CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-587

MEDICAL REVIEW(S)

Catterson

MEDICAL REVIEW OF NDA 20-587: Sclerosol® **(Talc)**
APPLICANT: Bryan Corporation
REVIEWING MEDICAL OFFICER: Lydia V. Larson, Pharm.D.

ODAC MEETING: December 14, 1995

JUL 18 1996

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1.0 GENERAL INFORMATION

- Name of drug:
  Generic: Hydrated magnesium silicate
  Trade: Sclerosol ®

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

- Pharmacologic Category: Sclerosing agent

- Proposed Indication: "For the treatment of malignant pleural effusions secondary to malignancies having spread to the pleural space."

- Dosage Form: Single use spray canisters containing 4.0 Gm of "
  which contains % sterile, asbestos-free talc and chlorite (magnesium and aluminum silicate). Associated minerals include dolomite %), calcite (trace elements), and quartz %). The aerosol canister propellant is dichlorodifluoromethane (CFC-12), 26 Gm per canister. The canister delivers 0.4 Gm of talc per second; the duration of delivery depends on manual compression of the spray button. The recommended dose is 4-8 Gm (1-2 cans).

- Route of Administration: Intrapleural administration.

2.0 BACKGROUND

Pleural effusions can be the initial presentation of a malignancy or, more commonly, a manifestation of advanced disease. Symptoms, such as dyspnea, cough and chest pain, are present in greater than 50% of patients. If effective treatment is no longer available for the primary disease, local palliative treatment instilling a variety of agents intrapleurally to induce a chemical sclerosis and obliteration of the pleural space, is commonly practiced. Until recently, no agent was approved for this indication. Intrapleural instillation of tetracycline, following complete drainage of the effusion, had become the treatment of choice until manufacture was discontinued for lack of availability of the sterile salt. Bleomycin has now been approved for this indication by the FDA. This NDA consists of a review of the literature in support of the use of talc for treatment of malignant pleural effusion. No clinical trials have been conducted with Sclerosol®. The first report of the use of talc intrapleurally dates to Bethune in 1935 (J Thorac Surg 4:251, 1935).

3.0 SCOPE OF REVIEW/METHODOLOGY OF THE LITERATURE SEARCHES

Materials reviewed by the fellow and medical officer include:

- Regulatory history of this application.
- Volume 1.1 (overall summary); volume 1.3 (samples/methods validation/labeling); and volume 1.6 (clinical data from the sponsor's literature search).
- Agency's literature search.

Methodology of the literature searches:

The **sponsor** searched Medline, Biosis and Embase from 1966-1994 by the parameters "malignant pleural effusions" and "talc pleurodesis." Medline and Biosis retrieved 32 references, Embase 13. A review article by Walker-Renard et al (Ann Intern Med 1994; 120: 56-64) reported a Medline search from 1966-1992 based on the search parameters of "malignant pleural effusion" and "chemical pleurodesis". Twelve additional articles were obtained from his bibliography. Reference lists for all other papers were reviewed and another list of 33 papers compiled. The sponsor excluded: a letter to the editor, an editorial, a single case report of talc in pneumothorax, an article in Chinese that described 19 patients treated with talc, papers that did not mention talc, papers based on iodized talc, talc used in combination, an article describing the preparation of talc, and studies in dogs. A total of 53 papers remained and served as the basis for the NDA.

- There are 9 reports of controlled clinical studies, 3 conducted in the U.S. and 6 abroad. Six are articles and 3 are abstracts:
  --one study reports chest tube drainage with and without talc i.e. a "no treatment" concurrent control;
  --five reports compare talc to another agent: tetracycline, bleomycin, doxycycline, and mustine hydrochloride (active concurrent controls);
  --three report talc vs. historical controls.

Note: One of the abstracts submitted by the sponsor (Hartman, 1992) was a preliminary report on an article that was also submitted (Hartman, 1993); therefore further information regarding Hartman's 1992 abstract will not be discussed due to duplication of data.

- There are 26 reports of uncontrolled studies or series of case reports, 12 in the U.S. and 14 foreign. Two of the 26 are studies of talc in patients with nonmalignant conditions and longer survival, which are submitted to provide data on long-term safety.

- Eighteen review articles were referenced by the sponsor as the balance of the literature identified and reviewed.

To validate the completeness of the sponsor's literature search, the **Agency** repeated the queries to Medline, Biosis and Embase as well as extending the search parameters to the three next largest databases, Cancerlit, International Pharmaceutical Abstracts and Derwent Drug File. Three additional abstracts, but no article, were found reporting controlled trials with talc (Lantos, et al, 1994; Muir, et al, 1988, and Jones, et al, 1989). The Agency also expanded the literature search to include treatment with iodinized talc, omitted by the sponsor as not relevant, in order to to ensure a comprehensive data base. Seven references were identified; while the data was incomplete and uncontrolled, the contents were scanned for rare adverse events that were not included in the noniodized talc literature.

4.0 REGULATORY HISTORY

No talc product has been approved in the U.S. for the treatment of malignant pleural effusion.

Depending on the source, talc's mineral content could include asbestos. There are no regulations including USP standards that currently address the issue of asbestos content or sterility, although recent surveys of pharmaceutical talc suggest that most samples are free of fibers in the asbestiform range (Blount, Environmental Health Perspectives Journal 199;94:225-230). If pharmaceutical talc is used for treatment of malignant pleural effusions, it must be sterilized on site, most often by

In October of 1993, in response to inquiries from pharmacists regarding these issues, the FDA's Center for Devices and Center for Drugs met and determined that talc could in theory be labeled for sclerosis of malignant pleural effusion if certain conditions were met, in which case it would be considered and handled as a drug. A letter was sent in March of 1994 by the FDA's Center for Drug Evaluation and Research (CDER) to all talc distributors informing them of the Agency's perspective and inviting submissions of New Drug Applications (NDA). Bryan Corporation, Woburn, MA was one of the few companies that responded to the Agency's letter and the only one to pursue an NDA to date. Bryan Corporation's talc formulation claims to be sterile, asbestos-free, and is packaged in an aerosolized single use canister.

Bryan Corporations's NDA, and its claims for efficacy and safety in the treatment of malignant pleural effusion, is based on an analysis of reports of controlled (9) and uncontrolled (24) trials published in the medical literature (see 3.0 for Methodology). There are no clinical trials that have been sponsored by Bryan Corporation. When Bryan's product is used in the literature reports (Colt and Dumon) or the talc is derived from the mine (Muir, Boniface & Guinn, Scarbonchi), an annotation is made in the appropriate tables. Bryan Corporation has been willing to provide the drug through individual patient INDs. Efficacy and safety data from these individual patient INDs reported to the FDA were presented at ODAC on December 14th (see Appendix).

The Agency accepted submission of a literature-based NDA per Federal Food, Drug and

Cosmetic Act Section 505(b)(2) which allows filing in the case of a sponsor not having conducted its own clinical trials. Citations of previous submission to the Division of Oncology that significantly relied on literature reports are: (l) Nolvadex for the treatment of metastatic breast cancer in men, which was supplemented by 40 case reports of patients; and, (2) Bleomycin for the treatment of malignant pleural effusions, which was supplemented by a single prospective, randomized trial. Although submission is allowed, criteria for "adequate and well-controlled studies" as outlined in CFR 314.126 (see appendix) must be met.

5.0 CHEMISTRY/MANUFACTURING (see chemistry review for details)
The molecular formula of talc is $Mg_3Si_4O_{10}(OH)_2$; the molecular formula of chlorite is $(Mg,Fe)_5Al\{AlSi_3O_{10}\}\{OH\}_8$. The manufacturer is
In addition to the manufacturing, is responsible for processing, packaging and labeling of the product. is mined from the
The filled canister (with attaches actuator, valve and nozzle) is sterilized by and placed in a sterile package.

Sclerosol® contains the propellant dichlorodifluoromethane (CFC) which requires a citizen's petition for use. Bryan Corporation has submitted such a petition and it is currently under review.

6.0 PRECLINICAL PHARMACOLOGY/TOXICOLOGY (see pharmacology/toxicology review for details)

7.0 CLINICAL PHARMACOLOGY/PHARMACOKINETICS (see Clinical Pharmacology/PK report for details)

8.0 RELATED IND SUBMISSIONS
There are no IND submissions for talc in the U.S. from Bryan Corporation or any other company. The Division of Oncology Drug Products has made aerosolized talc available to physicians and patients through individual INDs.

9.0 PUBLISHED CONTROLLED CLINICAL STUDIES

9.1 OVERVIEW TABLE OF DEMOGRAPHICS, TREATMENT, & EFFICACY RESULTS

Investigators, Publication	Design	Treatment	Dose per Patient	Source & Purity of Talc	Age, median or mean (range or SD)	# Evaluable / # Entered	"Success" (definition provided Y/N)	Symptom (sx) Relief
No-Treatment Concurrent Control								
Sorensen, Svendsen, Enk Eur J Respir Dis 1984; 65: 131-135	Prospective, randomized	Thcpy., 'Talc slurry via chest tube', chest tube drainage x 72 hrs	10 Gm in 250 ml NS, single dose retained x 2 hrs	sterile	62 (39-79) both groups combined	9/14	9/9 100% (Y)	9/9 "partial or complete dyspnea resolution"
	no drug treatment control	Thcpy., **chest tube drainage** x 72 hrs	N/A	N/A		12/17	7/12 58.3% (Y)	6/7 "subjective improvement"
Active Concurrent Control								
Fentiman, Rubens, Haywood Eur J Cancer Clin Oncol 1986; 22: 1079-81	Prospective, randomized	Talc insuf. at thcpy	not given, single dose	not given	50.6 ± 2.6	12/18	11/12 91.7% (Y)	not provided
	active concurrent control	Thcpy. then TCN w/chest tube drainage	500 mg in 50ml NS, single dose	N/A	54.2 ± 2.2	21/23	10/21 47.6% (Y)	not provided
Fentiman, Rubens, Haywood Cancer 1983;52:737-39	Prospective, randomized	Talc insuf. at thcpy.	not given, single dose	simple Talc, BP grade, Evans Medical	55.3 ± 2.2	20/23	18/20 90% (Y)	not given
	active concurrent control	Thcpy. then **Mustine** sclerosis	15 mg in 50 ml NS, single dose	N/A	50.3 ± 1.5	17/23	9/17 52.9% (Y)	not given
Hamed, et al Br J Surg 1989;76:1266-67	Prospective, randomized	Talc insuf. at thcpy	not given, single dose	non-iodized	54.7	10/13	10/10 100% (Y) procedures	not provided
	active concurrent control	Thcpy. then **Bleomycin** sclerosis	1 mg/kg in 50ml NS, single dose	N/A	53.1	12/16 [+]	5/15 33.3% (Y) procedures [a]	symptom relief [b]
Boutin, Rey, Villat Rev Mal Resp 1985; 2:374 **(abstract in French)**	Prospective, randomized	Talc poudrage at thcpy.	Not given, single dose	Not given	Not given	Not clear/20	14/14 100% (N)[c]	not given
	active concurrent control	Thcpy. then TCN instillation	Not given, single dose	N/A	Not given	Not clear/20	8/15 53.3% (N)[c]	not given

a = no further information on pts receiving bilateral therapy, b = 2 pts that relapsed and were subsequently treated with T with 1 pt. having symptom relief; c = at 6 months
B = bleomycin, D = doxycycline, M = mustine, T = talc, TCN = tetracycline, BP = British Pharmacopeia; NS = normal saline; N/A = not applicable
insuf = insufflation, thcpy = thoracoscopy, pts = patients
+ = 1 patient had talc in one lung and bleomycin in the other, 2 patients had bleomycin bilaterally (25 procedures total)

Investigators, Publication	Design	Treatment	Dose per Patient	Source & Purity of Talc	Age, mean (range)	# Evaluable / # Entered	"Success" (definition provided Y/N)	Symptom (sx) Relief
Active Concurrent Control (cont.)								
Muir, et al Am Rev Respir Dis 1987; 135: A244 **(abstract)**	Prospective, randomized	Talc insuf. at thcpy.	5 ml, single dose	Luzenac Talc	Not given	15/15	15/15 100% (N)	not given
	active concurrent control	Thcpy. then **Doxycycline** sclerosis	20 mg/kg in 200 ml Saline, repeated lavage-drainage	N/A	Not given	15/15	13/15 86.7% (N)	not given
Muir, et al Eur Respir J 1988; 1 (Suppl 2): 304S **(abstract)**	Prospective, randomized	Talc insuf at thcpy, then chest tube drainage	5 ml, single dose	Talc de Luzenac	not provided	12/not provided	11/12 91.7% (Y)	not provided
	Active concurrent control	**Rolitetracycline** insuf at thcpy then chest tube drainage	20 mg/kg	N/A	not provided	12/not provided	10/12 83.3% (Y)	not provided
Jones, et al Chest 1989; 96 (Suppl): 276S **(abstract)**	Prospective, "allocated"	Talc poudrage under general anesthesia	not provided	not provided	not provided	not provided/37	94% , no further data provided	not provided
	Active concurrent control	**TCN** instil via chest tube w/ local anesthesia	1.5 Gm + 40 mg xylocaine	N/A	not provided	not provided/17	95% , no further data provided	not provided
Historical Controls								
Adler, Rappole Surgery 1967; 62: 1000-6	Retrospective report	Talc aerosolization via trocar	6-8 Gm, single dose	USP	62.8 (57-67)	4/4	4/4 100% (N)	not provided
	historical review	Variety of agents [a]	not given, single dose	N/A	60, 58.6, 51 [b]	21/40	4/21 19% (N) [c]	not provided
Hartman, et al J Thora Cardiovasc Surg 1993; 105: 743-8	Prospective, non-randomized	Talc insuf. at thcpy.	3-6 Gm, single dose	USP, asbestos-free, sterile, Humco Lab	58.8 (41-88)	30 days 90 days 33/39 21/39	30 days 90 days 32/33 97%; 20/21 95.2% (Y)	dyspnea relief *
	historical controls	Thtmy., then **Bleomycin** or **TCN** sclerosis	B 60 units [d] TCN 1000 mg [d] single dose (B&TCN)	N/A	61 (19-86)	28/85 37/85 27/85 36/85	18/28 97%; 26/37 70% (Y) 9/27 33%; 17/36 47% (Y)	not provided
Unknown Controlled Trials								
Lantos, et al Tubercle and Lung Dis 1994; 75 (Suppl I) 139: 507 **(abstract)**		Chest tube drainage then Talc instil	3-10 Gm, single dose	not given	not given	25/25	24/25 96% (N)	not provided
	controls	Chest tube drainage then **Oxytetracycline** or **Doxycycline** sclerosis	20 mg/kg (Oxy) 10 mg/kg (Doxy)	N/A	not given	24/24 25/25 (unclear if # cases or # pts)	21/24 87.5% (N) 23/25 92% (N)	not provided

a = intrapleural installation of either thiotepa, nitrogen mustard, AB-132, radioactive phosphate, radioactive gold, or quinacrine; b = for the 3 main groups(breast, lung and lymphoma, respectively).
c = 1 thiotepa, 1 nitrogen mustard, 1 AB-132, and 1 radioactive phosphate patient, d = in 100 ml of normal saline,
* = patient numbers were not provided, T = talc; B = bleomycin, TCN = tetracycline; USP = United States Pharmacopeia; insuf = insufflation, thcpy = thoracoscopy, thtmy = thoracostomy, pts = patients

FINITION OF SUCCESS IN THE CONTROLLED STUDIES

Sorensen, Svendsen, Enk Eur J Respir Dis 1984; 65: 11-35	"The absence of fluid accumulation, with pleural thickening being considered acceptable. Failure was defined as the re-accumulation of pleural fluid confirmed within 3 months by thoracocentesis."
Fentiman, Rubens, Haywood Eur J Cancer Clin Oncol 1986; 22: 1079-81	"No re-accumulation of fluid throughout follow-up (minimum period 12 months); otherwise they were considered failures."
Fentiman, Rubens, Haywood Cancer 1983;52:737-39	"No re-accumulation of pleural fluid by radiographic exam on all follow-up visits (minimum of 6 months of follow-up time)."
Hamed, et al Br J Surg 1989;76:1266-67	"The continued absence of fluid re-accumulation on all follow-up radiographs; response assessment was performed if the patient survived for > 1 month after the procedure and had a repeat chest radiograph at that time. Any re-accumulation was regarded as a treatment failure."
Boutin, Rey, Villat Rev Mal Resp 1985; 2:374 **(abstract in French)**	"Definitions for patient evaluability (to include time points when assessments would be made), success, and treatment failure was not provided."
Muir, et al Am Rev Respir Dis 1987; 135: A244 **(abstract)**	Response, failure, and minimal follow-up times were not defined by the investigators.
Muir, et al Eur Respir J 1988; 1 (Suppl 2): 304S **(abstract)**	No recurrence of pleural effusion.
·nes, et al est 1989; 96 (Suppl): 276S abstract)	"relief of symptoms and satisfactory chest X-ray"
Adler, Rappole Surgery 1967; 62: 1000-6	Success and failure were not defined in the article.
Hartman, et al J Thora Cardiovasc Surg 1993; 105: 743-8	"No reaccumulation of pleural fluid by serial chest X-rays as compared to baseline films. Failure was defined as the reaccumulation of pleural fluid confirmed by chest X-rays. Follow-up visits that included chest X-rays were made at 30 and 90 days."
Lantos, et al Tubercle and Lung Dis 1994; 75 (Suppl I) 139: 507 **(abstract)**	Not stated.

Individual Summaries of Literature Reports

9.2.1 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 evaluate the efficacy of talc sclerosis compared to pleural drainage in malignant effusions.

- **Rationale**: To determine if more effective palliation occurs with talc sclerosis than pleural drainage alone in the management of malignant pleural effusion.

Study Design: Prospective, randomized two arm study: pleural drainage with talc sclerosis vs. pleural drainage alone.

Note: Patients were informed of the purpose of the investigation and verbal consent was obtained; the authors did not state whether the study underwent an IRB approval process.

- **Institution:** Department of Chemotherapy, The Finsen Institute and Department of Medicine, P. Bispebjerg Hospital, Copenhagen, Denmark.

- **Study Dates:** Not stated; article submitted for publication 18 November, 1982.

Eligibility:

Inclusion: Patients had histologically documented malignant pleural effusion causing "respiratory distress".

Exclusion: Non-malignant effusions; previous sclerosis.

- **Stratification/Randomization:** Subjects were randomized according to a closed-envelope system.

- **Treatment Plan:** All patients underwent thoracoscopy, pleural biopsies, and drain placement to a low pressure vacuum of 30 cm H_2O through a water trap. If initial re-expansion did not occur, constant suction was continued for a maximum of 72 hours. Failure to re-expand by 72 hours was a criterion for exclusion for evaluation of efficacy. Patients randomized to talc received 10 Gm of sterile talc in 250 ml Normal Saline instilled via chest tube. The purity and the source of the talc were not provided. Patients alternated positions "several times" for 2 hours with a clamped chest tube ending in the Trendelenburg position. Constant suction was resumed for 72 hours after which the pleural drain was removed. Patients randomized to pleural drainage only received constant suction for 72 hours after which the drain was removed.

- **Efficacy & Safety Monitoring:** Daily chest X-rays were to be performed for assessment of lung re-expansion. Chest X-rays were performed at 1 month and every 3 months after pleurodesis to evaluate response or "success". Patients whose lungs failed to expand by seventy-two hours were not evaluated for efficacy.

Statistical Plan: "Success" was defined by chest X-ray as the absence of reaccumulation of fluid for 3 months, as determined by chest X-ray. Failure was defined as the re-accumulation of pleural fluid within 3 months by thoracocentesis. "The aim of the trial was to evaluate the possibility of improving the treatment of malignant pleural effusion by at least 40%, through the addition of talc instillation to pleural drainage. Statistical evaluation was performed by the method of Clark & Downie. This requires at least 18 evaluable patients, with α equal to 0.05 and β to 0.5".

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

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	(14)	9/14	7 ovarian, 3 breast, 3 lung, 2 GI, 3 cervical, 1 hypernephroma, 6
CT	combined	(17)	12/17	mesothelioma, 1 prostate, 5 adenocarcinoma of unknown primary.

CT = chest tube drainage; T = talc

Ten patients (5 per arm) were considered to be inevaluable. Seven patients (2 chest tube plus talc/ 5 chest tube only) died of their malignant disease within 3 months; 2 patients were excluded for failure to re-expand their lungs; and 1 patient developed an empyema (chest tube plus talc) with no rationale provided for excluding the patient. No information was provided as to whether the 7 patients that died received the planned 1 month assessment by chest X-ray. Gender and performance status were not provided.

Response:

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"

Specific definitions for symptom relief, including partial versus complete resolution of dyspnea were not given.

All nine 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 nine patients "obtained subjective improvement with partial or complete resolution of dyspnea." None of the patients reported chronic chest discomfort post procedure.

Seven of the twelve evaluable patients in the chest tube only group achieved complete response lasting until their death (median 10 months, range 4-17 months). The author states that "subjective improvement was seen in 6 of the 7 patients that achieved complete response; but did not describe the nature of the improvement.

ty Results:

Treatment	Adverse Experiences	Chest Tube Drainage Time (hours)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
CT + T	pain (prolonged)14/14; empyema 1/14	72°	not provided	2 died < 3 mos; 9 survived 3-24 mos [a];
CT	pain 12/17; staphylococcal septicaemia 1/17	72°	not provided	5 died < 3 mos; 7 survived 4-17 mos [a]

a = data only on patients considered a success

All patients treated with the chest tube "suffered pain, requiring treatment for 2-3 days after insertion of the chest tube." No patient had prolonged pain.

Comments & Conclusions:

Investigator/Author: The authors conclude that chest tube plus talc is superior to chest tube alone in the management of malignant pleural effusion, if the malignant pleural effusion can be drained and the lung re-expanded.

Reviewer: *Strengths of this study include: 1) the prospective randomized trial design in patients with documented malignancy; 2) regular (at one month then every 3 months) follow-up in both treatment groups with objective measures to determine and document recurrence, 3) long term follow-up of patients for recurrence, and 4) inclusion of information about symptomatic relief and adverse events. Weaknesses are that an intent-to-treat analysis was not performed; only evaluable patients were used for response analyses. It appears that enrollment continued until sufficient numbers of evaluable patients (lung reexpanded, on study three months) were entered to allow analysis. If the intent-to-treat analysis is performed, the power is reduced to 0.5 (50% chance of error).*

9.2.2 Article: Fentiman I.S., Rubens R.D., Haywood J.L. A comparison of intracavitary talc and tetracycline for control of pleural effusions secondary to breast cancer. Eur J Cancer Clin Oncol 1986; 22: 1079-1081.

- **Objective:** To compare intracavitary talc to tetracycline for control of malignant pleural effusion secondary to breast cancer.

- **Rationale**: Intracavitary tetracycline had been gaining popularity over talc due to the ability of instilling tetracycline without the need for general anesthesia; but talc was considered to be superior at least when compared to mustine in a previous study by the author.

  Study Design: Prospective, randomized trial with an active concurrent control

  Note: Information on IRB approval or obtaining consent from the patients was not discussed.

- **Institution:** ICRF Clinical Oncology Unit, Guy's Hospital, London, U.K.

  Study Dates: Not given. Paper accepted for publication February 17, 1986.

Eligibility:

Inclusion: 1) Histological confirmation of breast cancer; 2) verification of a symptomatic pleural effusion radiographically with no evidence of non-malignant causes; 3) all patients had to be suitable for general anesthesia and able to receive either drug; 4) none of the patients could receive any form of therapy or indwelling tube drainage, with the exclusion of simple needle aspiration.

Exclusion: History of sensitivity to tetracycline.

- **Stratification/Randomization:** Patients were stratified according to the presence or absence of other metastatic lesions requiring treatment and were then randomly allocated to receive talc or tetracycline.

- **Treatment Plan:** Talc group - Pleural cavity drained to dryness and inspected thoracoscopically under general anesthesia. Talc would then be insufflated, intercostal drains inserted to remain in place for 5 days for additional pleural drainage. The author did not provide information on the dose, source, sterility or purity of the talc used.

  Tetracycline group - Pleural cavity drained to dryness and inspected thoracoscopically under general anesthesia with one intercostal drain inserted, followed by a 16 to 24 hour waiting period (to document lung expansion) prior to tetracycline instillation, 500 mg in 50 ml of normal saline. The patient was positioned to insure even distribution of the sclerosant. One intercostal drain was inserted prior to tetracycline instillation and left in place for 3 to 5 days. Five hundred milligrams of lignocaine was added to the tetracycline solution due to the first two patients complaining of severe pain during instillation

- **Efficacy & Safety Monitoring:** In order to be considered for assessment in either group, patients had to survive for more than 1 month after pleurodesis and undergo a chest X-ray to compare baseline radiographs. Success was defined as no re-accumulation of fluids throughout follow-ups (minimum period 12 months); otherwise they were considered failures.

- **Statistical Plan:** Not provided

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics**

Treatment	Age, mean (range)	# Evaluable/# Entered	Tumor Type
Talc	50.6 $\pm$ 2.6*	12/18	breast in both groups
TCN	54.2 $\pm$ 2.2*	21/23	

* = age at cancer diagnosis not at time of pleural symphysis

Forty-one patients (23 tetracycline and 18 talc) were randomized. The author stated that the randomization was unequal due to imbalance in the process; but did not state why or how this occurred. Eight patients (6 c, 2 Tetracycline) died within 1 month of pleurodesis and were excluded from any analysis; but no data was provided as to the TNM stage of those patients. Their deaths were attributed to progression of their disease.

Response:

Treatment	Success (definition provided Y/N)	Symptom (sx) Relief
T	11/12 (Y)	not provided
TCN	10/21 (Y)	not provided

Thirty-three patients (12 talc, 21 tetracycline) were evaluable for response with successful palliation in 11/12 talc patients (92%) and 10/21 tetracycline patients (48%). Four of the 11 patients with recurrence of effusion in the tetracycline group subsequently received talc with successful control.

Safety Results:

Treatment	Adverse Experiences per total # of patients Talc Control	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
Talc	surgical emphysema 2; wound infection 2; asystolic arrest 2 [b]; pain 18	5	1630ml ± 218 [a,c]	minimum f/u 12 mo; 8 died <1 mo (6T / 2TCN)
TCN	surgical emphysema 3; brain stem hemorrhage (fatal) 1; pain (severe) 2	3 to 5	1470ml ± 143 [a,c]	

a = mean ± standard deviation; b = while under general anesthesia with successful resuscitation;
c = unclear if total amount of pleural fluid drained

Comments & Conclusions:

Investigator/Author: The authors conclude that talc is superior to tetracycline in the prevention of recurrence of pleural effusions.

Reviewer: *The talc group had fewer patients randomized, and more post-op deaths. Thus, there were fewer evaluable patients. This could potentially bias the outcome of the talc group if the patients that died were ones with more advanced disease that would not have responded to pleurodesis. The tetracycline group had more patients randomized and fewer post-op deaths. Thus, this treatment group may have had a relatively longer period of follow-up, increasing the chances of developing another effusion. In addition, 500 mg of tetracycline may represent undertreatment as 1 gm is typically used. Nevertheless, the tetracycline arm can be considered a control arm.*

3 **Article:** Fentiman I.S., Rubens R.D., Haywood J.L. Control of pleural effusion in patients with breast cancer. Cancer 1983; 52: 737-739.

- **Objective:** To compare intracavitary talc to mustine at first presentation of a malignant pleural effusion secondary to breast cancer.

- **Rationale**: To improve the results of palliative treatment.

Study Design: Prospective, randomized study with an active concurrent control

Note: IRB approval and informed consent were not discussed in the article.

- **Institution:** ICRF Breast Cancer Unit, Guy's Hospital, London, U.K.

- **Study Dates:** Not provided. Article accepted for publication May 10, 1982.

- **Eligibility:**

  Inclusion: Not discussed in the article; however all patients had histological confirmation of breast cancer and radiographic verification of pleural effusion; none of the patients had non-malignant causes for the pleural effusion; no patient had prior local treatment for their effusions other than thoracentesis.

  Exclusion: Not reported.

- **Stratification/Randomization:** Patients were stratified by presence or absence of nonpleural metastasis requiring systemic therapy, then randomly allocated to one of the study treatment arms.

- **Treatment Plan:** Talc group - Under general anesthesia, pleural effusions were drained, talc insufflated under thoracoscopic visualization. Two intercostal drains were then inserted, attached to underwater seals. Suction was applied in the case of a "persistent pneumothorax" visualized on the immediate postoperative chest X-ray. Simple Talc British Pharmacopeia grade (Evans Medical) was then insufflated. The intercostal drains were removed after 5 days.

  Mustine group - Patients underwent thoracoscopy under general anesthesia for insertion of a chest tube attached to an underwater seal. After confirmation of lung reexpansion, patients would receive intrapleural instillation of mustine 15 mg dissolved in 50 ml NS. The chest tube was clamped for 2 hours and the patient positioned for drug distribution for 5-10 minutes. The chest tube was again attached to an underwater seal and remained in place until pleural drainage ceased. The tube was usuallly removed within 3 days.

- **Efficacy & Safety Monitoring:** Chest X-rays performed at 1 month following pleurodesis and then every 3 months after that.

  Statistical Plan: Success was defined as no re-accumulation of pleural fluid by radiographic exam on all follow-up visits (minimum of 6 months of follow-up time). Patients had to survive for more than one month in order to be considered evaluable for the study and comparisons made with baseline

radiograph. Otherwise not discussed.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age, mean (S.D.)	# Evaluable / # Entered	Tumor Type	TNM Stage 1&2	3&4	Menopausal Status pre	post
T	55.3 ± 2.2	20/23	Breast	17	6	6	17
M	50.3 ± 1.5	17/23	Breast	12	11	13	10

Twenty patients had prior thoracentesis for relief of their dyspnea, breakdown by treatment group is not provided. "Thirty-six patients were receiving or eventually received concomitant systemic therapy for other lesions" (and for which they were stratified).

A total of 36 patients (17 M, 19 T) did eventually receive systemic therapy for the treatment of advanced disease. The policy was to treat with endocrine therapy (ovarian ablation if premenopausal and tamoxifen if post-menopausal with random allocation to additional prednisolone) as a first measure. Relapsed patients were then followed with doxorubicin (± vincristine) followed by cyclophosphamide, 5-fluorouracil, and methotrexate.

- **Response:**

Treatment	Success (definition provided Y/N)	Symptom (sx) Relief
T	18/20 (Y)	not given
M	9/17 (Y)	not given

Nine patients died (3 talc, 6 mustine) within 1 month of receiving pleurodesis, attributed to metastatic disease.

At completion of the trial, 10 additional patients had died in the T arm (13/23 deaths); 8 of these 10 patients still had control of their effusion at death. Of the remaining 10 patients that were alive, none had evidence of recurrent effusion.

The M group had experienced 12 more deaths at the completion of the study (18 deaths total) with 8 of those 12 patients having effusion control until death. The remaining 5 patients that were still alive had 2 failures and 3 successes making the successes in the M group 11/17 (65%) instead of the reported 9/17 (56%).

Patients that received systemic therapy for their disease and died within the 1 month period were excluded from the final analysis.

Systemic therapy: The author stated that when the response to systemic treatment was assessed in the 36 patients with advanced disease using the UICC criteria, and compared with the response to pleurodesis, there : a systemic response, partial or complete, in 33% of the mustine successes and in 41% of the talc cesses.

Reviewer's comment: *The author did not provide dates of pleurodesis in relation to systemic therapy*

vered.

Safety Results:

Treatment	Adverse Experiences per total # of patients Talc Control	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
T	sc. emphysema 1; peroneal nerve palsy 1; post-op grand mal seizure 1	5	1314 ± 166 ml [a]	minimum f/u was 6 mos; 9 died < 1 mos (3T/6M); 18M/13T total deaths median survival 13.5 & 14.5 mos respectively; 5M/10T survivors at publication time median survival 16 & 17 mos respectively
M	sc. emphysema 1; drain site abscess 1; pulmonary embolism (nonfatal) 1	3	1057 ± 115 ml [a]	

a = mean ± standard deviation, unclear if total amount of pleural fluid drained.

Comments & Conclusions:

Investigator/Author: The authors conclude that talc is superior to mustine for control of malignant pleural effusions.

Reviewer: *The mustine patients were positioned for 5-10 minutes after instillation of the drug to ensure uniform distribution within the pleural space; this may not have been enough time to successfully distribute drug. The final analysis had discrepancies in the number of successes in the mustine group making interpretation and conclusions similar to the authors impossible for the reader. The authors provided data on the mean age of patients and the time interval between breast cancer diagnosis and effusion which they stated was not statistically significant.*

9.2.4 Article: Hamed H, Fentiman IS, Chaudary MA, Rubens RD. Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast. Br J Surg 1989; 76: 1266-1267.

- **Objective:** To directly compare bleomycin to talc in controlling pleural effusions secondary to breast cancer.

- **Rationale**: Effective control of malignant pleural effusion can significantly improve a patient's quality of life. Reports of bleomycin in the treatment of malignant pleural effusion seem promising; but had not been directly compared to talc.

Study Design: Prospective, randomized with an active concurrent control.

Note: IRB approval or patient informed consent was not discussed.

- **Institution:** ICRF Clinical Oncology Unit, Guy's Hospital, London, U.K.

- **Study Dates:** Not provided. Paper accepted for publication June 1, 1989.

Eligibility:

Inclusion: Inclusion criteria was not defined in the article. Methods employed to confirm the diagnosis of breast cancer was not discussed in the article. The authors radiographically confirmed the presence of pleural effusion and there was no evidence of non-malignant causes

for the effusion. Previous treatment received for malignant pleural effusion was limited to simple aspiration for immediate symptomatic relief.
Exclusion: Not provided.

- **Stratification/Randomization:** All patients were randomly allocated to either arm after undergoing stratification based on the presence or absence of other metastatic lesions requiring systemic therapy. Details of randomization were not provided.

- **Treatment Plan:** All patients underwent general anesthesia for pleurodesis and insertion of one intercostal drain.

  Talc group - Thoracoscopy under general anesthesia, effusion drained to dryness, and insertion of an intercostal drain followed by talc insufflation.

  Details regarding the dose, source and purity of talc other than being non-iodized were not provided in the article.

  Bleomycin group - Thoracoscopy under general anesthesia and effusion drained to dryness with insertion of an intercostal drain. Bleomycin was instilled if chest X-ray confirmed lung reexpansion and patient posturing was possible. The bleomycin group received 1 mg/kg in 50 ml of normal saline within 48 hours after a chest X-ray had shown re-expansion of the lung.

  Efficacy & Safety Monitoring: Chest X-ray 1 month post procedure. Follow-up chest X-rays were to be performed, but time points were not provided.

- **Statistical Plan:** Patients were considered evaluable if they survived for more than 1 month and received a chest X-ray at that time so that comparison with baseline films could be made. Success was defined as the continued absence of fluid re-accumulation on all follow-up radiographs; but assessment time points and minimum follow-up time were not provided. Any reaccumulation was regarded as a treatment failure. Further details are not provided.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age, mean (SD not provided)	No. M/F	# Evaluable / # Entered	Tumor Type	Menopausal Status		Stage of disease at presentation		
					Pre	Post	1 & 2	3	unknown
Talc	54.7	13F	10/13	Breast for both groups	4	9	5	6	2
B	53.1	16F	12/16+		6	10	10	3	3

+ = 1 patient had talc in one lung and bleomycin in the other, 2 patients had bleomycin bilaterally (25 procedures total)

Seven talc and 6 bleomycin patients were receiving systemic treatment for disseminated disease; but types of therapy administered were not discussed. Mean time to development of effusion from diagnosis of breast cancer was 46 months for the talc group versus 55 months for the bleomycin group. Mean delay between diagnosis of effusion and treatment was 6.6 versus 4.8 months in the talc and bleomycin groups, respectively.

bleomycin patient was unable to receive therapy due to rapid deterioration and death "within a few days"; 1 talc patient was unable to receive therapy due to loculations; 5 patients died (3 talc, 2 bleomycin) within 1 month of therapy.

- **Response:**

Treatment	Success (definition provided Y/N)	Symptom (sx) Relief
Talc	10/10 procedures (Y)	not provided
B	5/15 procedures (Y)	½ symptom relief [a]

a = 2 pts relapsed and were subsequently treated with T with 1 pt. having symptom relief;

Talc patients had control of their effusions compared to 5/15 procedures performed in patients who received bleomycin after a mean follow-up time of 9 months. The mean survival following pleurodesis in both groups was 9 months. The authors did not give additional information regarding the patient that had received talc in one pleural cavity and bleomycin in the other except that complete control of effusion was achieved on the side that had been sclerosed with talc. No information was provided on the two patients that underwent bilateral pleurodesis with bleomycin.

Safety Results:

atment	Adverse Experiences per total # of patients Talc Control	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
Talc	pain (mild) 10*	not provided	not provided	16 survived < 6 mos & 7 survived > 6 mos with overall mean survival of 9 mos; no data on survivors
B	pain (mild) 12*	not provided	not provided	

* = data on evaluable pts only

Complications reported included minimal post-operative pain attributed to the chest drain site which resolved with analgesics without the need for opiates in either group. Types of analgesics used in either arm were not discussed. Pleuritic pain was not observed in the talc group believed by the authors to be attributed to using the non-iodized form.

Comments & Conclusions:

Investigator/Author: The authors conclude that talc was superior to bleomycin in controlling malignant pleural effusions, although statistically it was not shown to be significant. The authors admitted that the sample size in the study was small.

Reviewer: *The authors revealed that 41% of the patients had bilateral and 18.5% had contralateral effusions in the discussion portion of the article; however the information presented in the methods section discussed a total of 3 patients receiving bilateral therapy. The staging system was not fully described in the article. The trial appears to meet criteria for an adequate and well-controlled study. In particular, there was an attempt to define the comparability of patients by baseline characteristics: all had a single malignancy and were stratified by ± need for systemic chemotherapy. The arms appear to be balanced for other prognostic factors such as menopausal status and age.*

9.2.5 Abstract: Boutin, C., Ray, F., Viallat, J.R. Etude randomisee de l'efficacite du talcage

acoscopique et de l'instillation de tetracycline dans le traitement des pleuresies cancereuses recidivantes. Rev Mal Resp 1985; 2:374.

Note: Abstract published in french and translated by sponsor.

- **Objective:** Unable to ascertain from translated abstract.
- **Rationale**: Unable to determine from abstract.

Study Design: Prospective, randomized with an active concurrent control group.

Note: Unable to determine if study underwent IRB approval and whether patient informed consent was obtained.

- **Institution:** Michel-Levy Hospital, Marseille, France.
- **Study Dates:** Article was published in 1985.
- **Eligibility:** (Methods employed for diagnosing and confirming the underlying malignancy were not discussed).
  Inclusion: Not provided.
  Exclusion: Not provided.
- **Stratification/Randomization:** Method of randomization was not discussed; stratification not discussed.
- **Treatment Plan:** Not described. Information on source, sterility and purity of talc was not available in the translated abstract.
- **Efficacy & Safety Monitoring:** Timing of assessments and required tests were not discussed.
- **Statistical Plan:** Not provided.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age *	No. M/F	No. of Evaluable Patients	Tumor Type
T	Not given	total 20pts	Not provided	16 metastatic cancers, 4 mesothelioma
TCN	Not given	total 20pts	Not provided	14 metastatic cancers, 6 mesotheliomas

ormance status, age and gender were not given.

Treatment Received: Patients received either talc poudrage or tetracycline instillation following

thoracoscopic drainage. Drug doses, and further description of methodology of the procedure, or other therapies were not described.

- **Response:**

Treatment	CR at 6 months (definition provided Y/N)	Symptom (sx) Relief
T	14/14 (N)	not given
TCN	8/15 (N)	not given

Safety Results:

Treatment	Adverse Experiences per total # of patients Talc Control	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
T	not provided	not provided	equal amounts in both arms *	11 died (6T/5TCN) by the 6 mos f/u
TCN	not provided	not provided		

* = further breakdown not provided

Eleven patients (6 talc and 5 tetracycline) died by 6 months and do not appear to be included in the denominator for efficacy. Fourteen talc patients and 8 out of the 15 tetracycline patients who were alive at six months were reported have complete resolution of their malignant pleural effusion.

ıments & Conclusions:

Investigator/Author: Based on the results obtained at six months, the authors conclude that talc pleurodesis is superior to tetracycline.

Reviewer: *Due to the small sample size and limited information provided in the abstract, no conclusive comparative comments can be made, although this report supports the general literature suggesting activity of talc used as a sclerosing agent..*

9.2.6 Abstract: Muir JF, Cerisel F, Defouilloy C, Brussier PM, Hermant A, Aubry P, Ndarurinze S, Boto MJ, Arlati S. Pleural drainage with talc vs doxycycline in the control of malignant pleural effusion. Am Rev Respir Dis 1987; 135: A244.

- **Objective:** To determine which agent (talc or doxycycline) is more effective as a sclerosing agent.

- **Rationale**: To control of malignant pleural effusions.

Study Design: Prospective, randomized with an active concurrent control.

Note: IRB approval and whether patient informed consent was obtained is unknown.

- **Institution:** Pulmonary Service ,C.H.U., Amiens, France.

Study Dates: Abstract published in 1987.

- **Eligibility:**

Inclusion: Not provided. Methodology of diagnosis of malignancy or pleural effusion were not provided.
Exclusion: Not provided.

- **Stratification/Randomization:** Method of randomization, or whether there was stratification, is not discussed in the abstract.

- **Treatment Plan:** Not provided

- **Efficacy & Safety Monitoring:** Not provided.

- **Statistical Plan:** Patients were considered evaluable if they survived more than 1 month after the sclerosis. Response, failure, and minimal follow-up times were not defined in the abstract. A statistical plan was not discussed.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age (range)	No. M/F	No. of Evaluable Patients	Tumor Type
T	not given	total 15pts	15	not provided
D	not given	total 15pts	15	

Treatment Received: All patients underwent thoracoscopy, chest tube drainage, and insertion of a pleural catheter.

The talc group received 5 ml of Luzenac talc via insufflation during thoracoscopy. Duration of chest tube was not discussed. Dose, concentration, and purity of talc were not provided.

After thoracoscopy, the doxycycline group received 20 mg/kg of the drug in 200 ml of saline through a pleural catheter followed by clamping of their chest tube for 3 hours and repositioning to insure uniform distribution of doxycycline in the pleural space. The chest tube was then unclamped for 24 hours to allow drainage. The procedure was repeated until the pleural volume was "minimal".

- **Response:**

Treatment	CR (definition provided Y/N)	Symptom (sx) Relief
T	15/15 (N)	not given
D	13/15 (N)	not given

ty Results:

Treatment	Adverse Experiences per total # of patients Talc Control	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
T	not provided	not provided	not provided	T f/u 4.8 ± 4.2 mos
D	not provided	10.3 ± 4.3 [a,b]	not provided	D f/u 3.9 ± 3.3 mos[c]

a = unclear if total amount of pleural fluid drained; b = mean ± SD c = for the patients without recurrence

The investigators reported that both drugs were well tolerated with no pleurocutaneous fistulas observed.

Reviewer's comment: *Follow-up in the talc group was 4.8 ± 4.2 months and 3.9 ± 3.3 months in the doxycycline arm; however the authors stated earlier in the abstract that in order for a patient to be considered for assessment they had to survive for at least 1 month. It is not clear whether these follow-up times were after the necessary 1 month survival period.*

Comments & Conclusions:

Investigator/Author: The authors felt that doxycycline was as effective as talc for control of malignant pleural effusion.

Reviewer: *Due to the small sample size, absence of information on tumor type or other prognostic factors addressing comparability between the treatment arms, definitive comparative conclusions can not be drawn. As a minimum conclusion, talc is again seen to have activity as a sclerosing agent and is not proven to be less effective than yet another control agent.*

9.2.7 Abstract: Muir JF, Rose JL, Defouilloy C, Broussier P-M, Hermant A, Aubry P, Ndarurinze S: Pleural drainage with talc vs rolitetracycline in the control of malignant pleural effusions. The Eur Respir J. 1988; 1 (Suppl 2): 304S.

- **Objective:** "To determine which agent produced the more effective pleurodesis."
- **Rationale:** Not stated.

Study Design: Prospective, randomized with an active concurrent control.

Note: No information was provided regarding IRB approval or obtaining patient consent.

- **Institution:** Service de Pneumologie et Reanimation Respiratoire C.H.U. Amiens 80000 France.
- **Study Dates:** Not stated. Article published in 1988.
- **Eligibility:**

  Inclusion: First diagnosis of malignant pleural effusion in patients with pleural effusions secondary to disseminated cancer.

- **Exclusion:** Survival less than one month post procedure.

- **Stratification/Randomization:** Not stated.
- **Treatment Plan:** Not stated. Source, dose and purity of talc are not provided.
- **Efficacy & Safety Monitoring:** Not stated.
- **Statistical Plan:** Success was defined as no recurrence of pleural effusions. Evaluable patients had to survive 1 month post-procedure. A statistical plan was not stated.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age, mean (range)	No. M/F (total pts)	# Evaluable / # Entered	Tumor Type
Talc	not provided	(12)	12 (unclear if this number represents evaluable or entered)	not provided
Roli	not provided	(12)	12 (unclear if this number represents evaluable or entered)	not provided

rolitetracycline

Age was not provided; gender breakdown was misprinted. Patients had to survive 1 month after instillation of the sclerosing agent in order to be considered evaluable.

- **Treatment Received:** All patients had a thoracoscopy followed by chest tube drainage of their effusion "until pleural flow was minimal." Five ml of Luzenac talc was insufflated over as much of the pleural space as possible for the talc arm; the rolitetracycline group received 20 mg/kg "vaporized according to the same procedure as for the talc".

- **Response:**

Treatment	# Evaluable / # Entered	Success (definition provided Y/N)	Duration, median (range)	Symptom Relief
Talc	12 (unclear if this number represents evaluable or entered)	11/12 91.7% (Y)	not provided, f/u 5.7 ± 4.9 mos	not provided
Roli	12 (unclear if this number represents evaluable or entered)	10/12 83.3% (Y)	not provided, f/u 8.2 ± 5.1 mos	

The authors cite successes of 11/12 (91.7%) in the talc arm (f/u 5.7 ± 4.9 mo; 10 deaths) and 10/12 (83.3%) in the rolitetracycline arm f/u 8.2 ± 5.1 mo; 9 deaths). However, the authors also state that, "On a long term basis, recurrence rates of pleural effusion were similar in the two groups (talc group: 87.5%; rolitetracycline p: 83.3%)."

ty Results:

Treatment	Adverse Experiences	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure); mean ± SD
Talc	none observed	7.8 ± 3.2 *	not provided	min.30 d; 5.7 ± 4.9 mo w/ 10 deaths
Roli	none observed	7.7 ± 2.1 *	not provided	min. 30 d; 8.2 ± 5.1mo w/ 9 deaths

* = reported for evaluable patients

The authors state that there were no cases of pleurocutaneous fistulas observed.

Comments & Conclusions:

Investigator/Author: The authors conclude that "pleurodesis with rolitetracycline is as effective as talc for control of malignant pleural effusion."

Reviewer: *Due to the small sample size, absence of information on tumor type or other prognostic factors addressing comparability between the treatment arms, definitive comparative conclusions can not be drawn. As a minimum conclusion, talc is again seen to have activity as a sclerosing agent and is not proven to be less effective than yet another control agent.*

9.2.8 Abstract: Jones DP: Talc vs. Tetracycline pleurodesis for malignant pleural effusions. Chest. 1989; 96 ›pl): 276S.

- **Objective:** To compare the previous "gold standard", talc poudrage, to tetracycline pleurodesis for malignant pleural effusions.
- **Rationale:** Not stated.

Study Design: Prospective, non-randomized study with an active concurrent control. Patients considered to be high risk for general anesthesia were allocated to receive tetracycline.

Note: No information was provided regarding IRB approval or obtaining patient informed consent.

- **Institution:** F.C.C.P., Toronto Western Hospital, Toronto, Canada.
- **Study Dates:** Not stated. Article published in 1989.
- **Eligibility:**

  Inclusion: Symptomatic, malignant pleural effusion unresponsive to systemic therapy.

  Exclusion: Not stated.

- **Stratification/Randomization:** This was a non-randomized study with higher operative risk patients (definition not provided) allocated to the tetracycline group.
- **Treatment Plan:** Not stated. Information on dose, source and purity of talc was not provided.

Efficacy & Safety Monitoring: Average follow-up for the talc group was 9.9 months and 8.7 months for the tetracycline group; however assessment time points for efficacy and safety were not defined.

- **Statistical Plan:** "Success" was defined as relief of symptoms and satisfactory chest X-ray. Statistical plans were not described in the abstract.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age	No M/F (total pts)	# Evaluable / # Entered	Tumor Type
Talc	Not provided	(37)	Not provided/37	Not provided
TCN	Not provided	(17)	Not provided/17	Not provided

TCN = tetracycline

- **Treatment Recieved:** "Talc poudrage was done under general anesthesia; tetracycline under local (1.5 Gm tetracycline + 40 mg xylocaine in 200 ml normal saline infused via chest tube)."

- **Response:**

Treatment	# Evaluable / # Entered	Success (definition provided Y/N)	Duration	Symptom (sx) Relief
c	Not provided/37	94% (Y)	Not provided	relief of sx to qualify for success; but description of sx not provided
TCN	Not provided/17	95% (Y)	Not provided	

The authors enrolled an additional 190 patients in the tetracycline arm and obtained a success rate of 96.7%.

Safety Results:

Treatment	Adverse Experiences	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Average Length of f/u (post procedure)
Talc; n = 37	bleeding from chest wall tumor 1/37	Not provided	Not provided	9.9 mos
TCN; n = 17	discomfort *	Not provided	Not Provided	8.7 mos

* = exact numbers not provided

Discomfort was experienced by "most" patients in the tetracycline arm and was described as "easily controllable."

Comments & Conclusions:

Investigator/Author: The authors conclude that with "proper patient selection, tetracycline pleurodesis by this method offers excellent, palliative, symptomatic relief of malignant pleural effusion."

Reviewer: *Proper patient selection is not defined in the abstract except that high operative risk patients were allocated to the tetracycline group. The authors also state that treatment offers symptomatic relief of malignant pleural effusions; but do not describe symptoms or the relief of*

symptoms. The authors do not attempt to make any conclusions regarding superiority of one drug over the other, which is appropriate.

9.2.9 Article: Adler RH, Rappole BW. Recurrent malignant pleural effusions and talc powder aerosol treatment. Surgery 1967; 62: 1000-1006.

- **Objective:** To introduce a new method of talc insufflation for the treatment of recurrent symptomatic malignant pleural effusions by using a newly developed talc aerosol unit.

- **Rationale:** The newly developed talc aerosol unit might allow for a simple, quick, and closed technique that would ensure uniform insufflation of talc for treating symptomatic recurrent malignant pleural effusions.

Study Design: Talc group: Anecdotal report of 4 "selected " patients at Buffalo General Hospital with "massive, recurrent MPE," two patients previously treated with other agents.
Controls: Charts of all inpatients from Buffalo General Hospital and Roswell Park Memorial Institute who had a diagnosis of MPE recorded during the period from July 1, 1956 through June 30, 1965 were reviewed. Forty patients with large symptomatic recurrent MPE were selected based on the number of thoracenteses, total amount of fluid removed, and adequate clinical records.

Institution: Talc group - The Buffalo General Hospital, Buffalo N.Y.
Controls - The Buffalo General Hospital and the Roswell Park Memorial Institute, Buffalo, N.Y.

- **Study dates:** Originally submitted for publication 17 April, 1967.
Talc group - Unclear.
Controls - Between July 1, 1956 and June 30, 1965.

- **Eligibility:**

Inclusion: Talc group - Prospective criteria not stated. All four patients had: (1) diagnosis of malignant pleural effusion made by either tissue examination or by the identification of malignant cells in the pleural fluid; (2) multiple thoracenteses; (3) associated dyspnea; (4) "massive" malignant pleural effusion.

Controls - See definition of controls, above. All patients had: (1) diagnosis of malignant pleural effusion made as per talc group; (2) more than 3 prior thoracenteses with at least 2 liters of pleural fluid drained; and (4) "satisfactory" clinical records with complete follow-up data.

Exclusion: Not specifically stated for either group.

Stratification/Randomization: Nonrandomized.

- **Treatment Plan:**
Talc group - Trocar administration followed by pleural fluid aspiration and temporary induction of a

partial pneumothorax. Talc is insufflated via a newly developed talc aerosol unit followed by insertion of a chest tube and reexpansion of the lung. Chest tube is left in place for additional drainage.
Controls - N/A--historical review of patient charts. Thoracenteses with intrapleural instillation of a sclerosing agent (see below for specific agents used).

- **Efficacy & Safety Monitoring:** A schedule for evaluations was not provided. .

- **Statistical Plan:** Not reported.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age, mean	# Evaluable / # Entered	Tumor Type
Talc	62.8	4/4	1 mesothelioma, 2 bronchogenic carcinoma, 1 breast
Other [a]	60, 58.6, 51 [b]	21[c]/40	15 breast, 10 lung, 6 lymphoma, 2 ovarian, 7 other

a = thiotepa, nitrogen mustard , AB-132, radioactive phosphate, radioactive gold, and quinacrine;
b = for the 3 main groups (breast, lung and lymphoma, respectively)
c = only 21 of the 40 had instillation of a sclerosing agent

Main symptoms experienced by the control group consisted of dyspnea (36), cough (13), pain (12), and hemoptysis (3). Main symptoms experienced in the talc group consisted of dyspnea and distress associated with the massive recurrent effusions.

Treatment Received:
Talc group - A single 6 - 8 Gm dose of USP talc was insufflated in 4 patients. Three patients were treated under general anesthesia and 1, local anesthesia. Two to 3 liters of pleural fluid were removed during pleurodesis. All 4 patients had a chest tube inserted for additional drainage.
Controls - Twenty-one of the 40 patients received intrapleural instillation of a single agent consisting of either thiotepa (7), nitrogen mustard (6), AB-132 (3), radioactive phosphate (3), radioactive gold (1), or quinacrine (1).

Reviewer's comment: *Additional information regarding methodology and dose delivered were not provided.*

- **Response:**

Treatment	Success (definition provided Y/N)	Symptom (sx) Relief
Talc	4/4 (N)	not provided
Other [a]	4/21 (N) [b]	not provided

CR = complete response; a = intrapleural installation of either thiotepa, nitrogen mustard, AB-132, radioactive phosphate, radioactive gold, or quinacrine; b= 1 thiotepa, 1 nitrogen mustard, 1 AB-132, and 1 radioactive phosphate patient;

:ty Results:

Treatment	Adverse Experiences per total # of patients Talc Control	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
T n = 4	pain (mild-moderate) 4/4; fever 4/4	2 to 3 *	2 to 3 L [c]	3(T) died 5-10 mos.; 1(T) survivor at publication time 17 mos.
Other [b]	not provided	not provided	> 3 L (31 pts.) * > 2 L (9 pts.) *	incomplete data for hx review

a = chest tube inserted after T insufflation; b = thiotepa, nitrogen mustard, AB-132, radioactive phosphate, radioactive gold, or quinacrine; c = amount aspirated at pleurodesis
* = further data not provided; T = talc; pts. = patients

Comments & Conclusions:

Investigator/Author: The authors concluded that the talc aerosolization technique presented in this article is simple, quick, and effective in controlling malignant pleural effusion.

Reviewer: *Conclusions regarding drug superiority can not be made based on the limited number of patients treated with talc and the heterogeneous, retrospective control arm.*

9.2.10 Article: Hartman DL, Gaither JM, Kesler KA, Mylet DM, Brown JW, Mathur PN. Comparison of insufflated talc under thoracoscopic guidance with standard bleomycin and tetracycline pleurodesis for control of malignant pleural effusions. J Thorac Cardiovasc Surg 1993; 105: 743-8.

- **Objective:** To evaluate the effectiveness and morbidity rate of talc insufflation during thoracoscopy in comparison to historical controls in the treatment of symptomatic malignant pleural effusions.

- **Rationale**: To evaluate talc insufflation under thoracoscopic guidance "as a potentially more effective treatment of symptomatic malignant pleural effusions with a lower morbidity rate."

Study Design:

Prospective, non-randomized, phase II study that evaluated talc insufflation under thoracoscopic guidance as compared to controls consisting of patients who participated in a multicenter, randomized, controlled trial of bleomycin vs tetracycline.

Note: The study was performed with IRB approval. Informed consent was obtained prior to therapy.

- **Institution:**
  Talc group - Three Indiana University Medical Center hospitals (Indiana University Hospital, Wishard Memorial County Hospital, and the Richard R. Roudebush Veterans' Administration Medical Center).
  Historical Controls - Patients who participated in a multicenter study (unclear if patients were only those enrolled at investigator's institution or included controls from other centers.)

- **Study dates:**
  Talc group - Between October 1990 and February 1992.
  Historical Controls - Information not provided.

Eligibility:

Inclusion:

Talc group - "1) Dyspnea that improved after large-volume thoracentesis with subsequent recurrence of a symptomatic pleural effusion, 2) no radiographic evidence of conditions that might

prevent lung reexpansion (i.e. visceral pleural entrapment atelectasis as a result of bronchial occlusion), 3) pleural fluid cytologic studies or pleural biopsies positive for malignant cells, and 4) an ECOG performance score ≤ 2".

Historical controls - Same as the talc group.

Exclusion:

Talc group -

"1) The inability to lie in the lateral decubitus position, 2) previously attempted ipsilateral pleurodesis, 3) a non-correctable bleeding diathesis, 4) any change in the chemotherapy regimen within 4 weeks before the patient entered the study and 5) radiation therapy < 2 weeks before referral for pleurodesis".

Historical controls -

1) same as the talc group except no restrictions regarding patient positioning or bleeding diathesis 2) history of previous systemic bleomycin therapy

- **Stratification/Randomization:**
Talc group - Non-randomized (phase II) trial. No stratification was performed.
Historical controls - No information is provided as to how controls were selected, other than participation in multi center trial.

- **Treatment Plan:**
Talc group - Large volume thoracentesis the day prior to thoracoscopy. Talc insufflation via trocar under thoracoscopic guidance with a chest tube left in place for additional pleural fluid drainage.
Historical controls - When tube thoracostomy drainage had decreased to no more than 100 ml/day, 60 mg of bleomycin or 1000 mg of tetracycline, both diluted in 100 ml NS, was instilled intrapleurally.

- **Efficacy & Safety Monitoring:** Success was defined in all treatment groups as no reaccumulation of pleural fluid by serial chest roentgenograms as compared to baseline films. Failure was defined as the reaccumulation of pleural fluid confirmed by chest roentgenograms. Follow-up visits that included chest roentgenograms were made at 30 and 90 days. Symptom relief was not defined or included as part of the response criteria. A large volume thoracentesis was performed the day prior to thoracoscopy to relieve dyspnea, estimate the potential for lung reexpansion, and minimize the risk of reexpansion pulmonary edema. Computed tomography scans of the chest were obtained when indicated; but was not defined, to further define pulmonary and pleural anatomy. Pleural space was inspected prior to talc instillation to assure no adhesions were present which would prevent distribution of talc.

- **Statistical Plan:** "Univariate statistical analysis was applied to discrete preoperative and postoperative variables (X^2 analysis, with continuity correction when appropriate) and to continuous variables (Student's *t* test) using Statview II software."

cacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age, mean (range)	# Evaluable / # Entered 30 days / 90 days		Tumor Type in Evaluable Patients at 30 days
Talc	58.8 (41-88)	33/39	21/39	Lung 13, Breast 8, Ovary 4, Other 8
B or	61 (19-86) (both combined)	28/44	37/44	Lung 13B/13TCN, Breast 9B/10TCN
TCN		27/41	36/41	Ovary 1B/2TCN, Other 15B/11TCN

B = bleomycin; TCN = tetracycline

Reviewer's comment: *In the control group, 55 (28 B, 27 T) and 73 (37 B, 36 T) patients were considered evaluable at 30 days and 90 days, respectively. The author did not provide information for the increase in evaluable patients. The patient numbers in the table describing tumor type at 30 days does not match the patient numbers in the article.*

Treatment received:

Talc group - A single 3 to 6 Gm dose of USP-grade, sterilized, asbestos-free talc was insufflated at thoracoscopy in the lateral decubitus position under local anesthesia and IV sedation. A chest tube was inserted and left in place until pleural fluid drainage was less than 100 ml per day.

Historical controls - A single dose of 60 units of bleomycin or a single 1000 mg dose of tetracycline, both diluted in100 ml normal saline, was instilled into the chest cavity when chest tube drainage was less than 100 ml/day. It is not stated when chest tube was withdrawn.

- **Response:**

Treatment	Success 30 days	90 days	Symptom Relief
Talc	32/33 (97%)*	20/21 (95%)	dyspnea relief [a]
B	18/28 (64%)	26/37 (70%)	not provided
TCN	9/27 (33%)	17/36 (47%)	

* = Six patients died prior to thirty day evaluation, twelve between the thirty and ninety day evaluation.
a = patient numbers were not provided

Reviewer's comment: *The two talc patients reported as failures had tumor compression of the right lower lobe bronchus preventing complete lung reexpansion. In an intent-to-treat analysis with talc pleurodesis at 90 days, 20/39 (51%) would be considered to have responded, rather than 95%.*

The control group had more patients evaluated for response at 90 days than 30 at days. The reason for this is unclear, possibly due to failure to have an X-ray at 30 days. In an intent-to-treat analysis, 59% and 41% of patients would have been considered to have responded.

ety Results:

Treatment	Adverse Experiences	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Follow-up (post procedure)
Talc n=39	discomfort (mild) 38/39; severe[a] 1/39; fever [b] 7/39; sc. emphysema (minor) 6/39	4.0 ± 1.2 [c]	up to 1.5 L *	6 died <30 d; 12 died <90 d.
B or TCN n=85 (44 B, 41TCN)	not provided	6.6 ±1.6 (B, n=11) [c] 6.5 ± 2.1(TCN, n=10) [c]	not provided	survival data for controls not provided

a = MI ruled out; b = 37.5 to 39°C lasting about 24 hrs. (range 12 to 72 hrs.); c = mean ± standard deviation
* = the day prior to procedure

Reviewer's comment: *The conclusion that the shorter duration of chest tube drainage in the talc group is significant is questionable since only subgroups from a historical control were used and the techniques may have been different.*

Comments and Conclusions:

Investigator/Author: The authors conclude that thoracoscopically guided talc pleurodesis is safe, efficacious, and cost effective in the management of malignant pleural effusions.

Reviewer: *Since this was not a randomized study, the comparability of the patient populations is unproven. While no comparative statements can be made, talc is seen as an active agent in pleurodesis.*

9.2.11 Abstract: Lantos A, Zsaray M, Falus F, Szondy K, Bartfai Z, Varnai Zs, Mark Zs: Chemical pleurodesis with oxytetracyclin, doxycycline or talc in malignant pleural effusions. Tubercle and Lung Dis. 1994; 75(Suppl. I) 139: 507.

- **Objective:** Not provided in the abstract.
- **Rationale:** Not provided in the abstract.

Study Design: Two active controls; unclear if they were concurrent or sequential; no information on assignment to treatment.

Note: No information provided on IRB approval process or obtaining of patient's informed consent.

- **Institution:** Presumed to be the authors' business address, Semmelweis University, Department Pulmonology, Diosarok u. 1/C, Budapest H-1125.
- **Study Dates:** Not stated. Article published in 1994.
- **Eligibility:**

  Inclusion: Patients with malignant pleural effusions. No further data provided.

  Exclusion: Not provided.

Stratification/Randomization: Not stated.

- **Treatment Plan:** Not stated.
- **Efficacy & Safety Monitoring:** Schedule for follow-up examination was not provided.
- **Statistical Plan:** Not stated.

Efficacy Results:

- **Evaluability, Demographics & Patient Characteristics:**

Treatment	Age	No. M/F (total pts)	# Evaluable / # Entered	Tumor Type
Talc	Not provided	Not provided	25/25	Not provided
Oxy			24/24	
Doxy			25/25 (unclear if # of cases or # pts)	

Oxy = oxytetracyclin; Doxy = doxycycline

All patients underwent chest tube drainage and intrapleural instillation of oxytetracyclin, doxycycline or talc suspended in saline. Further information describing the method of pleural drainage, sclerosing agent instillation, the preparation of the sclerosing agent was not stated. Patients receiving oxytetracycline were administered a dose of 20 mg/kg; the doxycycline group received 10 mg/kg; and the talc group received 3-10 Gms. Source and purity of talc was not provided.

The denominator of 74 is greater than the stated number of patients entered, 69.

Follow-up of patients was performed "inside 3 months."

- **Response:**

Treatment	# Evaluable / # Entered	Success (definition provided Y/N)	Duration	Symptom Relief
Talc	25/25	24/25 96% (N)	"inside 3 months" for all arms	Not provided
Oxy	24/24	21/24 87.5% (N)		
Doxy	25/25 (unclear if # cases or # pts)	23/25 92% (N)		

ety Results:

Treatment	Adverse Experiences	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post-procedure)
Talc Oxy Doxy	not reported	Not provided	Not provided	"inside 3 months" for all arms

The authors report that, "As opposed to tetracycline, there were no pain and fever after talc instillation, however pleural thickening and clinically insignificant loculated fluids were more frequent (10/25), then in the tetracycline group." It seems pleural thickening and clinically insignificant loculated fluids were observed in the oxytetracyclin and doxycycline groups; but incidence was not provided.

Comments & Conclusions:

Investigator/Author: The authors concluded that chest tube drainage with talc instillation is an inexpensive, effective and "comfortable" method; however it requires a "proper" thorax drainage with large and well positioned chest tubes.

Reviewer: *It would be reasonable to say that talc appears to be an active sclerosing agent; but further conclusions are not possible due to the lack of information in the abstract.*

9.3 ADVERSE EXPERIENCE IN THE CONTROLLED TRIALS

9.3.1 TABLE OF ADVERSE EXPERIENCES BY TRIAL

Author No. Patients	Treatment	Dose of Agent Source & Purity of T	Adverse Experiences	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
No-Treatment Concurrent Control						
Sorensen et al; 1984 n = 14 (CT + Talc)	Thcpy. w/bx then talc slurry	10 Gm in 250 ml Normal Saline; sterile	pain (prolonged) 14/14; empyema 1/14	not provided	not provided	2 died < 3 mos; 9 survived 3-24 mos [a]
n = 17 (CT)	Thcpy. then **pleural drainage**		pain 12/17; staphylococcal septicaemia 1/17	not provided	not provided	5 died < 3 mos; 7 survived 4-17 mos [a]
Active Concurrent Control						
Fentiman, et al; 1986 n = 18 (Talc)	Talc insuf. at thcpy.	simple Talc	surgical emphysema 2/18; infection 2/18; asystolic arrest 2/18; pain 18/18	5 [b]	1630 ml ± 218 [d,e]	minimum f/u 12 mos; 6 died < 1 mos
n = 23 (**TCN**)	Thcpy. then **TCN** w/chest tube drainage	500 mg in 50 ml Normal Saline	surgical emphysema 3/23; brain stem hemorrhage (fatal) 1/23; pain (severe) 2/23	3 to 5 [c]	1470 ml ± 143 [d,e]	minimum f/u 12 mos; 2 died < 1 mos
Fentiman, et al; 1983 n = 20 (Talc)	Talc insuf. at thcpy.	not provided; simple Talc, BP grade (Evans Medical)	subcutaneous emphysema 1/23; peroneal nerve palsy 1/23; post-op grand mal seizure 1/23	5	1314 ± 166 ml [d]	minimum f/u was 6 mos; 3 died < 1 mos; 13 total deaths median survival 14.5 mos; 10 survivors at publication time median survival 17 mos
n = 17 (**Mustine**)	Thcpy. then **Mustine** sclerosis	15 mg in 50 ml Normal Saline	subcutaneous emphysema 1/23; drain site abscess 1/23; pulmonary embolism (nonfatal) 1/23	3	1057 ± 115 ml [d]	minimum f/u was 6 mos; 6 died < 1 mos; 18 total deaths median survival 13.5 mos; 5 survivors at publication time median survival 16 mos
Hamed et al; 1989 n = 10 (Talc)	Talc insuf. at thcpy.	not provided, non-iodized	pain (mild) 10/10 [f]	not provided	not provided	16 survived < 6 mos & 7 survived > 6 mos with overall mean survival of 9 mos; no data on survivors (further breakdown not provided)
n = 12 (**Bleomycin**)	Thcpy. then **Bleomycin** sclerosis	1 mg/kg in 50 ml Normal Saline	pain (mild) 12/12 [f]	not provided	not provided	
Boutin, et al; 1985 n = 20 (Talc)	Talc poudrage at thcpy.	not provided	not provided	not provided	equal amounts in both arms (further breakdown not provided)	6 died by the 6 mos f/u
n = 20 (**TCN**)	Thcpy. then **TCN** sclerosis	not provided	not provided	not provided		5 died by the 6 mos f/u
Muir, et al; 1987 n = 15 (Talc)	Talc insuf. at thcpy.	5 ml; Luzenac Talc	not provided	not provided	not provided	f/u 4.8 ± 4.2 mos
n = 15 (**Doxycycline**)	Thcpy. then **Doxycycline** sclerosis	20 mg/kg in 200 ml Saline	not provided	10.3 ± 4.3 [d,g]	not provided	f/u 3.9 ± 3.3 mos

CT = chest tube drainage, TCN = tetracycline; Doxy = doxycycline; Insuf = insufflation; Thtmy = thoracostomy; thcpy = thoracoscopy; hx = historical; mos = months; bx = biopsy
a = data on success pts only; b = chest tube inserted after Talc insufflation; c = chest tube inserted 16 to 24 hrs prior to TCN instillation; d = mean ± standard deviation; e = unclear if total amount of pleural fluid drained; f = data on evaluable pts only; g = data on patients without recurrence.

Author No. Patients	Treatment	Dose of Agent Source & Purity of Talc	Adverse Experiences	Chest Tube Drainage Time (days)	Amount Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
Active Concurrent Control (cont.)						
Muir, et al; 1988 n = 12 (Talc)	Talc insuf at thcpy, then chest tube drainage	5 ml Talc de Luzenac, single dose, not given	none observed	7.8 ± 3.2 [l]	not provided	minimum 30 d; 5.7 ± 4.9 mo w/ 10 deaths
n = 12 **(Rolitetracycline)**	**Rolitetracycline** insuf at thcpy then chest tube drainage	20 mg/kg	none observed	7.7 ± 2.1 [l]	not provided	minimum 30 d; 8.2 ± 5.1mo w/ 9 deaths
Jones; 1989 n = 37 (Talc)	Talc poudrage under general anesthesia	not provided	bleeding from chest wall tumor 1/37	not provided	not provided	average f/u 9.9 mos
n = 17 **(TCN)**	**TCN** instil via chest tube w/ local anesthesia	1.5 Gm	discomfort [m]	not provided	not provided	average f/u 8.7 mos
Historical Controls						
Adler, Rappole; 1967 n = 4 (Talc)	Talc aerosolization via trocar with bx	6-8 Gm; USP	pain (mild-moderate) 4/4; fever 4/4	2 to 3 [c]	2 to 3 L [d]	3 died 5-10 mos; 1 survivor at publication time 17 mos
n = 21 [a]	Variety of agents [b]	not provided	not provided	not provided	> 3 L (31 pts.) [e] > 2 L (9 pts.) [e]	incomplete data for historical review
Hartman, et al; 1993 n = 39 (Talc)	Talc Insuf. at thcpy w/bx	3-6 Gm; USP, asbestos-free, sterilized	discomfort (mild) 38/39; chest pain (severe) [f] 1/39; fever [g] 7/39; subcutaneous emphysema (minor) 6/39	4.0 ± 1.2 [h, i]	up to 1.5 L	f/u 30 & 90 d; 6 died < 30d; 12 died < 90d
n = 85 (44 **Bleomycin**, 41 **TCN**)	Thtmy., then **Bleomycin** or **TCN** sclerosis w/bx	**Bleomycin** 60 units **TCN** 1000 mg	not provided	6.6 ± 1.6 (**B** n = 11) [h, j] 6.5 ± 2.1 (**TCN** n = 10) [h, j]	not provided	f/u 30 & 90 d; survival data for controls not provided
Other Controlled Trials						
Lantos, et al; 1994 n = 25 (Talc)	Chest tube drainage then Talc instil	3-10 Gm, single dose, not given	pleural thickening and "insignificant loculated fluids" 10/25	not provided	not provided	"within 3 months"
n = 24 **(Oxytetracycline)** n = 25 **(Doxycycline)**	Chest tube drainage then **Oxytetracycline** or **Doxycycline** sclerosis	20 mg/kg **(Oxytetracycline)** 10 mg/kg **(Doxycycline)**	pain [k], fever [k], pleural thickening and "insignificant loculated fluids" [k] pain [k], fever [k], pleural thickening and "insignificant loculated fluids" [k]	not provided	not provided	"within 3 months"

T = talc; TCN = tetracycline; Insuf. = insufflation; Thtmy. = thoracostomy; thcpy. = thoracoscopy; mos = months; pts = patients; bx = biopsy

a = thiotepa 7, nitrogen mustard 6, AB-132 3, radioactive phosphate 3, radioactive gold 1, and quinacrine 1; b = intrapleural instillation of either thiotepa, nitrogen mustard, AB-132, radioactive phosphate, radioactive gold, or quinacrine; c = chest tube inserted after T insufflation; d = amount aspirated at pleurodesis; e = further data not given; f = MI ruled out; g = 37.5 to 39°C lasting about 24 hrs. (range 12 to 72 hrs.);

h = mean ± standard deviation; i = chest tube was inserted immediately after thoracoscopy; j = chest tube inserted and remained in place until pleural fluid was < 100 ml/d followed by instillation of sclerosing agent;

k = exact numbers were not provided; l = reported for the group without recurrence; unclear if reported for the initial success group or the long term without recurrence group; m = exact numbers not provided.

: TABLE OF ADVERSE EXPERIENCES ACROSS STUDIES

Of the 11 studies, 8 reported presence or absence of adverse events to talc. The 2 studies comparing talc to historical controls reported adverse events to talc only (Adler & Rappole 1967; Hartman 1993) and a third study (Jones 1989) did not provide frequency of events on the comparator arm. Therefore 5 studies report adverse events secondary to comparators versus 8 secondary to talc:

ADVERSE EXPERIENCE	TALC 8 Studies (154 pts. total)	BLEOMYCIN 1 Study (23 pts. total)	TETRACYCLINE (includes rolitetracycline) 2 Studies (35 pts. total)	MUSTINE 1 Study (17 pts. total)	CT 1 Study (17 pts. total)
ADVERSE EXPERIENCES IN ≥ 5% OF PATIENTS					
Pain	84/154 (54.5%)	12/12 (100%)	2/35[a] (5.7%)		12/17 (70.6%)
Fever	11/154 (7.1%)				
SC/surgical Emphysema [b]	9/154 (5.8%)		3/35 (8.6%) (surgical)	1/17 (5.9%) (SC)	
Staphylococcus septicaemia					1/17 (5.9%)
Drain site abscess				1/17 (5.9%)	
Pulmonary embolism				1/17 (5.9%)	
ADVERSE EXPERIENCES OCCURRING IN < 5% OF PATIENTS					
INFECTION					
Empyema	1/154 (0.6%)				
Infection not otherwise specified	2/154 (1.3%)				
CARDIAC DISORDER					
Asystolic arrest	2/154 (1.3%)				
NEUROLOGIC DISORDER					
Peroneal nerve palsy	1/154 (0.6%)				
Post-op grand mal seizure	1/154 (0.6%)				
Brain stem hemorrhage			1/35 (2.8%)		
OTHER					
Bleeding from chest wall tumor	1/154 (0.6%)				

a = after the first 2 cases developed severe pain on instillation of TCN, despite being given opiates, lignocaine 500mg was added to the instilled solution preventing this adverse effect. b = the adverse event is included in the table, as reported in the literature, but is considered procedure-related rather than drug related.

9.4 SUMMARY AND EVALUATION OF DATA

Eleven literature reports of controlled studies (6 articles, 5 abstracts, excluding Hartman's abstract as duplicative) were either submitted by the sponsor or retrieved via the Agency's literature search (see section 3), describing the treatment of malignant pleural effusion with talc administered via insufflation (9) or slurry (2). At least 208 talc patients were considered entered in 10 studies (Muir 1988 did not identify his 12 patients as those entered). A variety of comparators were utilized: one study reports chest tube drainage with and without talc

› treatment," concurrent control); 8 reports comparing talc to another agent, e.g., tetracycline, ıolıtetracycline, doxycycline, oxycycline, bleomycin, and mustine hydrochloride (active concurrent controls); and two studies report talc versus historical controls. Nine of the 11 studies did not include information on relief of symptoms with treatment (see Table 9.1). Sorensen and colleagues provided the only comparative data. Dyspnea was relieved with talc administration in 9/9 patients who had a CR compared to "subjective improvement" in 6/7 patients that had a CR treated with chest tube drainage only. A variety of talcs were used in the 11 reports: Hartman 1993 & Adler 1967 used USP-grade talc; Fentiman 1983 administered BP-grade talc; Muir 1987 & 1988 used talc de Luzenac; one article reported instilling sterile talc, and another reported using non-iodized talc. The remaining three articles did not include any information regarding the source or purity of the talc administered. Five studies did not report the dose of talc used. Of the remaining 6 studies, 4 used 3 to 10 Gm of talc per procedure. Muir 1987 & 1988 reported using 5 ml of talc, but a concentration was not provided.

Despite the weaknesses described above (incomplete detail, small sample sizes, heterogeneity of type and dose of talc) as well as possible publication bias, the following four studies appear to meet the criteria for adequate and well controlled trials: Sorensen 1984, Fentiman 1986, Fentiman 1983, and Hamed 1989. These 4 studies were prospectively conducted, randomized, entered only patients with malignant pleural effusion, and provided a definition of success which included objective measures (for trial details see Table 9.1).

Of the 11 studies, eight reported the presence or absence of adverse experiences to talc. Pain (84 reported cases), fever (11 cases), and emphysema (9 cases; 2 surgical and 7 subcutaneous) were the most commonly reported ·erse experiences. Life threatening adverse experiences reported were not clearly related to talc ıinistration. Two patients experienced asystolic arrest (Fentiman 1986) under general anesthesia with successful resuscitation and without sequelae.

10.0 PUBLISHED NONCOMPARATOR CLINICAL STUDIES.

NOTE: Efficacy data from the noncomparator trials is presented in table format only because the Agency believes that the burden of proof of efficacy for this submission rests with the controlled trials.

10.1 OVERVIEW TABLE OF DEMOGRAPHICS, TREATMENT, & EFFICACY RESULTS

Investigators, Publication	Design	Treatment	Dose per patient (Source & Purity of Talc)	Age, mean (range)	Tumor Type	# Evaluable / # Entered (# procedures)	Successes (# procedures)	Success Definition	Symptom (sx) Relief
UNITED STATES STUDIES									
Adler and Sayek Ann Thorac Surg 1976; 22 (1): 8-15.	Retrospective report of 41 pts with MPE	Intercostal tube thoracostomy, then T instillation	10 Gm in 250 ml sterile saline, single dose, (USP, sterilized)	58 (43-81) [a] 66 (57-72) [b] 52 (44-58) [c] 36 (18-73) [d]	Breast 20, Lung 7, Ovary 7, Lymphoma 3, Colon 1, MST 1, Ewing's Sarcoma 1, Unknown 1	not given/41 (44)	41/44	No fluid recurrence at last f/u Breast 1-41 mos Lung 1-10 mos	not given
Aelony, King & Boutin Ann Intern Med 1991; 115:778-82.	Prospective evaluation of pts. with benign pleural effusions (n=11) & MPE (n=28)	T poudrage at thoracoscopy then chest tube insertion	5 ml (2.5 Gm), single dose, (USP asbestos-free; sterilized; Spectrum Medical Manuf. Corp.)	66.2 (35 -89) both groups combined	Bronchogenic 3, Nonbronchogenic pleural mets 13, MST 8, Equivocal MST vs met 1, Lymphoma 1, Myeloma 2 --- Idiopathic 6, Pleural plaque from asbestos 3, Mediastinal fibrosis from XRT 1, Dressler Syndrome 1 (evaluable pts only)	39/41 (28MPE, 11PE) (42 effusions)	23/28 [e] 11/11 [f]	Not requiring further thoracentesis to relieve dyspnea for 1 year or more	39/39 (dyspnea)
Camishion, Gibbon & Nealon Surg Clinics of NA 1962; 42: 1521-6. (updated series of 1960)	Retrospective report of 34 pts. with MPE	T poudrage, thoracotomy and chest tube insertion; decortication in 4 pts	"2 - 3 full test tubes", single dose, (USP; sterilized)	56.4 (30-73)	Breast 7, Lung 19, MST 1, Malignant MST of pleura 1, hypernephroma 1, malignant thymoma 1, rhabdomyosarcoma 1, thyroid 1, Undetermined 2	31/34	31/31	No fluid recurrence at last f/u 2-16 mos	30/31 (dyspnea)
Chambers West J Surg Obstet. Gynecol 1958; 66: 26.	Retrospective report of 20 pts. with MPE	T instillation/ intercostal intubation	2-4 drams * suspended in 1% procaine solution, single dose, (USP; sterilized)	55.1 (36-73)	Breast 9, Bronchus 8, Thyroid 1, Ovary 1, Cervix 1	not reported/20	17/20	No fluid recurrence	not given
Colt & Dumon Chest 1994; 106 (6): 1776-8.	Retrospective report of pts. with MPE (n=12) & pneumothoraces(n=9)	T insufflation thoracoscopically	4 Gm, single dose, (asbestos-free, sterile **Bryan Corp.**)	not reported	not reported	not reported/21*	11/12 [e] 9/9 [h]	Absence of sxs, clinically insignificant increase of PE by CXR when compared to baseline, & requiring no further thoracenteses at 90 days; F/u 1 year	11/12 "sx relief" 9/9 "sx relief"
Daniel, Tribble & Rodgers Ann Thorac Surg 1990; 50: 186-9	Retrospective report of pats. with PE (n=20) & pneumothoraces(n=20)	T poudrage and thoracoscopy	up to 10.5 Gm., single dose, (USP, Humco Laboratories, asbestos-free, sterilized)	(10mos-78yrs)	Lung 9, Breast 2, Lymphoma 1, Ovary 1, Cervix 1	not reported/40[g]	12/14 [e] 6/6 [f] 19/20 [g]	No recurrence during hospitalization or up to 1 mo. No recurrence	not given

a = Breast Cancer 20 pts, b = Lung Cancer 7pts, c = Ovarian Cancer 7 pts, d = Lymphoma 3 pts, e = patients with malignancies, f = patients with benign conditions, g = persistent pneumothorax patients, h = pneumothoraces patients,
* = unclear if unit of weight is in Apothecaries' (60 grains or 1/8 ounce) or Avoirdupois (27.3 or 1/16 ounce) system, N/A = not applicable, pts = patients, USP = United States Pharmacopeia, MPE = malignant pleural effusion

Investigators, Publication	Design	Treatment	Dose per patient (Source & Purity of Talc)	Age, mean (range)	Tumor Type	# Evaluable / # Entered (# procedures)	Success	Success Definition	Symptom (sx) Relief
UNITED STATES STUDIES (cont.)									
Factor Arch Pathol 1975;99:499-502	Case report of a recurrent possible MPE	Thoracentesis & Q; then T instillation w/thoracotomy	400 mg (Q) not reported for (T), single dose of each agent,(not reported)	73	Met. adenocarcinoma vs primary pleural MST; however unable to verify underlying malignancy at autopsy	N/A; case report of 1 patient	0/1	N/A	no
Haupt, Camishion, Templeton & Gibbon JAMA 1960; 172: 918-21. (was updated in Camishon, et al, 1962)	Retrospective report of 19 pts. with MPE	T poudrage and insertion of intercostal tubes	not reported, single dose, (USP, sterile)	56.6 (30-72)	Breast 3, Lung 10, Hypernephroma 1, Anaplastic ca. of lung 2, malignant thymoma 1, rhabdomyosarcoma 1, Malignant MST 1	not reported/19	19/19	No fluid recurrence at last f/u 1-13 mos.	19/19 (dyspnea)
LoCicero Ann Thorac Surg 1993; 56(3): 641-3	Retrospective report of pts. with MPE	T instillation during video-assisted thoracoscopy	5 Gm in 100 ml saline, single dose, (sterilized)	not reported	not reported	not given / > 40	unclear (near 100% success in > 40 pts.)	Not provided	not given
Prorok & Nealson Bull Soc Intern Chir 1968;6: 630-6 (update from Camishion 1962)	Updated report of 29 pts. with MPE	T poudrage and limited thoracotomy	not reported, single dose, (not reported)	57.5 (31-73)	Unknown origin 8, Colon 1, Ovary 1, Breast 1, Malignant thymoma1, Bronchogenic ca. lung 14, Gingiva 1, Stomach 1, Malignant MST 1	not reported/29 (60/63 total experiences)	60/60	no pt. required repeated thoracentesis	60/60 (dyspnea)
Rinaldo, Owens & Rogers J Thorac Cardiovasc Surg 1983;85:523-6	Case report of 3 pts. with MPE	Intrapleural T instillation	10 Gm in 250 ml saline., single dose, (not reported)	35; 81; 37	Lymphocytic lymphoma 1, Rectum 1, Ovary 1	N/A case report of 3 patients	1/3 (N/A)	N/A	none
Sheldbalkar, et al J Thorac Cardiovasc Surg 1971; 61: 492-7	Retrospective report of 28 pts. with MPE	T pleural symphysis	not reported, single dose, (not reported)	60.6 (49-77)	Adenoca. of lung 7, Squamous cell ca. of lung 2, Undifferentiated ca. lung 4, Pleural ca. 1, Adenoca. of breast 5, Squamous cell ca. of pharynx 1, Undifferentiated ca. of ovary 1, Undetermined 3, Lymphosarcoma 1, Transitional cell ca. urinary bladder 1, Renal call ca. kidney 2	27/28	21/27	symptomatic relief, complete expansion of involved lung, complete or nearly complete effusion disappearance so that repeated thoracentesis is not indicated	8/18(cough) 20/26 (SOB) 15/20 (pain) 6/26 (no relief)

SOB = shortness of breath, MST = mesothelioma