles Section 9 in Volume 6 "Safety Update", but this actually is a discussion of adverse events that have been reported in the literature for talc and contains 10 articles published from 1994-2001. Of these, only one, Kennedy et al (1994) is cited elsewhere in the NDA to support efficacy. (See section 7.6 for discussion.)

#### **7.9 Drug Withdrawal, Abuse, and Overdose Experience**

Not applicable.

#### **7.10 Adequacy of Safety Testing**

The applicant is seeking approval for Sterile Talc Powder under 505(b)(2) regulations with safety and efficacy referenced to data from the literature. The 5 randomized trials from the literature are adequate and well controlled. The 13 single arm trials from the literature are supportive. The data from the literature demonstrate efficacy and safety for talc instilled as a slurry into the pleural space via chest tube as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients.

The main limitation of the data available for safety is that it is not possible to determine retrospectively if there is or is not definite evidence for dose-related toxicity, particularly regarding serious adverse pulmonary events, including ARDS. (See section 7.6 for details, and further discussion, section 7.11.) Patients in the literature studies were treated with doses of talc slurry ranging from 2-10 gm. The observed cases of acute respiratory insufficiency requiring prolonged mechanical ventilation post talc therapy occurred in 3 patients treated with talc 10 gm and a patient treated with 5 gm twice in a 48 hour period. This SAE was not observed in patients in the data base treated with lower doses. In the literature safety database of 455 patients, which is the subject of this review, only 114 patients were treated with a 10 gm dose. (See table 16.) Almost two-thirds (64%) of the patients (293/455) were treated with a 5 gm dose.

#### **7.11 Labeling Safety Issues and Postmarketing Commitments**

"Potential pulmonary complications: Acute Pneumonitis and Acute Respiratory Distress Syndrome (ARDS) have been reported in association with intrapleural talc administration" appears in the precautions section of the label for Sterile Talc Powder. A similar statement is in the Sclerosol label. There are rare reports of ARDS in association with talc, but attribution

is difficult in a population with advanced cancer, immunocompromise and underlying lung disease. None of the investigators in the 5 randomized trials identified ARDS in their patients treated with talc slurry. In the single arm trials, which support the efficacy and safety of talc slurry, 3 patients treated with talc 10 gm developed ARDS, as did one patient treated with 5 gm twice in 48 hours for bilateral effusion. In the postmarketing surveillance for Sclerosol since 1997, 3 cases of ARDS were reported to FDA. The article by Rinaldo et al, published in 1983, is extensively cited in the literature. They reported 3 patients, each treated with talc slurry 10 gm intrapleurally, who developed dyspnea in the subsequent 24 hours and progressed to respiratory failure over 72 hours. Two of the patients recovered and 1 died. They suggested that talc induced the syndrome through "unknown mechanisms." In the literature safety database of 455 patients, which is the subject of this review, only 114 patients were treated with a 10 gm dose. (See table 16.) Almost two-thirds (64%) of the patients (293/455) were treated with a 5 gm dose. There is insufficient data to reach a conclusion, but there may be a dose-related basis for this uncommon, but serious, toxicity of ARDS.

There will not be a request for postmarketing commitment studies.

## 8 Dosing, Regimen, and Administration Issues

The recommended dose of Sterile Talc Powder as a slurry administered intrapleurally to prevent recurrence of MPE is 5 gm in 50-100 ml sodium chloride. The optimal dose for effective pleurodesis is unknown, but 5 gm was the dose most frequently reported in the published literature (see table 16). In the studies that provide the database for this NDA, 293 of 435 patients were treated with a 5 gm dose. Control of MPE was not improved in the studies that used higher doses. None of the patients in the randomized trials developed ARDS, but 3 patients treated with talc 10 gm in the single arm trials developed ARDS, as did one patient treated with 5 gm twice in 48 hours for bilateral effusion, at least raising the question of dose-related toxicity. The 3 patients reported by Rinaldo et al (1984) who developed ARDS were also treated with the 10 gm dose.

The recommended volume of solution with which talc should be mixed for administration is 50-100 ml, based on the most common practice in the literature. Some investigators used larger volumes of solution in which to suspend the talc, 150 or 250 ml in some cases. The optimal volume is unknown.

Optimal positioning of the patient following instillation of slurry is also unknown. In most of the trials from the literature, patients were repositioned at frequent intervals for 1-4 hours with the chest tube clamped, in hopes of facilitating dispersion of talc over the pleural surfaces. The most common duration of time for repositioning patients was 2 hours. The value of this is unknown. Of interest, a randomized clinical trial was performed by Mager et al (2002) with 20 patients to see if rotation of the patients influenced the dispersion of the talc after 1 minute or 1 hour. The talc was tagged with a radioisotope. Scintigraphic imaging showed that repositioning patients did not affect talc dispersion in the study. The authors recommend abandoning this long-standing clinical tradition, which they believe not to be of benefit, but the cause of discomfort to patients.

Sorensen et al (1984) demonstrated a 58% success rate for pleurodesis of MPE using a large bore catheter to induce pleural inflammation and sclerosis, without the addition of a chemical sclerosant. In this study, the addition of talc was shown to improve the efficacy of the procedure. Studies have shown that substituting small-bore catheters for large-bore chest tubes does not compromise efficacy. Therefore, the recommended dose of talc is the same, without regard to size of the pleural catheter.

## **9 Use in Special Populations**

### **9.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity**

For the 4 of 5 randomized trials which provided gender data, 54% (43) of the patients in the talc arm were male and 46% (37) were female. For the 10 of 13 single arm trials which provided gender data, 122 of 334 were male (37%) and 212 (63%) were female. If the total numbers of patients who received talc are combined from the controlled and single arm trials, 165 (40%) were male and 249 (60%) were female. The estimated mean and median ages of patients treated with talc in the clinical studies are 60-62 years, with a range of 26-88 years of age. Many of the treated patients were older than age 65. No children were treated in the trials. None of the studies provided information about racial or ethnic subgroups of the participants.

The applicant stated that they were unable to provide a complete analysis of efficacy and safety data by demographic parameters because of limited demographic data provided in the clinical trials in the published literature. In the trials, Kennedy et al (1994) reported the only data on response by age. They found the average age of responders to be 54.8+/-2.0 years and non-responders, 54.8+/-5.76 years. Since the number of patients in the literature who failed to respond or had life-threatening toxicity was small across the trials, it would not be possible to identify differences in response or toxicity by gender or age.

### **9.2 Pediatric Program**

No pediatric development program is planned.

### **9.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy**

No additional data is required in special populations. Talc is not metabolized.

## **10 Conclusions, Recommendations, and Labeling**

### **10.1 Conclusions Regarding Safety and Efficacy**

The 5 randomized trials from the literature are adequate and well controlled. The 13 single arm trials from the literature are supportive. The data from the literature demonstrate efficacy and safety for talc instilled as a slurry into the pleural space via chest tube as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients.

### 10.2 Recommendations on Approvability

Although Sterile Talc Powder is safe and effective for the treatment of MPE, Bryan Corporation has failed to validate its sterilization procedure for the product. To qualify for approval, the applicant must design and implement an acceptable validation program.

Sterile Talc Powder is approvable. The 5 randomized trials from the literature are adequate and well controlled. The 13 single arm trials from the literature are supportive. The data from the literature demonstrate efficacy and safety for talc instilled as a slurry into the pleural space via chest tube as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients. The product cannot be approved until the applicant validates the sterilization procedure.

### 10.3 Labeling

In the Clinical Studies section, for the applicant's table showing the response rate of talc pleurodesis in the single arm trials, we substituted a table showing comparative efficacy for talc versus a control in the 5 randomized controlled trials from the literature. These studies provide a better level of evidence of efficacy and were critical for approval. We rewrote the Dosage and Administration section to add clarity to the drug preparation instructions.

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## Appendix

### A. Individual More Detailed Study Reviews, if Performed

Not applicable.

### B. Detailed Labeling Changes or Revised Drug Label

The revised drug label will be attached to the approvable letter to the applicant.

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