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November 28, 2007

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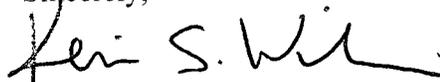
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Re: Our File: 1811-71
For: Bryan Corporation v. Novatech SA
Cancellation No. 92046037
Trademark "STERITALC"
U.S. Registration No.: 3,093,389
Registration Date: May 16, 2006

Dear Sir/Madam:

Please find the attached Registrant Novatech SA's Motion for Summary Judgment Dismissing This Cancellation Proceeding, Memorandum of Law in Support of Registrant's Motion for Summary Judgment, Declaration of Kevin Wilson and the fifteen (15) exhibits attached thereto.

Sincerely,



Kevin S. Wilson

JSE:ksw
Enclosures



11-30-2007

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD**

In the Matter of Trademark Registration No. 3,093,389
Registered on: May 16, 2006

BRYAN CORPORATION,

Petitioner,

v.

NOVATECH SA,

Registrant.

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Cancellation No. 92046037

**REGISTRANT NOVATECH SA's MOTION FOR SUMMARY JUDGMENT
DISMISSING THIS CANCELLATION PROCEEDING**

NOVATECH SA ("Registrant"), moves, under Rule 2.127 of the Trademark Rules of Practice and Federal Rule of Civil Procedure 56, for summary judgment and dismissal of BRYAN CORPORATION's ("Petitioner") petition to cancel Registrant NOVATECH SA's trademark registration No. 3,093,389 for the mark STERITALC. Summary judgment and dismissal is proper in this proceeding because there is no genuine issue of fact and because Registrant is entitled to judgment as a matter of law. Specifically, Petitioner lacks standing to prosecute this Cancellation proceeding against Registrant. In the unlikely event the Board determines that standing exists, Registrant argues in the alternative that there is no genuine issue of material fact and that Registrant is entitled to judgment as a matter of law as to the pleaded grounds of likelihood of confusion and fraud contained within the Petition for Cancellation.

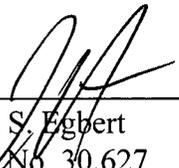
This motion is submitted prior to the commencement of Petitioner's testimony period. This Motion for Summary Judgment is based on the attached Memorandum of Law in Support of Registrant's Motion for Summary Judgment, the attached Declaration of Kevin Wilson, the attached

exhibits, and all pleadings and papers on file. The interests of judicial economy and fairness to both parties are best served by concluding this cancellation at this time. Therefore, It is respectfully requested that this Motion be granted and that the Cancellation proceeding be dismissed with prejudice. Pursuant to Rule 1.127(d) of the Trademark Rules of Practice it is requested that the proceedings be suspended pending the disposition of this motion.

Respectfully submitted,

Date

11.28.07



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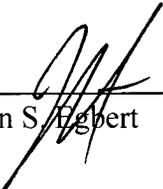
ATTORNEYS FOR REGISTRANT
NOVATECH SA

CERTIFICATE OF SERVICE

I hereby certify that Registrant's Motion for Summary Judgment and all documents attached hereto are being sent by first class mail on this 28th day of November 2007, to the attorney of record for Petitioner at the following address:

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ATTORNEYS FOR PETITIONER
BRYAN CORPORATION



John S. Egbert

CERTIFICATE OF MAILING

I hereby certify that on this 28th day of November 2007, this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to:

United States Patent and Trademark Office
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P.O. Box 1451
Alexandria, VA 22313-1451



John S. Egbert

JSE:ksw
Our File: 1811-71

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD**

In the Matter of Trademark Registration No. 3,093,389
Registered on: May 16, 2006

BRYAN CORPORATION,

Petitioner,

v.

NOVATECH SA,

Registrant.

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Cancellation No. 92046037

**MEMORANDUM OF LAW IN SUPPORT OF REGISTRANT NOVATECH SA's
MOTION FOR SUMMARY JUDGMENT DISMISSING THIS CANCELLATION
PROCEEDING**

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I. PRELIMINARY STATEMENT

Petitioner Bryan Corporation (“Petitioner”) filed its Petition for Cancellation on July 11, 2006 basing its standing on an alleged common law trademark interest in the term “STERILE TALC POWDER”. As will be shown in this Memorandum of Law, Petitioner’s “mark” is actually the generic name for the goods on which it is printed. Therefore, Petitioner cannot have a proprietary interest in the term “STERILE TALC POWDER” and Registrant Novatech SA’s (“Registrant”) Motion for Summary Judgment should be granted and this Cancellation proceeding should be dismissed with prejudice. In the alternative, summary judgment should be entered against Petitioner on each of its claims of likelihood of confusion and fraud on the trademark office.

II. STATEMENT OF FACTS

A. Registrant Novatech SA

Registrant is a société anonyme of France with an address of Voie Antiope, ZI ATHELIA III F-13600 LA CIOTAT FRANCE. Registrant is the sole owner of the “STERITALC” mark in the United States, U.S. Registration No. 3,093,389, which was filed on December 28, 2004 and was registered on May 16, 2006. *See* [Wilson Decl., Ex. 1, U.S. Reg. No. 3,093,389].

B. Petitioner Bryan Corporation

Upon information and belief, Petitioner is a corporation organized under the laws of Massachusetts, with an office and principal place of business at 4 Plympton Street, Woburn, MA 01801. Petitioner does not own a federal or state trademark for the term “STERILE TALC POWDER” but has alleged a common law trademark right in said term. *See* [Pet. for Cancellation, ¶ 7].

C. Bryan Corporation's Petition for Cancellation of the STERITALC Mark

Petitioner filed its Petition for Cancellation on July 11, 2006 challenging the registration of Registrant's STERITALC mark. [Pet. for Cancellation, ¶ 22]. Petitioner based its standing to bring the cancellation action on an alleged existence of a common law trademark right to the term "STERILE TALC POWDER" with a claimed date of first use of at least December 15, 2003. *See id.* at ¶¶ 1-7, 14. Petitioner alleged that Registrant is not entitled to continued use of its "STERITALC" mark due to a likelihood of confusion with the alleged "STERILE TALC POWDER" common law trademark and due to Registrant's alleged fraud on the trademark office. *See id.* at ¶ 22. Notably, Petitioner states in its Petition for Cancellation that "talc powder" is the active ingredient in the products sold under the term "STERILE TALC POWDER" and that Petitioner added the term "sterile" to the term "talc powder" in its New Drug Application when the FDA pointed out that "the active ingredient - talc powder - is sterilized." *See id.* at ¶¶ 3, 5.

D. Novatech SA's Answer

Registrant timely filed its answer on August 2, 2006 denying the allegations of likelihood of confusion and fraud on the trademark office. [Answer to Pet. for Cancellation, ¶ 22]. Registrant also denied that Petitioner had any common law trademark rights to the term "STERILE TALC POWDER", and in fact, affirmatively alleged that "the Petitioner lacks standing in order to bring the present cancellation proceeding." *Id.*

E. Registrant and Petitioners' Motions to Compel Discovery

Both Registrant and Petitioner filed a Motion to Compel Discovery in this proceeding and the Trademark Trial and Appeal Board ruled on the motions on October 3, 2007. *See* [Board's Order

of October 3, 2007]. At this time, both parties have served multiple sets of discovery requests and have provided/received responses and supplemental responses. See [Wilson Decl., ¶ 3].

III. ARGUMENT

A. Summary Judgment Standard

Summary judgment is appropriate where there are no genuine issues of material fact to be tried and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56. The Supreme Court has held that the "[s]ummary judgment procedure is properly regarded not as a disfavored procedural shortcut, but rather as an integral part of the Federal Rules as a whole, which are designed 'to secure the just, speedy and inexpensive determination of every action.'" *Celotex Corp. v. Catrett*, 477 U.S. 317, 327 (1986); see also *Sweats Fashions, Inc. v. Pannill Knitting Co.*, 833 F.2d 1560, 1562 (Fed. Cir. 1987). The evidence must be sufficient for the court to hold that no reasonable trier of fact could find other than for the moving party. *First Nat 'I Bank v. Cities Service Co.*, 391 U.S. 253 (1968). The burden of the moving party may be met by showing "that there is an absence of evidence to support the nonmoving party's case." See *Celotex Corp.*, 477 U.S. at 327 (no requirement that moving party support its motion with affidavits or other similar materials negating the opponent's claim but may be based on nonmovant's failure to make sufficient showing as to its own case on which it has burden of proof).

Summary judgment is proper if the non-movant fails to show a genuine issue of fact concerning an element essential to its case. Fed. R. Civ. P. 56(c); *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-50 (1986). To overcome a summary judgment motion, the non-movant must "do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986). Furthermore, simple conclusory

denials are insufficient to defeat a summary judgment motion. *See, e.g., Wilson Sporting Goods Co. v. Northwestern Golf Co.*, 172 USPQ 182, 184 (T.T.A.B. 1971); *Spin Physicas, Inc. v. Matsushita Elec. Indus. Co.*, 168 USPQ 605 (T.T.A.B. 1970).

Summary judgment is particularly appropriate where, as here, actual testimony is unlikely to address any new or additional evidence which might bear on the critical factual issues or which would reasonably be expected to change the result. *Pure Gold, Inc. v. Syntex (U.S.A.) Inc.*, 222 USPQ 741,743 (Fed. Cir. 1984); *Person's Co., Ltd. v. Christman*, 9 USPQ2d 1477, 1478 (T.T.A.B. 1988), *affd*, 900 F.2d 1565 (Fed. Cir. 1990). There is no basis to believe that further proceedings can possibly controvert the fact that the term "STERILE TALC POWDER" is the generic name for the products on which the mark is displayed and that there can therefore be no likelihood of confusion.

B. Petitioner Lacks Standing to Bring This Cancellation Proceeding

1. Elements of Standing

Standing is a threshold issue that must be proven by a plaintiff in every inter partes case. *Ritchie v. Simpson*, 170 F.3d 1092, 50 USPQ2d 1023 (Fed. Cir. 1999); *Lipton Industries, Inc. v. Ralston Purina Co.*, 213 USPQ 185 (CCPA 1982). Therefore the Board should first turn to the question of whether Registrant has shown that there is no genuine issue of material fact as to Petitioner's lack of standing to bring this cancellation proceeding.

The purpose of the standing requirement, which is directed solely to the interest of the plaintiff, is to prevent litigation when there is no real controversy between the parties. *Lipton Industries, Inc.*, 213 USPQ at 189. In the case of a petition to cancel, the standing requirement of a plaintiff has its statutory basis in Section 14 of the Trademark Act which provides that "any person

who believes he is or will be damaged . . . by the registration of a mark on the principal register” may file a petition to cancel.

To establish standing, it must be shown that the plaintiff has a “real interest” in the outcome of a proceeding; that is, plaintiff must have a direct and personal stake in the outcome of the cancellation. *Ritchie*, 50 USPQ2d at 1023. Facts regarding the legitimate personal interest are a part of the plaintiff’s case and must be proved. *Lipton Industries, Inc.*, 213 USPQ at 189. In addition, plaintiff must have a reasonable basis for its belief that it would be damaged by the registration to establish standing. *Chemical New York Corp. v. Conmar Form Systems, Inc.*, 1 USPQ2d 1139, 1142 (TTAB 1986). When pleading allegations relative to standing, the plaintiff’s belief in damage must have some reasonable basis in fact. *Universal Oil Products Co. v. Rexall Drug and Chemical Co.*, 463 F.2d 1122, 174 USPQ 458, 459-60 (CCPA 1972).

2. Petitioner Cannot Satisfy the Standing Requirements

a. Petitioner Has No Ownership Interest in the Generic “STERILE TALC POWDER” Term

The Board may determine that a term is not proprietary on summary judgment. *Teleflora, Inc. v. Florists Transworld Delivery Association*, 217 USPQ 1081 (C.D.Cal. 1981); *Data National Corporation v. Bell South Corporation*, 18 USPQ2d 1862 (TTAB 1994), *aff’d.*, 60 F.3d 1565 (Fed. Cir. 1995). In this proceeding, there is no genuine issue that the “STERILE TALC POWDER” term is in fact generic, inasmuch as Petitioner is using the term generically, and the evidence below clearly shows that this term is generic.

Generic terms are terms that the relevant purchasing public understands primarily as the common or class name for the goods or services. *In re Dial-A-Mattress Operating Corp.*, 240 F.3d

1341, 57 USPQ2d 1807, 1811 (Fed. Cir. 2001); *In re American Fertility Society*, 188 F.3d 1341, 1346, 51 USPQ2d 1832, 1836 (Fed. Cir. 1999); TMEP § 1209.01(c). “A generic term cannot be exclusively appropriated as a common law trademark or as a statutory trademark, regardless of its length of use and promotion. [citation omitted]. A generic term . . . is by its very nature, a term that applies equally to all goods, services, or concerns within a group and, as such, cannot serve to identify any one product, service or company in that group to the exclusion of others and therefore bestow a proprietary right therein upon any one user thereof.” *Fluid Energy Processing & Equipment v. Fluid Energy, Inc.*, 212 USPQ 28, 35-36 (TTAB 1981).

There is a two-step inquiry that is used to determine whether a term is generic: 1) What is the genus of goods or services at issue? and 2) Does the relevant public understand the term primarily to refer to that genus of goods or services? *H. Marvin Ginn Corp. v. Int’l Assoc. Of Fire Chiefs, Inc.*, 228 USPQ 528, 530 (Fed. Cir. 1986). Therefore, a term should be considered generic if the relevant purchasing public understands that the “STERILE TALC POWDER” designation primarily refers to genus of the goods. *See id.*

Petitioner answers the first step of the inquiry in its Petition for Cancellation when it explains that the alleged “STERILE TALC POWDER” common law mark is used on goods consisting of talc powder that is sterilized and used as a sclerosing agent for the prevention of recurrent malignant pleural effusion (“MPE”). *See* [Pet. for Cancellation, ¶ 1, 7]. The second step of the inquiry can be answered with evidence showing whether the relevant public understands the “STERILE TALC POWDER” term to primarily refer to the above-mentioned goods. *See H. Marvin Ginn Corp.*, 228 USPQ at 530.

The *National Cancer Institute* online Dictionary of Cancer Terms defines “sterile talc powder” as “a mineral, usually used in powdered form . . . used to prevent pleural effusions . . .” [Wilson Decl., Ex. 2 at p.1, 2]. Furthermore, the *Dana-Farber Cancer Institute* online Dictionary of Medical Terms definition of “talc” is “a mineral, usually used in powdered form. In cancer treatment, sterile talc is used to prevent pleural effusions . . . Also called sterile talc powder.” [Wilson Decl., Ex. 3 at p.2]. Such online dictionaries of various medical terms exist to help the layperson understand common terms in the clinical trial and general practice environments and show how the relevant public would understand the term. *See id* at 1.

Traditional medical reference books would lead physicians prescribing the drug and pharmacists dispensing the drug, members of the relevant public, to conclude that “STERILE TALC POWDER” is the generic term for Petitioner’s goods. *See H. Marvin Ginn Corp.*, 228 USPQ at 530. Generic terms are considered “the ultimate in descriptiveness.” *Id.* When the definitions of “sterile”, “talc”, and “powder,” as found in a general medical dictionary, are compared to the goods at issue in this proceeding, it is clear that Petitioner has chosen the ultimate descriptive term. *See* [Wilson Decl., Ex. 4, *Stedman’s Medical Dictionary* 1435, 1697, 1784 (27th ed. 2000)]. In addition, The American Society of Health-System Pharmacists’ *AHFS Drug Information* publication includes an entry for “talc” explaining that the drug is a “sclerosing agent” administered by aerosol or slurry via a “commercially available talc powder.” *See* [Wilson Decl., Ex. 5, *AHFS Drug Information* 1801 (2007)]. The entry goes on to explain that such commercially available talc powder is “sterile.” *See id.* Thoracic surgeons consistently refer to “sterile talc powder”, “sterile talc”, or “talc powder” as a generic term when referring to the treatment of “malignant pleural effusion” using Video-Assisted Thoracoscopic Surgery (VATS). [Wilson Decl., Ex. 6, VATS Article, p.2]; [Wilson Decl., Ex. 7,

CA Danby et. al., *Video-assisted talc pleurodesis for malignant pleural effusions utilizing local anesthesia and I.V. sedation*, Chest 113:740 (1998)].

Many other medical journal entries use “STERILE TALC POWDER” to refer to the genus of goods at issue in this proceeding. One such article refers to the varying particle size of “sterile talc” and how graded “sterile talc” creates less lung inflammation than mixed “sterile talc.” [Wilson Decl., Ex. 8, Nick A. Maskel et. al., *Randomized Trials Describing Lung Inflammation after Pleurodesis with Talc of Varying Particle Size*, American Journal of Respiratory and Critical Care Medicine 170: 377-78 (2004)]. A journal article in 1997, before Petitioner’s claimed date of first use, compares the results of four different methods of pleurodesis after introduction into ten animal subjects. See [Wilson Decl., Ex. 9, Henri G. Colt et. al., *A Comparison of Thoracoscopic Talc Insufflation, Slurry, and Mechanical Abrasion Pleurodesis*, Chest 111: 442 (1997)]. The study refers to a sclerosing agent as “asbestos- free [USP]-approved sterile talc powder.” *Id.* at 443. This list of journal entries is not exhaustive, and indeed, examples of generic use of the term “sterile talc powder” can be found in a number of other journal entries. See, e.g., [Wilson Decl., Ex. 10, Jean-Regis Viallat et. al., *Thoracoscopic Talc Poudrage Pleurodesis for Malignant Effusions*, Chest 110: 1391 (1996) (referring to “sterile talc powder” available in Europe); see also [Wilson Decl., Ex. 11, Julius P. Janssen et. al., *Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study*, The Lancet, 369: 1536 (2007) (referring to “sterile graded talc” and “talc powder”)].

Interestingly, Petitioner has used the term “STERILE TALC POWDER” in a generic manner in connection with its “SCLEROSOL” brand drug. “SCLEROSOL”, a sterile talc powder that in single use, pressurized spray canister form, has had “sterile talc powder” published as the generic

name for the drug. *See* [Wilson Decl., Ex. 12, USFDA Product Label Information, p.1]; [Wilson Decl., Ex. 13, *The NDA Pipeline* Sec. VI-29 (17th ed. 1998) (referring to Registrant's "STERITALC" generic name as "sterile talc" and Petitioner's "SCLEROSOL" generic name as "sterile talc powder")]. In the FDA Center for Drug Evaluation and Research's report to the nation regarding drugs, the "STERILE TALC POWDER" drug for which Petitioner bases its claim of common law rights has its generic drug name listed as "sterile talc powder." [Wilson Decl., Ex. 14, *CDER Report to the Nation* 13, 16 (2003) (showing the generic name of the drug to the left of the "brand" name in parenthesis)]. It is quite clear, when comparing Petitioner's "STERILE TALC POWDER" drug with other drugs within Chapter One of the *Report to the Nation*, that Petitioner simply did not choose a traditional brand name for its drug. *See id.* at 14-18 (showing for example the brand name PLENAXIS used on the generic drug abarelix and the brand name CIALIS used on the generic drug tadalafil).

b. Petitioner Does Not Have the Sufficient Personal Interest in the "STERILE TALC POWDER" Term Required to Demonstrate Standing

Due to the generic nature of the term "STERILE TALC POWDER", there is no genuine issue of material fact that Petitioner lacks a legitimate commercial interest in the mark and, as a result, Petitioner's belief in damage resulting from an alleged likelihood of confusion between the asserted mark and Registrant's mark is wholly without merit. This motion, and the evidence submitted herewith, shows that Petitioner cannot establish a right to use the "STERILE TALC POWDER" mark. A generic mark cannot serve to identify any one product or bestow a proprietary right thereto. *See Fluid Energy Processing & Equipment*, 212 USPQ at 35-36. As a result, Petitioner, as a matter of law, has no standing to maintain this proceeding and cannot prevail herein. *See, e.g., Coup v.*

Vornado Inc., 9 USPQ2d 1824 (TTAB 1988) (stating that Petitioner's failure to prove standing warrants grant of summary judgment for Registrant).

3. The Board Has Granted Summary Judgment For Lack of Standing in a Proceeding With a Similar Fact Situation

In *Rudolph Wild GMBH & Co. v. The Coca-Cola Co.*, the Board granted summary judgment for Applicant after determining Opposer lacked proprietary rights in the generic term "pouch." [Wilson Decl., Ex. 15, *Rudolph Wild GMBH & Co. v. The Coca-Cola Co.*, 1999 TTAB LEXIS 284, 8-9]. The Applicant submitted evidence of the generic nature of the term "pouch" to the Board in helping them reach such a decision. *See id.* at 6. The Board considered evidence such as the appearance of the term on Opposer's packaging in a generic context, media usage of the term, and dictionaries including the term to come to the conclusion that there was no genuine issue that the term was in fact generic and, therefore, no genuine issue concerning Opposer's lack of proprietary rights in the term. *See id.* at 5, 8-9. In the case at bar, Registrant has submitted similar types of evidence showing the generic nature of the term "STERILE TALC POWDER" and has supplemented such evidence with various medical journal entries showing generic use of the term. Such evidence should enable the Board to come to the same conclusions as those in the *Rudolph Wild GMBH & Co.* proceeding.

C. Registrant Is Entitled to Judgment as a Matter of Law as to the Pleaded Ground of Likelihood of Confusion

In the event that the Board determines that Petitioner has standing, Registrant is still entitled to summary judgment as to the pleaded ground of likelihood of confusion. It has been held that a party wishing to attack the registration of a mark based on likelihood of confusion must prove that he has "propriety rights in the term he relies upon to demonstrate likelihood of confusion as to

source. . . ." See *Otto Roth & Co. v. Universal Foods Corp.*, 209 USPQ 40, 43 (CCPA 1981). However, as discussed above, the "STERILE TALC POWDER" term relied upon here is the generic name of the goods in question, and therefore, such a term cannot be the subject of proprietary rights. See *Fluid Energy Processing & Equipment*, 212 USPQ at 35-36. Since it is impossible for there to be a likelihood of confusion with Petitioners' generic mark, there is no genuine issue of material fact and that Registrant is entitled to judgment as a matter of law as to the pleaded grounds of likelihood of confusion. See also [Wilson Decl., Ex. 15, *Rudolph Wild GMBH & Co.*, 1999 TTAB LEXIS 284 at 9 (stating "there can logically be no likelihood of confusion unless opposer has some rights in an asserted term . . .")].

D. Registrant Is Entitled to Judgment as a Matter of Law as to the Plead Ground of Fraud

In the event that the Board determines that Petitioner has standing, Registrant is still entitled to judgment as a matter of law as to the pleaded ground of fraud. The Board is governed by the following principles of what constitutes fraud in matters involving the Trademark Office:

"Fraud implies some intentional deceitful practice or act designed to obtain something to which the person practicing such deceit would not otherwise be entitled. Specifically, it involves a willful withholding from the Patent and Trademark Office by an applicant or registrant of material information or facts which, if disclosed to the Office, would have resulted in the disallowance of the registration sought or to be maintained. Intent to deceive must be "willful." If it can be shown that the statement was a "false misrepresentation" occasioned by an "honest" misunderstanding, inadvertence, negligent omission or the like rather than one made with a willful intent to deceive, fraud will not be found. Fraud, moreover, will not lie if it can be proven that the statement, though false, was made with a reasonable and honest belief that it was true or that the false statement is not material to the issuance or maintenance of the registration. It thus appears that the very nature of the charge of fraud requires that it be proven "to the hilt" with clear and convincing evidence. There is no room for speculation, inference or surmise and obviously, any doubt must be resolved against the charging party."

Smith International, Inc. v. Olin Corp., 209 USPQ 1033, 1043-44 (TTAB 1981), *see also First Int'l Services Corp. v. Chuckles, Inc.*, 5 USPQ2d 1628 (TTAB 1986). Petitioner can offer no evidence, much less "clear and convincing evidence," in support of its conclusory statement that "Registrant procured registration of the Re-filed mark by false means and/or by knowingly and willfully making false and/or fraudulent declarations to the PTO" that Registrant was "entitled to use the mark in commerce." *See* [Petitioner's Trial Brief, ¶ 13]. In addition, Petitioner can offer no evidence showing intentional deceit by Registrant and no evidence that the alleged false statement was material to the issuance of the registration. *See id.* The burden of proof lies in the Petitioner to prove its claim of fraud, therefore, Summary Judgment is proper if Registrant shows "that there is an absence of evidence" supporting Petitioner's claim. *See Celotex Corp.*, 477 U.S. at 327.

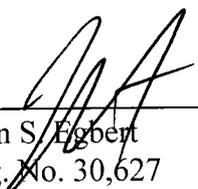
IV. CONCLUSION

For the foregoing reasons, Registrant Motion for Summary Judgment should be granted, and the Petition for Cancellation should be dismissed in all respects.

Respectfully submitted,

Date

11-28-07



John S. Egbert
Reg. No. 30,627
L. Jeremy Craft

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Houston, Texas 77002
Tel: (713)224-8080
Fax: (713)223-4873

ATTORNEYS FOR REGISTRANT
NOVATECH SA

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD**

In the Matter of Trademark Registration No. 3,093,389
Registered on: May 16, 2006

BRYAN CORPORATION,

Petitioner,

v.

NOVATECH SA,

Registrant.

§
§
§
§
§
§
§
§

Cancellation No. 92046037

DECLARATION OF KEVIN S. WILSON

1. “My name is Kevin S. Wilson. I am over the age of eighteen, have never been convicted of a felony, and am fully qualified to make this Declaration. I file this Declaration under 28 U.S.C. 1746.

2. I am an attorney with the office of Egbert Law Offices, PLLC, attorneys for NOVATECH SA (“Registrant”), in the above-entitled and numbered opposition proceeding. I have personal knowledge of the matters contained in this declaration. I submit this affidavit in support of Registrant’s Motion for Summary Judgment.

3. Petitioner has served three sets of written discovery requests and provided/received responses and supplemental responses to the same. Registrant has served two sets of written discovery requests and provided/received responses and supplemental responses to the same. On November 5, 2007, Registrant filed its Supplemental Answers to Petitioner’s Second Set of Interrogatories (No. 5) in accordance with the Board’s October 3, 2007 Order. Although each party has a duty to supplement written discovery if it becomes necessary, to the best of my knowledge and belief there are no outstanding written discovery issues in this proceeding.

4. Registrant’s STERITALC mark, U.S. Reg. No. 3,093,389, was registered on May 16, 2006 and covers “pharmaceutical products containing talcum powder, namely, pharmaceutical preparations containing talcum powder for the treatment of malignant pleural effusions, pneumothorax, mesothelioma, skin disorders, cancer, and gout; sanitary products containing talcum powder, namely sanitary pads, sanitary napkins, and sanitary preparations for medical use all containing talcum powder; talcum powder for medical use, namely, medicated talcum powder. Attached hereto as **Exhibit 1** is a true and correct copy of the TARR printout and Assignment page showing the Registration for said mark.

5. Attached hereto as **Exhibit 2** is a true and correct copy of the Definition of “sterile talc powder” as defined in the NCI (National Cancer Institute) Dictionary of Cancer Terms. I personally printed out a copy of the pages on November 27, 2007. The first page of the exhibit was downloaded from <http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=507639> and the second page of the exhibit is a “printer-friendly” copy that was downloaded from <http://www.cancer.gov/Templates/db_alpha.aspx?print=1&cdrid=507639>.

6. Attached hereto as **Exhibit 3** is a true and correct copy of the portion of a Dictionary of Medical Terms that includes the term “talc.” The source of the online dictionary is the Dana-Farber Cancer Institute. Also included is a short history of the Dana-Farber Cancer Institute, one of the world’s premier cancer centers based out of Boston, Massachusetts. I personally printed out a copy of the attached documents on November 27, 2007. The first two pages of the exhibit were downloaded from <<http://www.dana-farber.org/can/dictionary/?index=t>> and the last page of the exhibit was downloaded from <<http://www.dana-farber.org/abo/history/>>.

7. Attached hereto as **Exhibit 4** is a true and correct copy of *Stedman’s Medical Dictionary* 1435, 1697, 1698, 1784 (27th ed. 2000). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

8. Attached hereto as **Exhibit 5** is a true and correct copy of *AHFS Drug Information* 1801 (2007). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

9. Attached hereto as **Exhibit 6** is a true and correct copy of a portion of the University of Southern California Keck School of Medicine webpage discussing a Video-Assisted Thoracoscopic Surgery (VATS). I personally printed out a copy of the attached document on November 21, 2007. The exhibit was downloaded from <<http://www.cts.usc.edu/videoassistedthoroscopicsurgery.html>>.

10. Attached hereto as **Exhibit 7** is a true and correct copy of CA Danby et. al., *Video-assisted talc pleurodesis for malignant pleural effusions utilizing local anesthesia and I.V. sedation*, *Chest* 113:740 (1998). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

11. Attached hereto as **Exhibit 8** is a true and correct copy of Nick A. Maskel et. al., *Randomized Trials Describing Lung Inflammation after Pleurodesis with Talc of Varying Particle Size*, *American Journal of Respiratory and Critical Care Medicine* 170: 377-78 (2004). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

12. Attached hereto as **Exhibit 9** is a true and correct copy of Henri G. Colt et. al., *A Comparison of Thoracoscopic Talc Insufflation, Slurry, and Mechanical Abrasion Pleurodesis*,

Chest 111: 442 (1997). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

13. Attached hereto as **Exhibit 10** is a true and correct copy of Jean-Regis Viallat et. al., *Thoracoscopic Talc Poudrage Pleurodesis for Malignant Effusions*, Chest 110: 1391 (1996). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

14. Attached hereto as **Exhibit 11** is a true and correct copy of Julius P. Janssen et. al., *Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study*, The Lancet, 369: 1536 (2007). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

15. Attached hereto as **Exhibit 12** is a true and correct copy of the U.S. Food and Drug Administrations product label details for Bryan Corporation's SCLEROSOL drug. I personally printed out a copy of the attached document on November 21, 2007. The exhibit was downloaded from <<http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=talc>>.

16. Attached hereto as **Exhibit 13** is a true and correct copy of *The NDA Pipeline* Sec. VI-29 (17th ed. 1998). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

17. Attached hereto as **Exhibit 14** is a true and correct copy of *CDER Report to the Nation*, Chapter 1-Drug Review (2003). The proffered material is from a printed publication, as described in 37 CFR § 2.122(e), and is therefore self-authenticating evidence.

18. Attached hereto as **Exhibit 15** is a true and correct copy of *Rudolph Wild GMBH & Co. v. The Coca-Cola Co.*, 1999 TTAB LEXIS 284 (Opposition No. 99,709).

I declare under the penalty of perjury under the laws of the United States of America that the foregoing statements are true and correct."

Executed on the 28th day of November 2007.



Kevin S. Wilson

Exhibit 1

Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2007-11-27 13:31:24 ET

Serial Number: 79008374 Assignment Information Trademark Document Retrieval

Registration Number: 3093389

Mark

STERITALC

(words only): STERITALC

Standard Character claim: Yes

Current Status: A cancellation proceeding has been filed at the Trademark Trial and Appeal Board and is now pending.

Date of Status: 2006-07-15

Filing Date: 2004-12-28

Transformed into a National Application: No

Registration Date: 2006-05-16

Register: Principal

Law Office Assigned: LAW OFFICE 102

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: L20 -TMEG Law Office 102

Date In Location: 2006-01-27

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. NOVATECH SA

Address:

NOVATECH SA
Voie Antiope, ZI ATHELIA III F-13600 LA CIOTAT
France

Legal Entity Type: société anonyme
State or Country Where Organized: France

GOODS AND/OR SERVICES

International Class: 005

Class Status: Active

Pharmaceutical products containing talcum powder, namely, pharmaceutical preparations containing talcum powder for the treatment of malignant pleural effusions, pneumothorax, mesothelioma, skin disorders, cancer, and gout; sanitary products containing talcum powder, namely, sanitary pads, sanitary napkins, and sanitary preparations for medical use all containing talcum powder; talcum powder for medical use, namely, medicated talcum powder

Basis: 66(a)

First Use Date: (DATE NOT AVAILABLE)

First Use in Commerce Date: (DATE NOT AVAILABLE)

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

International Registration Number: 0667961

International Registration Date: 1997-01-13

Priority Claimed: No

Date of Section 67 Priority Claim: (DATE NOT AVAILABLE)

International Registration Status: Request For Extension Of Protection Processed

Date of International Registration Status: 2005-03-03

International Registration Renewal Date: 2017-01-13

Notification of Designation Date: 2005-03-03

Date of Automatic Protection: 2006-09-03

Date International Registration Cancelled: (DATE NOT AVAILABLE)

First Refusal: Yes

PROSECUTION HISTORY

2007-03-29 - International Registration Renewed

2007-01-11 - Final Disposition Notice Sent To IB

2007-01-11 - Final Disposition Processed

2006-11-20 - Final Disposition Notice Created, To Be Sent To IB

2006-08-17 - Notification Of Possible Opposition - Processed By IB

2006-08-03 - Notification Of Possible Opposition Sent To IB

2006-08-03 - Notification Of Possible Opposition Created, To Be Sent To IB
2006-07-15 - Cancellation Instituted No. 999999
2006-05-16 - Registered - Principal Register
2006-02-21 - Published for opposition
2006-02-01 - Notice of publication
2006-01-09 - PAPER RECEIVED
2006-01-07 - Law Office Publication Review Completed
2006-01-06 - Assigned To LIE
2006-01-03 - Approved for Pub - Principal Register (Initial exam)
2006-01-03 - Examiner's Amendment Entered
2006-01-03 - EXAMINERS AMENDMENT E-MAILED
2006-01-03 - Examiners Amendment - Written
2005-12-15 - Teas/Email Correspondence Entered
2005-12-11 - Communication received from applicant
2005-12-11 - TEAS Response to Office Action Received
2005-12-11 - TEAS Change Of Correspondence Received
2005-08-18 - Refusal Processed By IB
2005-08-03 - Non-Final Action Mailed - Refusal Sent To IB
2005-08-03 - Non-Final Action (Ib Refusal) Prepared For Review
2005-08-02 - Non-Final Action Written
2005-08-01 - Assigned To Examiner
2005-03-04 - New Application Entered In Tram
2005-03-03 - Sn Assigned For Sect 66a Subseq Desig From IB

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For Serial Number: 79008374

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Exhibit 2



In English | En español

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- [NCI Home](#)
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- [Clinical Trials](#)
- [Cancer Statistics](#)
- [Research & Funding](#)
- [News](#)
- [About NCI](#)

Dictionary of Cancer Terms



[In English](#) | [En español](#)

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[In English](#) | [En español](#)

sterile talc powder (STER-il...)

A mineral, usually used in a powdered form. In cancer treatment, sterile talc powder is used to prevent pleural effusions (an abnormal collection of fluid in the space between the lungs and the chest wall). Sterile talc powder is inserted into the space, causing it to close up, so fluid cannot collect there. Also called talc.

Previous Definitions: [stereotactic radiosurgery](#), [stereotaxic radiation therapy](#), [stereotaxic radiosurgery](#), [stereotaxis](#), [sterile](#)

Next Definitions: [sternum](#), [steroid cream](#), [steroid drug](#), [steroid metabolism gene](#), [steroid therapy](#)

Questions about cancer?

• [1-800-4-CANCER](#)

NCI Highlights

- [Report Finds Cancer Death Rate Decline Doubling](#)
- [The Nation's Investment in Cancer Research FY 2008](#)
- [Statement on Fiscal Year 2008 Budget Request](#)
- [President's Cancer Panel Annual Report: 2006-2007](#)
- [Cancer Trends Progress Report: 2005 Update](#)
- [NCAB Working Group Report on Biomedical Technology](#)
- [Past Highlights](#)

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A Service of the National Cancer Institute





Dictionary of Cancer Terms

[Send to Printer](#)

sterile talc powder (STER-il...)

A mineral, usually used in a powdered form. In cancer treatment, sterile talc powder is used to prevent pleural effusions (an abnormal collection of fluid in the space between the lungs and the chest wall). Sterile talc powder is inserted into the space, causing it to close up, so fluid cannot collect there. Also called talc.

Previous Definitions: stereotactic radiosurgery, stereotaxic radiation therapy, stereotaxic radiosurgery, stereotaxis, sterile

Next Definitions: sternum, steroid cream, steroid drug, steroid metabolism gene, steroid therapy

Exhibit 3



Dictionary of Medical Terms

Although not an exhaustive list of medical terminology, the purpose of this glossary is to help the layperson with common terms in the clinical trial and general practice environments.

#ABCDEFGHIJKLMNOPQRSTUVWXYZ

T

T cell

One type of white blood cell that attacks virus-infected cells, foreign cells, and cancer cells. T cells also produce a number of substances that regulate the immune response. Also called T lymphocyte.

T lymphocyte

One type of white blood cell that attacks virus-infected cells, foreign cells, and cancer cells. T lymphocytes also produce a number of substances that regulate the immune response. Also called T cell.

t test

A statistical test that is used to find out if there is a real difference between the means (averages) of two different groups. It is sometimes used to see if there is a significant difference in response to treatment between groups in a clinical trial.

T-3

A thyroid hormone. Also called triiodothyronine or liothyronine sodium.

T-cell acute lymphoblastic leukemia (...LIM-foh-BLAS-tik loo-KEE-mee-uh)

A type of leukemia (blood cancer) in which too many T-cell lymphoblasts (immature white blood cells) are found in the blood and bone marrow. Also called T-cell acute lymphocytic leukemia and precursor T-lymphoblastic leukemia.

T-cell acute lymphocytic leukemia (...LIM-foh-SIH-tik loo-KEE-mee-uh)

A type of leukemia (blood cancer) in which too many T-cell lymphoblasts (immature white blood cells) are found in the blood and bone marrow. Also called T-cell acute lymphoblastic leukemia and precursor T-lymphoblastic leukemia.

T-cell depletion (... sel dih-PLÉE-shun)

Treatment to destroy T cells, which play an important role in the immune response. Elimination of T cells from a bone marrow graft from a donor may reduce the chance of an immune reaction against the recipient's tissues.

T-cell lymphoma (... sel lim-FOH-muh)

A disease in which certain cells of the lymph system (called T lymphocytes) become cancerous.

T-lymphoblastic lymphoma (LIM-foh-BLAS-tik lim-FOH-muh)

A type of non-Hodgkin's lymphoma in which too many T-cell lymphoblasts (immature white blood cells) are found in the lymph nodes and spleen. It is most common in young men. Also called precursor T-lymphoblastic lymphoma.

T138067

An anticancer drug that belongs to the family of drugs called mitotic inhibitors. It inhibits the growth of cancer cells by preventing cell division.

T4

A hormone that is made by the thyroid gland and contains iodine. T4 increases the rate of chemical reactions in cells and helps control growth and development. T4 can also be made in the laboratory and is used to treat thyroid disorders. Also called thyroxine, L-3,5,5'-tetraiodothyronine, and thyroxin.

T4N5 liposomal lotion

Enzyme lotion used in treating xeroderma pigmentosum.

T900607

A substance that is being studied in the treatment of cancer. It belongs to the family of drugs called tubulin-binding agents.

TAC-101

A substance that is being studied in the treatment of cancer. It belongs to the families of drugs called synthetic retinoids and angiogenesis inhibitors.

tachycardia

Rapid beating of the heart, usually defined as greater than 100 beats per minute.

tachypnea

Rapid breathing.

tacrolimus

A drug used to help reduce the risk of rejection by the body of organ and bone marrow transplants.

TAG-72 antigen

A protein/sugar complex found on the surface of many cancer cells, including breast, colon, and pancreatic cells.

tai chi (ty chee)

A form of traditional Chinese mind/body exercise and meditation that uses slow sets of body movements and controlled breathing. Tai chi is done to improve balance, flexibility, muscle strength, and overall health.

tailbone

The small bone at the bottom of the spine. It is made up of 3-5 fused bones. Also called coccyx.

talabostat (tal-AB-oh-stat)

A substance being studied in the treatment of cancer, including certain types of lung, pancreas, and brain cancer. Talabostat may help the immune system block the growth of cancer cells. It may also increase the growth of new blood cells. It is a type of enzyme inhibitor. Also called talabostat mesylate and PT-100.

talabostat mesylate (tal-AB-oh-stat MEH-zih-layt)

A substance being studied in the treatment of cancer, including certain types of lung, pancreas, and brain cancer. Talabostat mesylate may help the immune system block the growth of cancer cells. It may also increase the growth of new blood cells. It is a type of enzyme inhibitor. Also called talabostat and PT-100.

talampanel

A substance that is being studied in the treatment of brain tumors and other brain disorders, such as epilepsy and Parkinson's disease. It belongs to the family of drugs called AMPA receptor antagonists.

talaporfin sodium (tal-uh-PORE-fin SOH-dee-um)

A drug used in photodynamic therapy. When absorbed by cancer cells and exposed to light, the drug becomes active and kills the cancer cells.

talc

A mineral, usually used in a powdered form. In cancer treatment, sterile talc is used to prevent pleural effusions (an abnormal collection of fluid in the space between the lungs and the chest wall). Talc is inserted into the space, causing it to close up, so fluid cannot collect there. Also called sterile talc powder.

talk therapy (...THAYR-uh-pee)

Treatment of mental, emotional, personality, and behavioral disorders using methods such as discussion, listening, and counseling. Also called psychotherapy.

talotrexin (tal-oh-TREX-in)

A substance that is being studied in the treatment of leukemia and some other types of cancer. It belongs to the family of drugs called antifolates.

tamoxifen (tuh-MOK-sih-FEN)

A drug used to treat certain types of breast cancer in women and men. It is also used to prevent breast cancer in women who have had ductal carcinoma in situ (abnormal cells in the ducts of the breast) and are at a high risk of developing breast cancer. Tamoxifen is also being studied in the treatment of other types of cancer. It blocks the effects of the hormone estrogen in the breast. Tamoxifen belongs to the family of drugs called antiestrogens. Also called tamoxifen citrate and Nolvadex.

tamoxifen citrate (tuh-MOK-sih-FEN SIH-trayt)

A drug used to treat certain types of breast cancer in women and men. It is also used to prevent breast cancer in women who have had ductal carcinoma in situ (abnormal cells in the ducts of the breast) and are at a high risk of developing breast



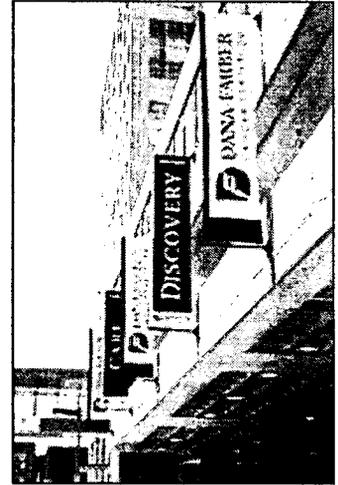
History

In 1947, the late Sidney Farber, MD, founded a Children's Cancer Research Foundation dedicated to providing children with cancer with compassionate, state-of-the-art treatment and simultaneously developing the cancer preventatives, treatments, and cures of the future. The Institute officially expanded its programs to include patients of all ages in 1969, and in 1974 became known as the Sidney Farber Cancer Center in honor of its founder. The long-term support of the Charles A. Dana Foundation was acknowledged by incorporating the Institute under its present name in 1983.

Today, the Institute employs about 3,000 people supporting more than 150,000 patient visits a year, is involved in some 200 clinical trials, and is internationally renowned for its blending of research and clinical excellence. The Institute's expertise in these two arms of the fight to eradicate cancer uniquely positions it to bring novel therapies that prove beneficial and safe in the laboratory setting into clinical use.

Dana-Farber Cancer Institute is a principal teaching affiliate of Harvard Medical School, a federally designated Center for AIDS Research, and a founding member of the Dana-Farber/Harvard Cancer Center (DF/HCC), a federally designated comprehensive cancer center. Providing advanced training in cancer treatment and research for an international faculty, the Institute conducts community-based programs in cancer prevention, detection, and control throughout New England, and maintains joint programs with other Boston institutions affiliated with Harvard Medical School and the Partners Health Care System, including Brigham & Women's Hospital, Children's Hospital, and Massachusetts General Hospital.

Dana-Farber Cancer Institute is supported by the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the generous support of numerous foundations and individuals, who contribute to the Institute's individual research and clinic programs or to the Jimmy Fund, the principal charity of the Institute named for one of its child patients.



- ▶ [Who was Sidney Farber, MD?](#)
- ▶ [Milestones in the history of Dana-Farber Cancer Institute and the Jimmy Fund](#)
- ▶ [Advances in Patient Care and Research at Dana-Farber](#)
- ▶ [Important Developments in Dana-Farber's AIDS Research Program](#)

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Video (4:05)

PBS HealthWeek profiles Dr.Farber's pioneering role in cancer treatment and research. (Nov. 23, 1999)

- 📧 [56k Dialup](#)
- 📧 [Broadband](#)

Exhibit 4

STEDMAN'S Medical Dictionary

27th Edition

Illustrated in Color



LIPPINCOTT WILLIAMS & WILKINS

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ranging from 10,000 to 70,000; used as a dispersing and suspending agent; p. with molecular weight between 20,000 and 40,000 has been used as a plasma extender. It is not metabolized, but is excreted unchanged by the kidney. SYN polyvidone, polyvinylpyrrolidone.

po-vi-done-io-dine. SYN povidone iodine.

pow-der. 1. A dry mass of minute separate particles of any substance. 2. In pharmaceuticals, a homogenous dispersion of finely divided, relatively dry, particulate matter consisting of one or more substances; the degree of fineness of a p. is related to passage of the material through standard sieves. 3. A single dose of a powdered drug, enclosed in an envelope of folded paper. 4. To reduce a solid substance to a state of very fine division. [Fr. *poudre*; L. *pulvis*]

bleaching p., SYN chlorinated lime.

pow-er (pō'wēr). 1. In optics, the refractive vergence of a lens. 2. In physics and engineering, the rate at which work is done. 3. The exponent of a number or expression that provides the number of times that number has to be multiplied by itself.

back vertex p., the effective p. of a lens as measured from a surface toward the eye; a standard for measurement of ophthalmic lenses.

carbon dioxide combining p., a measurement of the total CO₂ that can be bound as HCO₂ at a PCO₂ of 40 mmHg at 25°C by serum, plasma, or whole blood.

equivalent p., the p. equal to an infinitely thin lens as measured on an optical bench.

resolving p., (1) definition of a lens; in a microscope objective lens it is calculated by dividing the wavelength of the light used by twice the numerical aperture of the objective. SEE ALSO definition; (2) analogies to other modalities, e.g., two-point discrimination in neurologic examination. Commonly misinterpreted as random error, although it has none of its properties. (3) SYN resolution (2).

statistical p., in Neyman-Pearson hypothesis testing, the probability of rejecting the null hypothesis when it is false; the complement of an *error* of the second kind.

pox (poks). 1. An eruptive disease, usually qualified by a descriptive prefix; e.g., smallpox, cowpox, chickenpox. See the specific term. 2. Archaic or colloquial term for syphilis. [var. of pl. *pocks*]

Kaffir p., SYN alastrim.

Pox-vir-i-dae (poks-vir'i-dē). A family of large complex viruses, with a marked affinity for skin tissue, that are pathogenic for humans and other animals. Virions are large, up to 250 × 400 nm, and enveloped (double membranes). Replication occurs entirely in the cytoplasm of infected cells. Capsids are of complex symmetry and contain double-stranded DNA (MW 160 × 10⁶), the nucleoprotein antigen being common to all members of the family. A number of genera are recognized, including: Orthopoxvirus, Avipoxvirus, Capripoxvirus, Leporipoxvirus, and Parapoxvirus.

pox-vi-rus (poks'vi-rūs). Any virus of the family Poxviridae.

p. officina'lis, SYN vaccinia virus.

Pozzi, Samuel J., French gynecologist and anatomist, 1846-1918. SEE P. muscle.

PP Abbreviation for pyrophosphate.

PP Abbreviation for inorganic pyrophosphate (diphosphate).

P.p. Abbreviation for *punctum* proximum.

ppb Abbreviation for parts per billion.

PPCA Abbreviation for proserum prothrombin conversion accelerator.

PPCF Abbreviation for plasmin prothrombins conversion factor.

PPD Abbreviation for purified protein derivative of tuberculin.

PPLO Abbreviation for pleuropneumonia-like organisms, under organism.

ppm Abbreviation for parts per million.

PPO Abbreviation for 2,5-diphenyloxazole, a liquid scintillator; preferred provider organization.

PPPPPP A mnemonic of 6 Ps designating the symptom complex of acute arterial occlusion. {pain, pallor, paresthesia, pulselessness, paralysis, prostration}

PPRibb, PPRP Abbreviation for 5-phospho- α -D-ribose-1-pyrophosphate.

P pul-mo-na-le (pul-mō-nā'la). Tall, narrow, peaked P waves in electrocardiographic leads II, III, and aVF, and often a prominent initial positive P wave component in V₁, presumed to be characteristic of cor pulmonale. (Although this term is extensively used in the electrocardiographic literature, it is actually a misnomer and would be more appropriately called P-dextrocardiale, since it results from overload of the right atrium regardless of the cause, as in tricuspid stenosis, and may occur independently of cor pulmonale.) In lung disease, P-pulmonale is usually transient, occurring during exacerbations, usually asthmatic.

PQ Abbreviation for plastoquinone.

PQ-9 Abbreviation for plastoquinone-9.

P.r. Abbreviation for *punctum* remotum.

Pr 1. Abbreviation for presbyopia. 2. Symbol for praseodymium; propyl.

PRA Abbreviation for plasma renin activity; phosphoribosylamine.

prac-tice (prak'tis). The exercise of the profession of medicine or one of the allied health professions. [Mediev. L. *practica*, business, G. *praktikos*, pertaining to action]

extramural p., delivery of health care services by university faculties or full-time hospital staff to persons beyond the physical confines of their respective medical centers.

family p., a specialty of medicine in which the physician takes responsibility for the health and medical care of all members of a family group, regardless of age or gender, but usually does limited amounts of obstetrics and surgery.

general p., a relatively obsolete term for physicians who care for all types of medical problems, including internal medical, pediatric, obstetrical, and surgical diseases. Postgraduate training for general practitioners was limited and there was no specialty certification; the field has been replaced by more extensively trained family practitioners.

group p., the cooperative p. of medicine by a group of physicians, each of whom as a rule specializes in some particular field; such a group often shares a common suite of consulting rooms, laboratories, staff, equipment, etc.

intramural p., delivery of health care services by university faculties or full-time hospital staff conducted within the physical confines of their respective medical centers.

prac-ti-tion-er (prak-tish'un-er). A person who practices medicine or one of the allied health care professions.

Prader, Andrea, Swiss pediatrician, *1919. SEE P.-Willi syndrome.

△**prae-** SEE pre-

prag-matics (prag-mat'iks). A branch of semiotics; the theory that deals with the relation between signs and their users, both senders and receivers. [G. *pragmatikos*, fr. *pragma*, thing done]

prag-ma-tism (prag'mā-tizm). A philosophy emphasizing practical applications and consequences of beliefs and theories, that the meaning of ideas or things is determined by the testability of the idea in real life. [G. *pragma* (*pragmat-*), thing done]

2-pra-li-dox-ime (2-PAM). One of several oximes that are effective in reversing cholinesterase inhibition by organophosphates. The 2-PAM facilitates the hydrolysis of the phosphorylated enzyme so as to regenerate active cholinesterase.

pral-i-dox-ime chlo-ride (pral-i-dok'sēm, prā-li-). Used to restore the inactivated cholinesterase activity resulting from organophosphate poisoning; has some limited value as an antagonist of the carbamate type of cholinesterase inhibitors that are used in the treatment of myasthenia gravis. Dizziness, blurred vision, drowsiness, nausea, tachycardia, and muscular weakness may occur.

pra-mox-ine hy-dro-chlo-ride (prā-mok'sēm, -sīn). A nonester, nonamide local anesthetic for dermal and rectal use.

pran-di-al (prān'dē-āl). Relating to a meal. [L. *prandium*, breakfast]

prase-odym-i-um (Pr) (prā-sē-ō-dim'ē-ūm). An element of the lanthanide or "rare earth" group; atomic no. 59, atomic wt.

for studying the central visual fields while the fellow eye holds fixation. [stereo- + L. *campus*, field, + G. *metron*, measure]

ster-e-o-chem-i-cal (ster'ē-ō-kem'i-kāl). Relating to stereochemistry.

ster-e-o-chem-is-try (ster'ē-ō-kem'is-trē). The branch of chemistry concerned with the spatial three-dimensional relations of atoms in molecules, i.e., the positions the atoms in a compound bear in relation to one another in space.

ster-e-o-cil-i-um, pl. **ster-e-o-cil-ia** (ster'ē-ō-sil'ē-ūm, -ā). A nonmotile long microvillus. [stereo- + L. *cilium*, eyelid]

ster-e-o-cin-e-flu-o-rog-ra-phy (ster'ē-ō-sin'ē-flōr-og'rā-fē). Obsolete practice of recording on motion picture film the images obtained by stereoscopic fluoroscopy; three-dimensional views are obtained.

ster-e-o-col-po-gram (ster'ē-ō-kol'pō-gram). Picture taken with the stereocolposcope.

ster-e-o-col-po-scope (ster'ē-ō-kol'pō-skōp). Instrument that provides the observer with a magnified three-dimensional gross inspection of the vagina and cervix. [stereo- + G. *kolpos*, a hollow (vagina), *skopeō*, to view]

ster-e-o-e-lec-tro-en-ceph-a-log-ra-phy (ster'ē-ō-ē-lek'trō-en-sef-ā-log'rā-fē). Recording of electrical activity in three planes of the brain, i.e., with surface and depth electrodes.

ster-e-o-en-ceph-a-lom-e-try (ster'ē-ō-en-sef'ā-lom'ē-trē). The localization of brain structures by use of three-dimensional coordinates.

ster-e-og-no-sis (ster'ē-og'nō'sis). The appreciation of the form of an object by means of touch. [stereo- + G. *gnōsis*, knowledge]

ster-e-og-nos-tic (ster'ē-og-nos'tik). Relating to stereognosis.

ster-e-o-gram (ster'ē-ō-gram). A stereoscopic radiographic image of a pair.

ster-e-o-graph (ster'ē-ō-graf). A stereoscopic x-ray apparatus.

ster-e-og-ra-phy (ster'ē-og'rā-fē). SYN stereoradiography.

ster-e-o-i-so-mer (ster'ē-ō-i'sō-mer). A molecule containing the same number and kind of atom groupings as another but in a different arrangement in space; the stereoisomers are not interconvertible unless bonds are broken and reformed, by virtue of which it exhibits different optic properties, e.g., as between D- and L-amino acids, 5α- and 5β-steroids. Cf. isomer. [stereo- + G. *isos*, equal, + *meros*, part]

ster-e-o-i-so-mer-ic (ster'ē-ō-i'sō-mer'ik). Relating to stereoisomerism.

ster-e-o-i-som-er-ism (ster'ē-ō-i'som'er-izm). Molecular asymmetry, isomerism involving different spatial arrangements of the same groups (e.g., androsterone and isoandrosterone, differing only in that one has a 3α-OH, the other a 3β-OH). SEE ALSO stereoisomer, Le Bel-van't Hoff rule. SYN stereochemical isomerism.

ster-e-o-l-o-gy (ster'ē-ō-l'ō-jē). A study of the three-dimensional aspects of a cell or microscopic structure. [stereo- + G. *logos*, study]

ster-e-om-e-ter (ster'ē-ōm'ē-ter). An instrument used in stereometry. [stereo- + G. *metron*, measure]

ster-e-om-e-try (ster'ē-ōm'ē-trē). 1. Measurement of a solid object or the cubic capacity of a vessel. 2. Determination of the specific gravity of a liquid.

ster-e-o-or-thop-ter (ster'ē-ō-ōr-thop'ter). A type of stereoscope used in visual training. [stereo- + G. *orthos*, straight, + *optikos*, optical]

ster-e-op-a-thy (ster'ē-ōp'ā-thē). Persistent stereotyped thinking.

ster-e-o-pho-rom-e-ter (ster'ē-ō-fō-rom'ē-ter). A phorometer with a stereoscopic attachment.

ster-e-o-pho-to-mi-cro-graph (ster'ē-ō-fō'tō-mi'krō-graf). A stereoscopic photomicrograph that, when viewed with a stereoscope, appears three dimensional.

ster-e-op-sis (ster'ē-ōp'sis). SYN stereoscopic vision. [stereo- + G. *opsis*, vision]

ster-e-o-ra-di-og-ra-phy (ster'ē-ō-rā-dē-og'rā-fē). Preparation of a pair of radiographs with appropriate shift of the x-ray tube or film so that the images can be viewed stereoscopically to give a

three-dimensional appearance. SYN stereography, stereoroentgenography.

ster-e-o-roent-gen-og-ra-phy (ster'ē-ō-rent'gen-og'rā-fē). SYN stereoradiography.

ster-e-o-scope (ster'ē-ō-skōp). An instrument producing two horizontally separated images of the same object, providing a single image with an appearance of depth. [stereo- + G. *skopeō*, to view]

ster-e-o-scop-ic (ster'ē-ō-skop'ik). Relating to a stereoscope, or giving the appearance of three dimensions.

ster-e-os-co-py (ster'ē-ōs'kō-pē). 1. An optic technique by which two images of the same object are blended into one, giving a three-dimensional appearance to the single image. 2. SEE radio-stereoscopy.

ster-e-o-se-lect-ive (ster'ē-ō-sē-lek'tiv). As applied to a reaction, denoting a process in which of two or more possible stereoisomeric products only one predominates; a s. process is not necessarily stereospecific.

ster-e-o-spe-cif-ic (ster'ē-ō-spē-sif'ik). As applied to a reaction, denoting a process in which stereoisomerically different starting materials give rise to stereoisomerically different products; a s. process is thus necessarily stereoselective, but not all stereoselective processes are s.

ster-e-o-tac-tic, **ster-e-o-tax-ic** (ster'ē-ō-tak'tik, -tak'sik). Relating to stereotaxis or stereotaxy.

ster-e-o-tax-is (ster'ē-ō-tak'sis). 1. Three-dimensional arrangement. 2. Stereotropism, but applied more exactly where the organism as a whole, rather than a part only, reacts. 3. SYN stereotaxy. [stereo- + G. *taxis*, orderly arrangement]

ster-e-o-taxy (ster'ē-ō-tak'sē). A precise method of identifying nonvisualized anatomic structures by use of three-dimensional coordinates; more frequently used for brain and spinal surgery. SYN stereotactic surgery, stereotaxic surgery, stereotaxis (3).

ster-e-o-tro-pic (ster'ē-ō-trop'ik). Relating to or exhibiting stereotropism.

ster-e-of-ro-pism (ster'ē-ōf'rō-pizm). Growth or movement of a plant or animal toward (positive s.) or away from (negative s.) a solid body, usually applied where a part of the organism rather than the whole reacts. [stereo- + G. *tropos*, a turning]

ster-e-o-typy (ster'ē-ō-tī-pē). 1. Maintenance of one attitude for a long period. 2. Constant repetition of certain meaningless gestures or movements, as in certain forms of schizophrenia. [stereo- + G. *typos*, impression, type]

oral s., SYN verbigeration.

ster-ic (ster'ik, stēr-). Pertaining to stereochemistry.

s. **hindrance**, interference with or inhibition of a seemingly feasible reaction (usually synthetic) because the size of one or another reactant prevents approach to the required interatomic distance.

ster-id (ster'id, stēr-). SYN steroid (2).

ster-ig-ma, pl. **ster-ig-ma-ta** (ste-rig'mā, -mā-tā). A slender, pointed structure arising from a basidium upon which a basidiospore will develop. [G. *stērigma*, a support]

ster-ile (ster'il). Relating to or characterized by sterility. [L. *sterilis*, barren]

ster-il-i-ty (stē-ril'i-tē). 1. In general, the incapability of fertilization or reproduction. SEE female s., male s. 2. Condition of being aseptic, or free from all living microorganisms. [L. *sterilitas*]

aspermato-genic s., s. due to a failure to produce living spermatozoa.

dysspermato-genic s., male s. due to some abnormality in production of spermatozoa.

female s., the inability of the female to conceive, due to inadequacy in structure or function of the genital organs. SYN infecundity.

male s., the inability of the male to fertilize the ovum; it may or may not be associated with impotence.

normospermato-genic s., male s. due to some cause other than failure to produce live, normal spermatozoa; e.g., blockage of the seminiferous passages.

ster-il-i-za-tion (ster'i-li-zā'shūn). 1. The act or process by which an individual is rendered incapable of fertilization or reproduction, as by vasectomy, partial salpingectomy, or castration. 2. The

destruction of all microorganisms in or about an object, as, by steam (flowing or pressurized), chemical agents (alcohol, phenol, heavy metals, ethylene oxide gas), high-velocity electron bombardment, heat, or ultraviolet light radiation.

discontinuous s., SYN fractional s.

fractional s., exposure to a temperature of 100°C (flowing steam) for a definite period, usually an hour, on each of several days; at each heating the developed bacteria are destroyed; spores, which are unaffected, germinate during the intervening periods and are subsequently destroyed. SYN discontinuous s., intermittent s., tyndallization.

intermittent s., SYN fractional s.

ster-il-ize (ster'i-līz). To produce sterility.

ster-il-iz-er (ster'i-lī-zer). An apparatus for rendering objects sterile.

glass bead s., a s. for endodontic equipment; the heat is transmitted to the instruments, absorbent points, or cotton pellets by means of glass beads.

hot salt s., a s. for endodontic equipment in which table salt is heated in a container at 218–246°C; the dry heat is transmitted to root canal instruments, absorbent points, or cotton pellets for their rapid (5–10 seconds) sterilization.

Stern, Heinrich, U.S. physician, 1868–1918. SEE *S. posture*.

△**stern-**. SEE sterno-.

ster-na (ster'nā). Plural of sternum.

ster-nad (ster'nad). In a direction toward the sternum.

ster-nal (ster'nāl). Relating to the sternum.

ster-nal-gia (ster-nal'jē-ā). Pain in the sternum or the sternal region. SYN sternodynia. [stern- + G. *algos*, pain]

ster-na-lis (ster-nā'lis). SEE sternalis (*muscle*).

Sternberg, George M., U.S. bacteriologist, 1838–1915. SEE *S. cell*; *S.-Reed cell*; *Reed-S. cell*.

ster-nē-bra, pl. **ster-nē-brae** (ster'nē-brā, -brē). One of the four segments of the primordial sternum of the embryo by the fusion of which the body of the adult sternum is formed. [Mod. L. fr. stem(um) + (vert)ebra]

ster-nen. Relating to the sternum independent of any other structures. [stern- + G. *en*, in]

△**sterno-**, **stern-**. The sternum, sternal. [G. *sternon*, chest]

ster-no-chon-dro-sca-pu-la-ris (ster'nō-kon'drō-skap-ū-lā'ris). SEE sternochondroscapular *muscle*. [Mod. L.]

ster-no-cla-vic-u-lar (ster'nō-kla-vik'ū-lār). Relating to the sternum and the clavicle.

ster-no-cla-vi-cu-la-ris (ster'nō-kla-vik'ū-lā'ris). SEE sternoclavicular *muscle*.

ster-no-clei-dal (ster'nō-kli'dāl). Relating to the sternum and the clavicle. [sterno- + G. *kleis*, key (clavicle)]

ster-no-clei-do-mas-toid (ster'nō-kli'dō-mas'tōyd). Relating to sternum, clavicle, and mastoid process.

ster-no-clei-do-mas-toi-de-us (ster'nō-kli'dō-mas-tō-id'ē-ūs). SEE sternocleidomastoid (*muscle*). [Mod. L.]

ster-no-cos-tal (ster'nō-kos'tāl). Relating to the sternum and the ribs. [L. *costa*, rib]

ster-no-dyn-ia (ster-nō-din'ē-ā). SYN sternalgia. [sterno- + G. *odynē*, pain]

ster-no-fas-ci-a-lis (ster'nō-fash-ē-ā'lis). SEE *musculus sternofascialis*.

ster-no-glos-sal (ster-nō-glos'āl). Denoting muscular fibers that occasionally pass from the sternohyoid muscle to join the hyoglossal muscle.

ster-no-hy-oi-de-us (ster'nō-hī-oyd'ē-ūs). SEE sternohyoid (*muscle*). [Mod. L.]

ster-noid (ster'noyd). Resembling the sternum. [sterno- + G. *eidōs*, resemblance]

ster-no-mas-toid (ster'nō-mas'tōyd). Relating to the sternum and the mastoid process of the temporal bone; applied to the sternocleidomastoid muscle.

ster-no-pa-gia (ster-nō-pā'jē-ā). Condition shown by conjoined twins united at the sternum or more extensively at the ventral walls

of the chest. SEE conjoined *twins*, under *twin*. [sterno- + G. *pāgos*, something fixed]

ster-no-per-i-car-di-al (ster'nō-per'i-kar'dē-āl). Relating to the sternum and the pericardium.

ster-nos-chi-sis (ster-nos'ki-sis). Congenital cleft of the sternum. [sterno- + G. *schisis*, a cleaving]

ster-no-thy-roi-de-us (ster'nō-thī-royd'ē-ūs). SEE sternothyroid (*muscle*). [Mod. L.]

ster-not-o-my (ster-not'ō-mē). Incision into or through the sternum. [sterno- + G. *tomē*, incision]

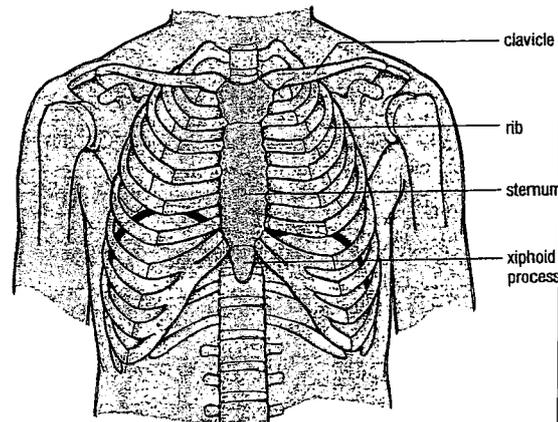
median s., incision through the midline of the sternum usually used to gain access to the heart, mediastinal structures, and great vessels.

ster-no-tra-che-al (ster'nō-trā'kē-āl). Relating to the sternum and the trachea.

ster-no-try-pe-sis (ster'nō-trī-pē'sis). Trephining of the sternum. [sterno- + G. *trypēsis*, a boring]

ster-no-ver-te-bral (ster'nō-ver'tē-brāl). Relating to the sternum and the vertebrae; denoting the true ribs, or the seven upper ribs on either side, which articulate with the vertebrae and with the sternum. SYN vertebrosteral.

■**ster-num**, gen. **ster-ni**, pl. **ster-na** (ster'nūm, -nī, -nā) [TA]. A long flat bone, articulating with the cartilages of the first seven ribs and with the clavicle, forming the middle part of the anterior wall of the thorax; it consists of three portions: the corpus or body, the manubrium, and the xiphoid process. SYN breast bone. [Mod. L. fr. G. *sternon*, the chest]



sternum and surrounding structures

ster-nu-ta-tion (ster'noo-tā'shūn). The act of sneezing. [L. *sternutatio*, fr. *sternuo* (*sternuto*), pp. *sternutatus*, to sneeze]

ster-nu-ta-tor (ster'noo-tā-ter, -tōr). A substance, such as a gas, that induces sneezing. SYN sneezing gas.

ster-nu-ta-to-ry (ster'noo-tā-tōr-ē). 1. Causing sneezing. 2. An agent that provokes sneezing. SYN ptarmic.

ste-roid (stēr'oyd, ster'oyd). 1. Pertaining to the steroids. SYN steroidal. Cf. steroids. 2. One of the steroids. SYN steroid. 3. Generic designation for compounds closely related in structure to the steroids, such as sterols, bile acids, cardiac glycosides, androgens, estrogens, corticosteroids, and precursors of the D vitamins.

anabolic s., a s. compound with the capacity to increase muscle mass; compounds with androgenic properties which increase muscle mass and are used in the treatment of emaciation. Sometimes used by athletes in an effort to increase muscle size, strength, and endurance. Examples include methyltestosterone, nandrolone, methandrostenolone, and stanozolol.

s. **hydroxylases**, SYN s. monooxygenases.

s. **21-monooxygenase**, an enzyme catalyzing the reaction of a steroid, O₂, and some reduced compound to produce water, the oxidized compound, and a 21-hydroxysteroid; a deficiency of this

leads into the ductus deferens; part of the reservoir of spermatozoa. *SYN* cauda epididymidis [TA]; cauda epididymis, globus minor.

t. of helix [TA], a flattened process terminating the cartilage of the helix of the ear; posteriorly and inferiorly. *SYN* cauda-helicis [TA].

t. of pancreas [TA], the left extremity of the pancreas within the lienorenal ligament. *SYN* cauda pancreatis [TA].

tail-gut (tā'gūt). *SYN* postanal gut.

Tait, Robert L., English gynecologist, 1845-1899. *SEE* T. law.

Ta-ka-di-as-tase (tā'kā-dī'as-tās). *SYN* α-amylase.

Takahara, Shigeo, 20th century Japanese otolaryngologist. *SEE* T. disease.

Takayama, Masao, Japanese physician, *1872. *SEE* T. stain.

Takayasu (Takayashu). Michishige, Japanese ophthalmologist, *1872. *SEE* Takayasu arteritis, Takayasu disease, Takayasu syndrome.

take (tāk). A successful grafting operation or vaccination.

ta-lal-gia (tā-lal'jē-ā). Pain in the ankle. [L. *talus*, ankle, G. *algos*, pain]

ta-lar (tā'lār). Relating to the talus.

Talbot, William Henry Fox, British scientist, 1800-1877. *SEE* Plateau-T. law.

talc (tālk). Native hydrous magnesium silicate, sometimes containing small proportions of aluminum silicate, purified by boiling powdered t. with hydrochloric acid in water; used in pharmacy as a filter aid, as a dusting powder, and in cosmetic preparations. *SYN* French chalk, soapstone, talcum. [Ar. *talq*]

tal-co-sis (tal-kō'sis). A pulmonary disorder related to silicosis, occurring in workers exposed to talc mixed with silicates; characterized by restrictive or obstructive disorders of breathing or the two in combination. [talc + G. -osis, condition]

pulmonary t., pneumoconiosis from inhaling talc dusts.

tal-cum (tal'kūm). *SYN* talc. [L.]

tal-i-on (tal'ē-on, tal'yūn). The principle of retribution in intrapsychic behavior. [Welsh *tal*, compensation]

t. dread, The symbolic anxieties that represent the unconscious dread of penalties for an act.

tal-i-ped-ic (tal-i-ped'ik). Clubfooted.

tal-i-pes (tal'i-pēz). Any deformity of the foot involving the talus. [L. *talus*, ankle, + *pes*, foot]

t. calcaneovalgus, t. calcaneus and t. valgus combined; the foot is dorsiflexed, everted, and abducted.

t. calcaneovarum, t. calcaneus and t. varum combined; the foot is dorsiflexed, inverted, and adducted.

t. calca'neus, a deformity due to weakness or absence of the calf muscles, in which the axis of the calcaneus becomes vertically oriented; commonly seen in poliomyelitis. *SYN* calcaneus (2).

☐ **t. ca'vus**, an exaggeration of the normal arch of the foot. *SYN* contracted foot, pes cavus, t. plantaris.

t. equinovalgus, t. equinus and t. valgus combined; the foot is plantarflexed, everted, and abducted. *SYN* equinovalgus, pes equinovalgus.

t. equinovarus, t. equinus and t. varus combined; the foot is plantarflexed, inverted, and adducted. *SYN* clubfoot, equinovarus, pes equinovarus.

t. equi'nus, permanent plantar flexion of the foot so that only the ball rests on the ground; it is commonly combined with t. varus.

t. planta'ris, *SYN* t. cavus.

t. pla'nus, *SYN* pes planus.

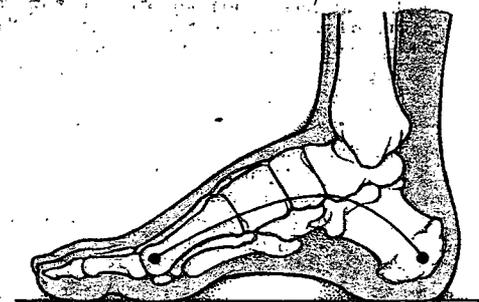
t. transversopla'nus, *SYN* metatarsus latus.

t. val'gus, permanent eversion of the foot, the inner side alone of the sole resting on the ground; it is usually combined with a breaking down of the plantar arch. *SYN* pes abductus, pes pronatus, pes valgus.

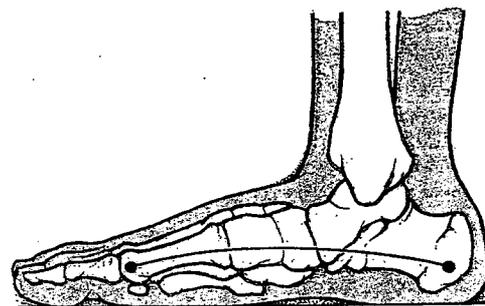
t. va'rus, inversion of the foot, the outer side of the sole only touching the ground; usually some degree of t. equinus is associated with it, and often t. cavus. *SYN* pes adductus, pes varus.

tal-low (tal'ō). The rendered fat from mutton suet.

prepared mutton t., *SYN* prepared suet.



Dor



talipes cavus (top) and talipes planus (bottom)

△ **talo-**. The talus. [L. *talus*, ankle, ankle bone]

ta-lo-cal-ca-ne-al, **ta-lo-cal-ca-ne-an** (tā-lō-kal-kā'nē-āl, tā-lō-kal-kā'nē-an). Relating to the talus and the calcaneus.

ta-lo-cru-ral (tā'lō-kroo'rāl). Relating to the talus and the bones of the leg; denoting the ankle joint.

ta-lo-fib-u-lar (tā'lō-fīb'ū-lār). Relating to the talus and the fibula.

ta-lo-na-vic-u-lar (tā'lō-nā-vik'ū-lār). Relating to the talus and the navicular bone. *SYN* astragaloscapoid, taloscapoid.

ta-lo-scaph-oid (tā'lō-skaf'oyd). *SYN* talonavicular.

tal-ose (tal'ōs). An aldohexose, isomeric with glucose; D-t. is epimeric with D-galactose.

ta-lo-tib-i-al (tā'lō-tīb'ē-āl). Relating to the talus and the tibia.

ta-lus, gen. **ta-li** (tā'lūs, -ī) [TA]. The bone of the foot that articulates with the tibia and fibula to form the ankle joint. *SYN* ankle bone, ankle (3). [L. ankle bone, heel]

tam-a-rind (tam'ā-rind). The pulp of the fruit of *Tamarindus indica* (family Leguminosae), a large tree of India; mildly laxative. [Mediev. L. fr. Ar. *tamr*]

tam-bour (tahn-bur'). The recording part of a graphic apparatus, such as a sphygmograph, consisting of a membrane stretched across the open end of a cylinder and the recording stylus attached to it. [Fr. *drum*]

Tamm, Igor, U.S. virologist, *1922. *SEE* T.-Horsfall mucoprotein, protein.

ta-mox-i-fen cit-rate (tā-mok'sī-fen). A synthetic nonsteroidal estrogen antagonist used in the prevention and treatment of breast cancer.

By competing with naturally occurring estrogen for binding sites on tissue cells, tamoxifen inhibits the stimulant effect of estrogen on breast cancers. Tumors that have been shown by biochemical assay to be rich in estrogen receptors are most likely to respond to treatment. Since 1985, tamoxifen has been used in patients who have undergone surgery or irradiation for breast cancer, to delay or prevent relapse. The drug has been found effective in reducing the risk of cancer recurrence or disease progression in women with or without axillary node metastasis. In women with extensive disease, tamoxifen therapy has

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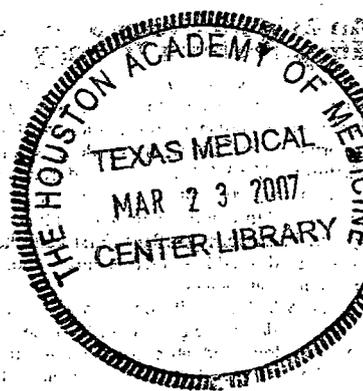
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Talc

■ Talc is a sclerosing agent.

Uses

■ **Pleural Effusions** Talc is used intrapleurally as a sclerosing agent to prevent the recurrence of malignant pleural effusions in symptomatic patients with advanced stages of metastatic tumors. When instilled into the pleural space, talc causes inflammation that results in fibrosis and adherence of serosal surfaces (pleurodesis), thereby obliterating the pleural space and reducing the chance of fluid reaccumulation. Safety and efficacy of talc, administered via a chest tube as a suspension (slurry) or by insufflation during thoracoscopy, or open thoracotomy, for the treatment of malignant pleural effusions are based on data from published literature. A review of published literature from 1966-1992 indicates that about 93% of patients with recurrent, symptomatic malignant pleural effusions were successfully treated (defined as absence of reaccumulation of the effusion as determined by clinical examination or chest radiograph) with talc pleurodesis. When analyzed by method of administration, talc poudrage and slurry pleurodesis methods resulted in similar rates of success.

Results of small randomized, comparative studies indicate that talc (administered as either a slurry or poudrage) may be at least as effective as bleomycin, doxycycline, mustine, or tetracycline (no longer commercially available as a parenteral formulation in the US) and more effective than therapeutic thoracentesis in preventing the recurrence of malignant pleural effusions (as observed on chest radiographs). In these studies, clinical success was variably defined, but was based principally on an absence of reaccumulation of the effusion as determined by clinical examination or chest radiograph. In some published studies of talc pleurodesis, complete and persistent absence of fluid was the determinant of response, whereas in other studies the lack of need for further pleural drainage was the sole criterion. Follow-up times also were variable, and dosages ranged from 2.5-10 g.

For additional information on the treatment of pleural effusions, see Uses: Pleural Effusions, in Bleomycin Sulfate 10:00 and Uses: Pericardial and Pleural Effusions, in Tetracyclines General Statement 8:12.24.

Dosage and Administration

■ **Reconstitution and Administration** Talc is administered intrapleurally by aerosol during thoracoscopy or open thoracotomy or via a chest tube as a slurry. Prior to instillation of talc, the pleural cavity should be adequately drained of the effusion. Success of talc pleurodesis appears to be related to the completeness of the drainage of the pleural fluid, as well as full reexpansion of the lung, both of which will promote symphyssis of the pleural surfaces.

Commercially available talc powder must be dispersed in 0.9% sodium chloride injection prior to administration. The manufacturer recommends preparation of a slurry containing 5 g of talc per 100 mL. Preparation of the slurry should take place in a laminar flow hood using aseptic technique. Once the slurry is prepared, it should be administered via irrigation syringes within 12 hours.

The manufacturer states that the syringes of the talc slurry should be appropriately labeled with the expiration date and time, the statement "For Pleurodesis Only—NOT FOR IV ADMINISTRATION," the identity of the patient intended to receive the preparation, and a cautionary statement to SHAKE WELL before use.

Consult the manufacturer's labeling for further directions for preparing and/or administering talc slurry or talc aerosol.

■ **General Dosage** When an extemporaneously prepared talc slurry is used, the recommended adult dose of talc is 5 g, dispersed in 50-100 mL of 0.9% sodium chloride injection and instilled into the pleural cavity through a chest tube. Although the optimal dose for effective pleurodesis is not known, 5 g was the dose most frequently reported in the published literature. Following introduction of the talc slurry, the chest tube should be flushed with 10-25 mL of 0.9% sodium chloride solution and the drainage tube clamped. The patient should then be asked to move, at 20- to 30-minute intervals, from supine to alternating decubitus positions, so that over a period of about 2 hours the talc is distributed within the chest cavity. However, the manufacturer states that recent evidence suggests that this step may not be necessary. At the end of this period, the chest drainage tube should be unclamped, and the excess saline removed by routine continual external suction on the tube.

When talc is administered by the commercially available aerosol during thoracoscopy or open thoracotomy, the usual adult dose of talc powder is 4-8 g given as a single dose, delivered intrapleurally from 1-2 spray canisters. The commercially available spray canisters deliver talc at a rate of 0.4 g (400 mg) per second, but are not considered to be metered dose delivery systems. The dose of talc delivered from the spray canister depends instead on the extent and duration of manual compression of the actuator button on the canister. For optimal distribution, the canisters should always be maintained in an upright position. In addition, in order to distribute the talc powder equally and extensively on all visceral and parietal pleural surfaces, the distal end of the delivery tube should be pointed in several different directions (but not adjacent to the

lung parenchyma or directly against the chest wall) while short bursts are administered. The duration of chest tube drainage following talc sclerosis is dictated by the clinical situation. After application, the canister and delivery tube should be discarded.

■ **Special Populations** No special population recommendations at this time.

Cautions

■ **Contraindications** The manufacturer states that there are no known contraindications to the use of talc.

■ **Warnings/Precautions** **General Precautions** **Potentially Curable Malignancies.** Talc has no known antineoplastic activity and should not be used alone for potentially curable malignancies when systemic therapy would be more appropriate (e.g., a malignant effusion secondary to a potentially curable lymphoma).

Implications for Future Procedures. Prior to administering talc for pleurodesis, clinicians should consider the possible need for future diagnostic and therapeutic procedures involving the hemithorax. Sclerosis of the pleural space may preclude subsequent diagnostic procedures of the pleura on the treated side. In addition, talc sclerosis may complicate or preclude future ipsilateral lung resective surgery, including pneumonectomy for transplantation purposes.

Pulmonary Complications. Acute pneumonitis and acute respiratory distress syndrome (ARDS) have been reported in association with intrapleural talc administration. Three of the case reports of ARDS have occurred after treatment with a relatively large talc dose (10 g) administered via intrapleural chest tube instillation. One patient died 1 month following treatment and 2 patients recovered without further sequelae.

Specific Populations **Pregnancy.** Category B. (See Users Guide.)

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age.

Geriatric Use. The estimated mean and median ages of patients treated with talc slurry in clinical studies (single-arm or randomized studies) were 60 and 62 years, respectively. Safety and efficacy of talc in geriatric patients have not been studied specifically to date.

■ **Common Adverse Effects** The most common adverse effects reported with intrapleural administration of talc are fever and pain. Almost all of the reported cases of fever and over half of the reported cases of pain occurred in patients who underwent diagnostic biopsies at the time of talc administration.

Drug Interactions

■ **Sclerosing Agents.** It is not known whether prior intrapleural administration of talc (because of its absorptive properties) would diminish the effectiveness of subsequent therapy with a second sclerosing agent.

Description

Commercially available talc is sterile, asbestos-free, and brucite-free, and the granule size is controlled.

The mechanism of action of talc in the prevention of recurrent malignant pleural effusions is believed to involve induction of an inflammatory reaction that results in pleurodesis, thereby obliterating the pleural space and reducing the chance of fluid reaccumulation.

The extent of systemic absorption of talc following intrapleural administration has not been fully elucidated. Systemic exposure to talc may be affected by the integrity of the pleural surface, and therefore may be increased if the drug is administered immediately following lung resection or biopsy.

Advice to Patients

Importance of describing the intrapleural procedure to patients prior to administration of talc.

Preparations

Talc

Intrapleural:

Aerosol: 0.4 g Sclerosol[®] Intrapleural Aerosol (with dichlorodifluoromethane [CFC-12] propellants), Bryan

Powder: 5 g Sterile Talc Powder, Bryan

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Exhibit 6

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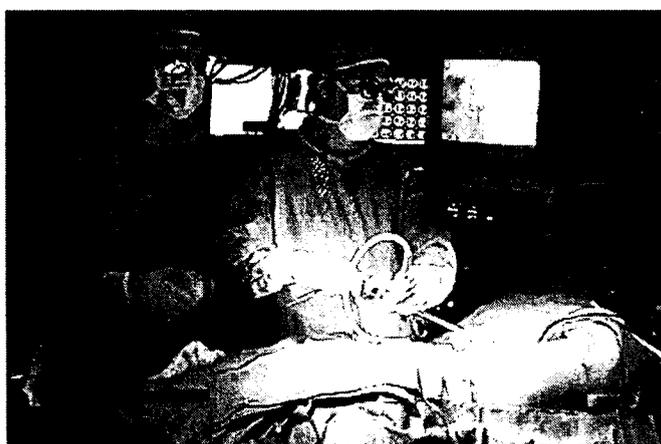
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The field of video-assisted thoracoscopic surgery (VATS) has evolved from our experience with laparoscopic procedures now routinely performed by the general surgeons. In the past we used rudimentary devices to peer into the chest; now we utilize advanced video technology, computers and high-tech electronics to perform many operations that formerly required open large incision thoracotomy. In essence, video-assisted surgery allows the thoracic surgeon to accomplish the same goal as the comparable open procedure but with less pain, less morbidity and a shorter hospital stay for the patients.

At USC the Thoracic surgeons utilize VATS to examine the chest cavity from within and to perform diagnostic procedures such as lung, diaphragmatic and pleural biopsies. Increasingly complex procedures are now being performed such as lung resections, evacuation of pleural based problems, decortication, anti-reflux procedures, diaphragmatic plication.

Watch the Movie: Video-Assisted Thoracoscopic Surgery



Watch: Video-Assisted Thoracoscopic Surgery

MPG file: 4 minutes, 29 seconds

Video Assisted Thoracoscopic Surgery, often referred to as VATS, is performed using a small video camera that is introduced into the patient's chest via a scope. With the video camera, the surgeon is able to view the anatomy along with other surgical instruments that are introduced into the chest via small incisions or "ports".

Traditional surgical approaches have utilized a single large incision (cut) that is placed between the patient's ribs. The ribs are then spread apart, allowing the surgeon to look directly into the patient's chest. The surgery is then performed via this single large opening. These incisions are known as thoracotomies, and while very safe, are uncomfortable. By utilizing VATS, this large incision is avoided, thereby sparing the patient some of the post-operative pain and assisting them with a potentially quicker recovery.

In this video, the surgeon uses small instruments that have been introduced into the patient's chest via small (1/2-inch) ports. The surgeon views a video screen that shows the camera image.

There are 4 parts to this video:

In Part 1, the surgeon is "exploring" the chest using VATS technology. The device that looks like a fan is used to move the lung around.

In Part 2, the patient has recurrent collection of fluid in the chest secondary to a cancer, which is referred to as a "malignant pleural effusion". In the video, you see the surgeon sucking out the fluid. The white flashing light is actually sterile talcum powder being introduced into the chest. The talcum powder causes the lung to adhere to the chest wall, hopefully not allowing fluid to collect in this space.

In Part 3, the surgeon is sampling a lymph node from the lung to get a biopsy, to see if cancer has spread to the lymph nodes.

In Part 4, the surgeon is removing an abnormal mass from the lung. The mass was being removed to see if it was a cancer. It is placed in a small plastic bag to prevent any cancer cells from coming into contact with the chest wall as it is removed through a small (1/2 inch) incision.

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Exhibit 7

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Video-assisted talc pleurodesis for malignant pleural effusions utilizing local anesthesia and I.V. sedation

CA Danby, SA Adebonojo and DM Moritz

Chest 1998;113:739-742

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.org/cgi/content/abstract/113/3/739>

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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Video-Assisted Talc Pleurodesis for Malignant Pleural Effusions Utilizing Local Anesthesia and IV Sedation*

Christopher A. Danby, MD; Samuel A. Adebonojo, MD, FCCP; and
Dennis M. Moritz, MD

Methods: Twenty-four consecutive patients aged 36 to 84 years (mean, 63.3 ± 12.9 years) underwent video-assisted talc pleurodesis (VATP) for malignant pleural effusion (MPE) utilizing local anesthesia with IV sedation at the Walter Reed Army Medical Center. The VATP procedure was performed in the operating room with the patient in the lateral decubitus position breathing spontaneously through a face mask with 4 L/min of oxygen. Anesthesia was achieved by intercostal nerve block using a 50/50 mixture of 1% lidocaine with epinephrine and 0.5% bupivacaine hydrochloride (Marcaine) supplemented with local infiltration of the access (Surgi-port) sites as necessary. Sedation was achieved with propofol, and pleurodesis was performed with 3 to 8 g (average, 5 g) of sterile talc insufflated through a talc atomizer.

Results: The mean operating time was 44.3 ± 14.9 min (range, 23 to 75 min). The average number of days of chest tube drainage was 2.9 ± 1.2 days (range, 1 to 5 days). Patients stayed on the cardiothoracic ward for an average of 4.4 ± 1.3 days before discharge home or transfer to a medical oncology ward. Seventeen of the 24 patients (71%) had excellent results, 4 patients (17%) had good results, and 3 patients (12%) had poor results. The three patients with poor results all had primary lung cancer as their underlying malignancy. The overall actuarial survival was 66% at 6 months, 48% at 12 months, and 32% at 24 months with a mean survival of 9 months. There was one operative death in an 84-year-old patient with primary lung cancer. Twelve of the 24 patients are alive 4 to 30 months after VATP.

Conclusions: VATP, performed under local anesthesia, is a safe and highly effective method of managing MPE. (*CHEST* 1998; 113:739-42)

Key words: local anesthesia; malignant pleural effusion; talc pleurodesis; video-assisted thoracoscopic surgery (VATS)

Abbreviations: MPE=malignant pleural effusion; VATP=video-assisted talc pleurodesis; VATS=video-assisted thoracic surgery

Traditional thoracoscopy has its origins in the treatment of pleural diseases. Reviews of the topic of malignant pleural effusion (MPE) support the use of thoracoscopy to assist in the diagnosis and treatment of malignant effusions when less invasive bedside procedures have failed.¹⁻³ The safety and efficacy of talc as a sclerosing agent has also been well documented.³⁻⁵ The recent development of

video-assisted thoracic surgical (VATS) techniques, combined with the known effectiveness of talc pleurodesis for palliation of MPEs, has resulted in a trend toward earlier video-assisted intervention for both diagnosis and treatment.^{2,3}

Recent reports favor general anesthesia with independent lung ventilation as the anesthetic technique of choice for these patients.^{1,3,6,7} However, we believe that local anesthesia has a continuing role in the diagnosis and treatment of simple pleural processes. We report our experience with video-assisted talc pleurodesis (VATP) utilizing local anesthesia and supplemental IV sedation for the treatment of MPE.

MATERIALS AND METHODS

From September 1993 to December 1995, 24 consecutive patients underwent VATP utilizing local anesthesia and IV sedation for MPE at Walter Reed Army Medical Center. Patients

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who had VATP under general anesthesia or talc slurry through a chest tube for MPE were excluded from this review. The diagnosis of MPE was made in 21 patients by preprocedure thoracentesis fluid cytology and in three patients by pleural biopsy specimens during VATP. The operating time was counted from the time of administration of the intercostal block to application of dressings. The result of pleurodesis was described as excellent if there was full lung expansion without residual effusion and marked improvement in respiratory symptoms; good if there was satisfactory lung expansion with minimal residual effusion and improved respiratory symptoms; poor if there was incomplete lung expansion with recurrent pleural effusion and/or no significant improvement in respiratory symptoms. No antibiotics or other treatment for the primary disease was given in the perioperative period. Patients were either discharged home or transferred to the referring ward after removal of chest tubes. Survival was calculated from the date of operation to the date of death or last follow-up. The 2-year actuarial survival was calculated using the Kaplan-Meier curve.

Clinical Presentation

Twenty of the 24 patients were in marked respiratory distress at the time of hospital admission requiring thoracentesis for palliation and diagnosis. Fifteen patients had an FEV₁ of <1,000 mL, 8 had significant weight loss, 5 were anemic, and 2 patients had associated ascites.

Preoperative Thoracentesis

Thoracentesis was performed prior to thoroscopic talc pleurodesis in all patients. This provided symptom relief, fluid for cytologic assessment, and enabled us to determine the ability of the lung to expand. In addition, 21 of 24 patients underwent their initial or a follow-up thoracentesis 1 to 2 days prior to pleurodesis to improve respiratory function at the time of VATP.

Technique of Thoroscopic Talc Pleurodesis Under Local Anesthesia

Patients were placed in a full lateral decubitus position breathing spontaneously with 4 L of oxygen via a face mask. Sedation was achieved with propofol and fentanyl. Adequate analgesia was achieved by intercostal nerve block at the level of the posterior ribs from the fifth through eighth intercostal space using a 50/50 mixture of 1% lidocaine with epinephrine and 0.5% bupivacaine hydrochloride (Marcaine), occasionally coupled with direct local anesthetic infiltration of the access site with 1% lidocaine.

One or two access sites were used depending on the preference of the operating surgeon and the extent of adhesions. A 0° video thoracoscope was inserted through the fifth intercostal space in the mid axillary line and the entire pleural surface was examined for metastatic disease. Any residual effusion was drained completely. Directed pleural biopsy specimens were obtained if the primary tumor type or the nature of the effusion was in question. If there were adhesions, a second port was used to lyse the adhesions and for insufflation of the talc. In the absence of adhesions, a second port was usually not required, and the atomizer was inserted through the same access site parallel to the thoracoscope. An average of 5 g (3 to 8 g) of sterile talc was insufflated onto all pleural surfaces in a systematic fashion from the apex to the diaphragm giving a "snow storm" appearance. One or two chest tubes were then inserted depending on the number of access sites utilized. One tube was always placed in a dependent position, and all tubes were connected to an underwater seal drainage system. The tubes were removed when their

drainage was <100 mL over 24 h. Daily chest radiographs were obtained to ensure full lung expansion and to check for any pneumothorax or residual effusion.

Follow-up

All patients were followed up in the clinic 1 week after hospital discharge, monthly for 3 months, then quarterly for 1 year. A chest radiograph was obtained at each clinic visit, the findings were noted, and patient's functional status was recorded.

RESULTS

There were 24 patients, 13 male and 11 female, with a mean age of 63.3±12.9 years (range, 36 to 84 years). Fourteen of the effusions were on the left and 10 were on the right. The site of the primary cancer is shown in Table 1. The mean operating time was 44.3±14.9 min (median, 43; range, 23 to 75 min); mean duration of chest tube was 2.9±1.3 days (median, 3; range, 1 to 5 days); the mean length of stay on the thoracic ward was 4.4 days (median, 4; range 3 to 7 days).

The results of the procedure are shown in Table 1. Two of the patients with good results and all of the patients with poor results had lung cancer as their primary diagnosis. Twelve patients are alive 4 to 30 months after pleurodesis with a mean survival of all patients of 9±3 months. The overall actuarial survival was 66% at 6 months, 48% at 12 months, and 32% at 24 months. There was one perioperative death (4.1%) in an 84-year-old patient with primary lung cancer, who died subsequent to hospital discharge within 30 days of surgery.

DISCUSSION

The origin of traditional thoracoscopy is credited to Jacobaeus.⁸ These early techniques were limited

Table 1—Clinical Results*

Site of Primary	Total	(% of All)	Excellent	Good	Poor
Lung	6	(25)	1	2	3
Breast	5	(20)	5		
Colon	5	(20)	4	1	
Kidney	3	(13)	3		
Stomach	2	(8)	2		
Prostate	1	(4)	1		
Ovary	1	(4)		1	
Unknown	1	(4)	1		
All patients	24		17 71%	4 17%	3 12%

*Notes: Excellent: full lung expansion, no residual effusion, and marked improvement in symptoms. Good: satisfactory lung expansion, minimal residual effusion, and improved symptoms. Poor: incomplete lung expansion, recurrence of pleural effusion, or no improvement in respiratory symptoms.

in complexity by the scopes and instruments of the era. Typically diagnostic and simple therapeutic procedures of the pleural space were undertaken under local anesthesia. Because most of the pleural processes of the early half of this century were related to underlying tuberculosis, the advent of effective chemotherapy and surgical therapy for tuberculosis resulted in a smaller role for traditional thoracoscopy.⁹⁻¹²

The advent of high-resolution video technology revolutionized thoracoscopy in much the same way that it had previously affected obstetrics, gynecology, orthopedic, and general surgery. As a result, increasingly complex thoracic procedures involving the pleura, lung, mediastinum, esophagus, and pericardium are now being performed.^{9,10,13-15} General anesthesia and intubation techniques allowing independent lung ventilation have facilitated the evolution of these complex video-assisted procedures. General anesthesia allows for urgent/emergent conversion to open thoracotomy while ipsilateral lung collapse allows optimal visualization and exposure. Consequently, reports of traditional thoracoscopy advocate the use of local anesthesia, while those of the modern era support the use of general anesthesia and independent lung ventilation.^{1,2,3,6,8,16}

We agree that complex VATS procedures are ideally performed under general anesthesia. However, selected diagnostic and therapeutic procedures of the pleura can still be performed safely under local anesthetic techniques. Local rib block achieves satisfactory anesthetic levels for one or two access sites in most cases. Supplemental local anesthetic infiltration can be used at the access site as necessary. Propofol provides excellent amnesia and fentanyl can be used for supplemental sedation, analgesia, and cough suppression. The induced simple pneumothorax affords enough exposure to assess visceral and parietal pleural surfaces, perform directed pleural biopsies, lyse simple adhesions, assess lung expansion, evacuate residual effusion, and insufflate talc evenly onto all pleural surfaces. Although ill, these patients are accustomed to the loss of lung volume and tolerate simple pneumothorax well. Patients recover quickly with rapid return to the ward where they generally report minimal pain, and resume oral intake with the next scheduled meal. Subsequent analgesia is obtained with oral narcotics supplemented as necessary with IM ketorolac tromethamine.

By simplifying the anesthetic treatment of these often debilitated patients, we have been able to offer the benefits of VATS to more patients, earlier in their hospital course. Postoperative recovery has been gratifyingly short and uncomplicated. While

the procedure is short and done under local anesthesia, we believe it is essential that it be done in an operating room with anesthesia support. This level of attention and expertise is needed to ensure proper titration of the IV sedation and maintenance of an effective airway.¹⁷

The use of talc as a slurry for pleurodesis via a chest tube at the bedside is also highly effective. The apparent advantages of VATS are the ability to lyse adhesions and enter areas of loculated fluid, take a biopsy specimen from the pleura if necessary to confirm the diagnosis (as done in three cases in this series), and evenly distribute the talc powder. The advantage of the bedside pleurodesis via chest tube is its simplicity and safety. This study did not attempt to compare these procedures, which are likely complementary with each being preferable in some cases. Results from studies such as that sponsored by the Cancer and Leukemia Study Group - B (CALG-B Protocol 9632) will aid in these decisions.

CONCLUSION

The increased complexity of VATS procedures has resulted in a necessary shift in anesthetic techniques from local anesthesia with induced pneumothorax to general anesthesia with independent lung ventilation. Despite these advances, the indications and therapeutic interventions performed for pleural diseases in the modern era of thoracoscopy vary little from those of the traditional era. We have shown that VATS can be performed safely and effectively using local anesthetic techniques with supplemental IV sedation. This technique combines the advantages of direct visualization with local anesthesia and talc sclerosis. We anticipate this will translate into effective patient palliation, at lower cost, with more rapid return to home and/or adjuvant therapy.

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Video-assisted talc pleurodesis for malignant pleural effusions utilizing local anesthesia and I.V. sedation

CA Danby, SA Adebanojo and DM Moritz
Chest 1998;113:739-742

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Exhibit 8

Randomized Trials Describing Lung Inflammation after Pleurodesis with Talc of Varying Particle Size

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Oxford Pleural Disease Clinic, Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, United Kingdom

We report two trials describing whether talc pleurodesis with a mean particle size of less than 15 μm ("mixed" talc) produces more lung and systemic inflammation than tetracycline or "graded" talc (most particles < 10 μm were removed). First, 20 patients with malignant effusions received tetracycline or mixed talc. Changes in lung and systemic inflammation from lung clearance scans, oxygen saturations, and C-reactive protein from baseline to 48 hours after pleurodesis were recorded. Lung inflammation (change in isotope clearance, talc -9.26, SD 14.3 vs. tetracycline 4.10, SD 13.8 minutes; difference = -13.4; 95% confidence interval [CI], -26.6 to -0.2; $p = 0.05$) and systemic inflammation (change in C-reactive protein, talc 198 SD 79.2 vs. tetracycline 74 SD 79.4 $\mu\text{g/L}$; difference = 124; 95% CI, 50 to 199; $p = 0.004$) were greater after talc. Second, 48 patients received mixed or graded talc, and gas exchange was assessed from changes in the alveolar-arterial oxygen gradient. Mixed talc worsened gas exchange (oxygen gradient change, mixed 2.17 SD 1.74 kPa, 16.3 13.1 mm Hg vs. graded 0.72 SD 2.46 kPa 5.4 18.5 mm Hg, difference = 1.45; 95% CI, 0.2 to 2.7; $p = 0.03$) and induced more systemic inflammation than graded talc. We conclude that the routine use of graded talc for pleurodesis would reduce the morbidity of this procedure.

Keywords: acute respiratory distress syndrome; pleural effusion; pleurodesis; randomized trial; talc

There are approximately 300,000 pleural effusions caused by cancer in the United Kingdom and United States each year (1). Many of these are symptomatic and require pleurodesis for their control. Sterile talc is the most effective agent for pleurodesis (2-4), but there are concerns that it may not be safe. There are over 30 reported cases of acute respiratory distress syndrome after intrapleural talc administration, and 9 of these have been fatal (2, 5-13). In a recent international survey of 859 pulmonologists, over half reported cases of respiratory failure after talc pleurodesis (14). This toxicity is seen after both talc slurry and talc poudrage (8). It is hypothesized that this toxicity may relate to the use of talc preparations that include particles of small (< 15 μm) size because most reports of acute respiratory distress syndrome are from countries where preparations including small particle sizes are prevalent (2, 8, 10, 11). In contrast, large observational series from countries that use talc containing only large particle sizes describe few serious adverse events (3, 15).

There are no randomized trials assessing the potential toxicity of varying talc preparations and no studies describing whether the reported cases of acute respiratory distress syndrome are

isolated idiosyncratic adverse reactions or the severe end of a spectrum of diffuse lung damage that could be detected from subtle indices of lung inflammation. This article reports two randomized trials addressing this question.

We hypothesized that inflammation in the lung contralateral to a pleurodesis might be detectable by $^{99\text{m}}$ technetium-labeled DTPA lung scanning because this test is capable of identifying subtle lung inflammation in other settings (16-19). This hypothesis led to the two randomized trials reported here. In the first, we assessed whether talc with a mean particle size of less than 15 μm ("mixed" particle size talc—the standard U.S. and U.K. preparation) produced DTPA scan-detectable lung inflammation and hypoxemia after pleurodesis compared with a non-talc-based control (tetracycline pleurodesis). In the light of the results of this first study, we then performed the second trial to compare the severity of arterial hypoxemia, fever, and systemic inflammation after pleurodesis with mixed (standard United Kingdom and United States) talc and talc that has had the majority of particles less than 10 μm size removed (mean particle size of > 25 μm —"graded" particle size talc—the standard European preparation). Despite its role in original hypothesis testing, DTPA scanning was not used in the second trial, as the results of the first had rendered this complex investigation unnecessary (20).

METHODS

Trial Designs and Setting

Both of these trials are prospective, parallel, randomized trials performed in a single center (the Oxford Pleural Disease Clinic, Oxford Centre for Respiratory Medicine, Oxford, UK). The population served by this unit is 500,000. Patients with proven or suspected malignant pleural effusions are referred to the Oxford unit directly from general practitioners (45%), from the regional oncology center (based on the same site) (35%), and from other local hospital consultants (20%).

Patients

The entry criteria for the two studies were the same. All patients eligible for the trial who presented over the 24-month recruitment period were offered entry into the trials. Patients were enrolled by N.A.M. and R.J.O.D. To be eligible for the trial, patients had to have a symptomatic pleural effusion proven to be due to pleural malignancy by cytology and/or histology. Exclusion criteria were as follows: expected survival of less than 6 weeks, bleeding diathesis sufficient to contraindicate chest tube insertion, extensive "trapped lung" after fluid drainage, previous pleurodesis on the side of the effusion, inability to give informed consent, or age of less than 18. The study was approved by the Central Oxford Research Ethics Committee, and all participants gave informed consent.

Pleurodesis Agents

The talc preparations were both commercially available preparations manufactured for pleurodesis. The mixed talc (Thornton and Ross, Huddersfield, UK) includes a range of particle sizes, with 50% being less than 10 μm in size. This preparation is typical of that usually used in the United States and the United Kingdom. The graded talc (Nořatěch, Grasse, France) is sorted during manufacture so that it contains less than 50% of particles smaller than 20 μm (see Figure E1 in the online supplement). This preparation is typical of that usually used in continental Europe. Both talc preparations are refined by the

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same manufacturer (Luznac Micro Milling, Porte, Italy) from raw talc mined from European mines and therefore are chemically identical. After manufacture, both talc preparations are prepared in 4-g aliquots and sterilized by irradiation before use. The tetracycline used was manufactured by Grunenthal (Aachen, Germany).

Clinical Follow-up

Patients were followed for 3 months or until death. A chest radiograph was taken at 3 months. A successful pleurodesis was defined as no reaccumulation of pleural fluid sufficient to require drainage at 3 months after randomization.

Individual Trial Designs

Trial 1: mixed (including 50% < 15 μm) talc versus tetracycline. In this trial subjects were randomized to 4 g of mixed (including 50% < 15 μm) talc or tetracycline, 20 mg/kg in 50-ml normal saline (see the online supplement for details of the randomization procedure and pleurodesis protocol).

The primary outcome for this study was the change in the DTPA clearance from the lung contralateral to the side undergoing pleurodesis from baseline to 48 hours after pleurodesis. Secondary outcome variables were the changes in the following indices from baseline to 48 hours after pleurodesis: arterial oxygen saturation sitting quietly recumbent and breathing air, the plasma C-reactive protein ($\mu\text{g/L}$), pleural fluid interleukin (IL)-8 concentrations, and the presence of visible ground glass shadowing on high-resolution thoracic computed tomography (CT) scanning 48 hours after pleurodesis.

The high-resolution computed tomograms were performed on a General Electric light-speed multislice CT scanner (General Electric, Milwaukee, WI) using 1-mm sections every 10 mm from the apex of the lungs to the costophrenic recess. They were reported by F.V.G. blind of the subject's randomization status. Because there have been no previous studies of DTPA lung clearance after pleurodesis, the sample size for this study was based on the size of sample capable of identifying subtle lung inflammation ($n = 10$) in other studies (16, 17).

Trial 2: mixed (including 50% < 15 μm) talc versus graded (including 50% > 25 μm) talc. In this trial, subjects were randomized to 4 g of mixed (including 50% < 15 μm) or 4 g of graded (including 50% > 25 μm) talc in 50-ml normal saline (see online supplement for details of the randomization procedure and pleurodesis protocol). Patients were blinded to which talc preparation they received.

The primary outcome for this study was the change in the alveolar to arterial oxygen gradient (A-a gradient) breathing air, sitting at quiet rest, and semirecumbent from baseline to 48 hours after pleurodesis. Secondary outcome variables were the changes in the following indices from baseline to 48 hours after pleurodesis: arterial partial pressure of oxygen breathing air, sitting at quiet rest and semirecumbent, the presence of a fever of more than 37.5°C at 48 hours after pleurodesis, the plasma C-reactive protein ($\mu\text{g/L}$), pleural fluid IL-8 concentrations (see online supplement for details), and the clinical efficacy of pleurodesis assessed at 3 months after pleurodesis.

Power Calculation

The sample size for trial 2 was calculated from the estimated change in PaO_2 in the mixed-talc group in Trial 1, inferred from the change in arterial oxygen saturation. Thus, it was assumed PaO_2 would fall by 15 mm Hg in the mixed-talc group with no change in the graded-talc group (SD of change in $\text{PaO}_2 = 15$ mm Hg). Using these assumptions, a trial of 50 patients was needed to exclude a difference of 15 mm Hg between the groups (90% power, $\alpha = 0.05$) (Power and Precision Software; Biostat, National Institutes of Health).

Statistical Analysis

In both trials, the data analysis was performed with SPSS version 10 (SPSS Inc., Chicago, IL). Parametric data were analyzed using the independent t test, and unless otherwise stated, the data are presented as mean (SD). Chi-squared analysis and Fisher's exact test were used when comparing proportions.

RESULTS

Subjects

Figures 1 and 2 show the two trial profiles. Total recruitment was over 24 months. During the recruitment period, 91 eligible patients were identified, and 87 of these consented to enter the studies.

The characteristics of the subjects agreeing to take part are shown in Tables 1–3. These show the groups were well matched at baseline.

Thirty-one patients were recruited to Trial 1. Eleven were excluded, five because of extensively "trapped lung" on the baseline chest radiograph, three because they were unable to perform the baseline DTPA lung clearance, one because of a myocardial infarction, and two because of chest tube displacement. Twenty patients were randomized to talc or tetracycline and completed this trial (Figure 1).

In Trial 2, 56 patients were identified. Eight were excluded because they had extensively trapped lung, and 48 were randomized. Two patients in the mixed-talc group were excluded after randomization because of chest tube displacement before pleurodesis (Figure 2).

Outcomes

Trial 1: mixed (including 50% < 15 μm) talc versus tetracycline. Primary end point. DTPA lung clearance from the lung contralateral to the pleurodesis. One patient (in the tetracycline group) could not perform the DTPA clearance at 48 hours after pleurodesis and was excluded from the analysis.

The fall in the isotope clearance half time was greater in the mixed-talc group than in the tetracycline group (-9.26 [SD 14.3] vs. 4.10 [SD 13.8] minutes; difference = -13.4 ; 95% CI, -26.6

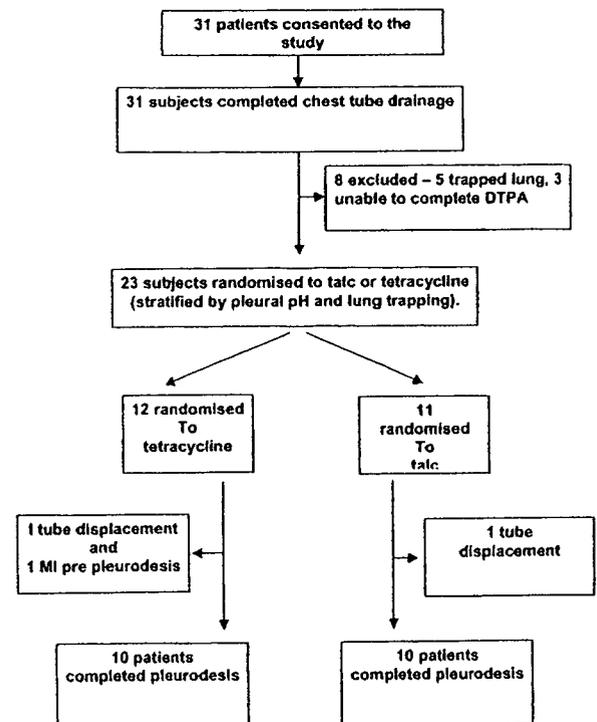


Figure 1. Flow diagram of the first trial (mixed talc vs. tetracycline).

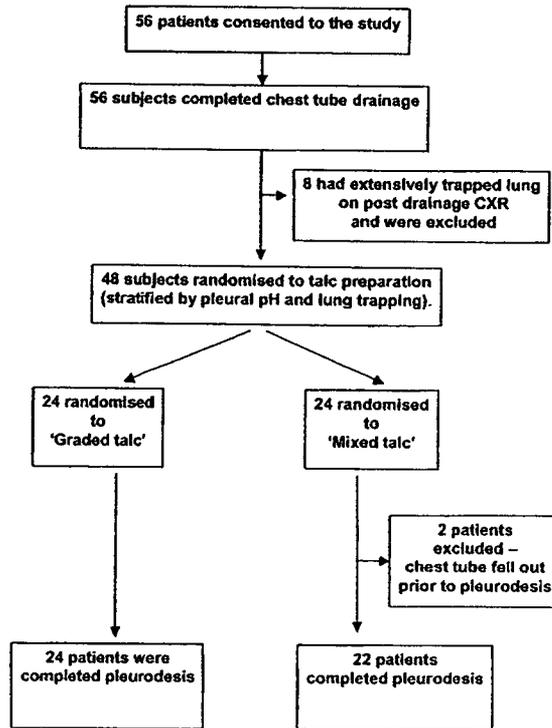


Figure 2. Flow diagram of the second trial (mixed talc vs. graded talc). CXR = chest radiograph.

to -0.2 ; $p = 0.05$, independent t test; Figure 3). A decline in the DTPA clearance half time is associated with increased lung inflammation in most disease states.

Secondary end points.

Arterial oxygen saturation. The arterial oxygen saturation fall was greater after pleurodesis with mixed talc than after pleurodesis with tetracycline (3.23% [1.6%] vs. 0.72% [1.5%]; difference = 2.51; 95% CI, 1.1 to 4.0; $p = 0.003$ independent t test; Figure 3). This shows that the increased lung inflammation identified by the DTPA analysis was associated with a fall in arterial oxygenation, indicating functionally significant impairment of gas exchange. This decline in gas exchange efficiency led to the selection of the alveolar to arterial oxygen gradient as the primary endpoint for the second trial.

Blood C-reactive protein. The C-reactive protein rise after mixed-talc pleurodesis was greater than after tetracycline pleurodesis (198 [79.2] vs. 74 [79.4] $\mu\text{g/L}$; difference = 124; 95% CI, 50 to 199; $p = 0.004$, independent t test, Figure 3). This shows that the systemic inflammatory response induced by mixed talc was greater than that induced by tetracycline pleurodesis.

Pleural fluid IL-8 levels. The pleural fluid IL-8 levels at 48 hours after pleurodesis were not different between the trial groups (mixed-talc pleurodesis, 18,584 [20,634] vs. tetracycline 6,314 [15,699] pg/ml ; difference = 12,270; 95% CI, $-4,955$ to 29,495; $p = 0.18$).

High-resolution thoracic CT. No changes were seen on the high-resolution thoracic CT images of the contralateral lung 48 hours after pleurodesis in either trial group.

Trial 2: mixed (including 50% < 15 μm) talc versus graded (50% > 25 μm) talc.

Primary endpoint.

A-a oxygen gradient. Four patients (two in each trial group) declined repeated arterial blood gas measurements 48 hours after pleurodesis.

Mixed talc resulted in a greater increase in the A-a oxygen gradient than did graded talc (which did not produce any significant increase) (2.17 [SD 1.74] kPa; 16.3 [13.1] mm Hg; vs. 0.72 [SD 2.46] kPa; 5.4 [18.5] mm Hg; difference = 1.45; 95% CI, 0.2 to 2.7; $p = 0.03$, independent t test; Figure 4). This shows that the pleurodesis with mixed talc produced a deterioration in blood oxygenation that was not seen with chemically identical graded talc.

Secondary endpoints.

Arterial partial pressure of oxygen. The arterial partial pressure of oxygen fall was greater after pleurodesis with mixed talc than it was after graded talc (1.9 [1.84] kPa; 14.6 [13.8] mm Hg; vs. 0.4 [1.7] kPa, 3.75 [12.5] mmHg; difference = 1.5; 95% CI, 0.45 to 2.55; $p = 0.01$, independent t test, Figure 4).

Fever after pleurodesis. Nine of 22 (41%) patients receiving mixed talc had a fever of more than 37.5°C at 48 hours after their pleurodesis, whereas this only occurred in 1 of 24 (4%) patients receiving graded talc (difference = 37%; 95% CI, 15% to 59%; $p < 0.001$, chi-squared test; Figure 5).

C-reactive protein. The rise in plasma C-reactive protein was greater after mixed-talc pleurodesis than it was after graded-talc pleurodesis (161 [72.2] vs. 111 [69.3] $\mu\text{g/L}$ tetracycline group; difference = 50; 95% CI, 8–92; $p = 0.04$, independent t test; Figure 4).

Pleural fluid IL-8. The change in pleural fluid IL-8 levels at 24 hours after pleurodesis showed no difference after the two talc preparations (mixed talc, 36,313 [27,424]; graded talc, 21,075 [22,237] pg/ml ; difference = 15,238; 95% CI, 457 to 30,019; $p = 0.18$, independent t test).

Clinical outcome and the success of the pleurodesis. Three patients were lost to follow-up (two in the mixed-talc group and one in the graded-talc group). In the mixed talc group, 7 of 21 (33%) patients died by 3 months. The pleurodesis was successful in 11 of the 14 (79%) survivors. In the graded-talc group, 8 of 22 (36%) patients died by 3 months. The pleurodesis was successful in 12 of 14 (85%) of the survivors.

TABLE 1. PATIENT CHARACTERISTICS—TRIAL 1: MIXED TALC VERSUS TETRACYCLINE

	Mixed Talc Pleurodesis (n = 10)	Tetracycline Pleurodesis (n = 10)
Age, yr, mean (SD)	57.6 (11.7)	61.4 (8.9)
Sex, n, male:female	3:7	2:8
Pleural fluid pH, mean (SD)	7.35 (0.1)	7.34 (0.15)
Type of malignancy, n		
Breast cancer	5	6
Lung cancer	1	1
Unknown primary cancer	1	1
Pleural mesothelioma	1	0
Bowel carcinoma	0	1
Other	2	1

DISCUSSION

These trials have shown that pleurodesis using mixed talc (containing small talc particles) produces more lung and systemic inflammation and more hypoxemia than graded talc (sorted during manufacture to exclude the vast majority of particles of less than 10 μm), or tetracycline. The magnitude of this effect is substantial. The A-a oxygen gradient increased after mixed talc by 2.17 (SD 1.74) kPa and 16.3 (SD 13.1) mm Hg with 43% of subjects experiencing an increase of more than 2 kPa (15 mm Hg)—sufficient to render a subject with moderate hypoxemia (8 kPa,

TABLE 2. PATIENT CHARACTERISTICS—TRIAL 2: MIXED VERSUS GRADED TALC

	Mixed Talc (n = 24)	Graded Talc (n = 24)
Age, yr, mean (SD)	64.2 (11.8)	69.8 (14.1)
Sex, male:female, n	7:17	10:14
Pleural fluid pH, mean (SD)	7.35 (0.14)	7.34 (0.12)
Pleural fluid protein, g/L, mean (range)	38 (26–74)	40 (18–67)
Pleural fluid LDH, IU/L, mean (range)	282 (150–1,874)	226 (119–743)
Partially trapped, n	8	8
Total pleural drainage before pleurodesis, ml	3,161 (1,800)	2,407 (1,803)

Definition of abbreviation: LDH = lactate dehydrogenase.

60 mm Hg) at baseline severely hypoxemic with an arterial partial pressure of less than 6 kPa (45 mm Hg). In this study, 8 of 23 (35%) of patients receiving mixed talc developed a postpleurodesis Pa_{O_2} of less than 8 kPa (60 mm Hg) in contrast to only 4 of 23 (17%) of those receiving graded talc (see Figure E2 on the online supplement).

This observation is likely to be helpful in understanding the cases of life-threatening hypoxemia after pleurodesis reported from the United Kingdom and the United States (2, 5–13) but rarely reported from Europe (3, 15). In the United Kingdom and the United States, the talc used for pleurodesis is of the mixed type studied here, whereas in Europe, graded talc is usually used. In the United States and the United Kingdom, there are approximately 300,000 malignant effusions each year, and many of these patients receive pleurodesis with mixed talc. Thus, these results suggest that many patients may be experiencing clinically significant hypoxemia, which could be reduced by the use of graded talc with its smallest particles removed. Therefore, we would recommend that all patients undergoing pleurodesis have oximetry measurements taken during and for 48 hours after pleurodesis.

The hypoxemia after mixed-talc pleurodesis is a reasonably consistent feature in the patients studied. This shows that the prevalence of hypoxemia is much higher than is suggested by the few reports of severe and life-threatening acute respiratory

distress syndrome and implies that these severe cases are simply the extreme end of a predictable adverse reaction, rather than isolated idiosyncratic events.

It is hypothesized that the mechanism for talc pleurodesis-induced hypoxemia may be the escape of very small talc particles from the pleural space through the parietal pleural pores (21). There is evidence to substantiate this hypothesis from animal models and an isolated human case where systemic talc dissemination after pleurodesis with small caliber talc has been demonstrated (22–24). These studies provide some indirect evidence to support this "escaped talc" mechanism. Our results suggest that postpleurodesis hypoxemia is due to generalized lung inflammation as well as increased systemic inflammation because we have seen both clinical and laboratory evidence of a greater systemic inflammatory responses with mixed talc but no difference in the intensity of the pleural inflammation. Nine of 22 (41%) patients receiving mixed talc developed fever after their pleurodesis, whereas fever was almost absent (1 of 24, 4%) in those receiving graded talc. The concentrations of C-reactive protein were higher after mixed talc when measured from the systemic compartment (blood), whereas the pleural IL-8 concentrations were similar after each of the three pleurodesis agents.

In trial 1, the hypothesis being tested was that subtle talc-induced lung inflammation would be detectable from the lung

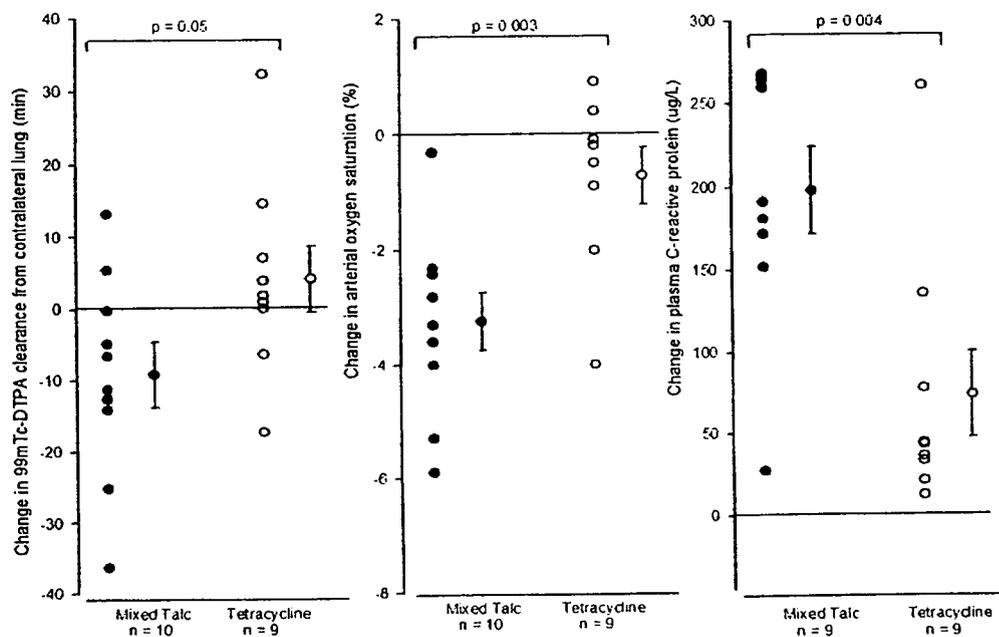


Figure 3. The primary and secondary outcomes of the first trial (mixed talc vs. tetracycline). The primary endpoint was the clearance of DTPA from the lung contralateral to the pleurodesis. Sa_{O_2} and C-reactive protein were secondary endpoints. Results after mixed talc are shown as filled circles and tetracycline as empty circles.

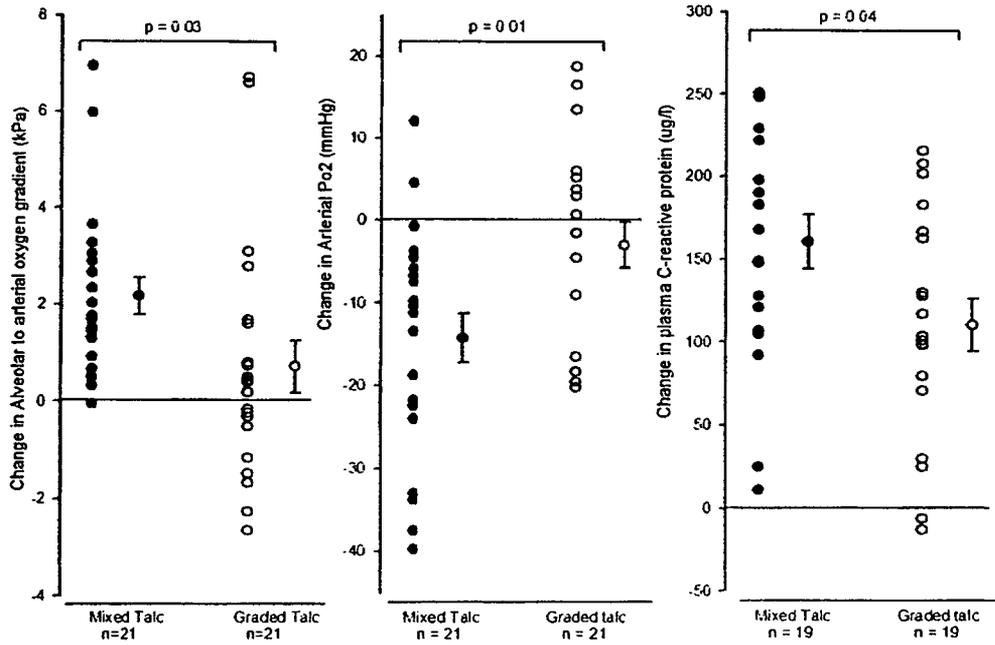


Figure 4. The primary and secondary outcomes of the second trial (mixed talc vs. graded talc). The primary endpoint was the change in alveolar to arterial oxygen gradient. PaO₂ and C-reactive protein were secondary endpoints. Results after mixed talc are shown as filled circles and graded talc as empty circles.

contralateral to a talc pleurodesis. Therefore, we chose to use the half time of the epithelial lung clearance of aerosolized DTPA as the primary outcome for this trial. DTPA clearance predominantly assesses the permeability of the epithelium of the terminal respiratory units to solutes and is a sensitive index of lung inflammation in diffuse inflammatory lung disease (16-18), including acute minor pneumonitis after radiotherapy to the other lung (17). Measurements of DTPA clearance are influenced by smoking and position. Both of these variables were controlled in this study, with similar numbers of smokers and ex-smokers in each group and all of the scans being undertaken in the supine position.

By studying DTPA clearance from the lung contralateral to the pleurodesis, we aimed to avoid the confounding effects of changes in chest tube placement, local pleurodesis inflammation, lung atelectasis, and changes in the volume of the pleural effusion on the side where the pleurodesis was performed. This contralateral lung clearance fell by 20% in the standard mixed-talc group, and no fall was seen in the tetracycline group. The magnitude of this fall is similar to that seen with postradiotherapy pneumonitis (17) and between patients with clinically progressive lung fibrosis and those with stable disease (18). It is therefore evidence of clinically significant lung inflammation.

Both talc preparations were traced back to the same mining region in Europe, and thus, the constituents of the talc prepara-

tions should have been identical apart from their size difference. This makes it unlikely that the differences seen were due to impurities in one preparation that were not present in the other.

The frequency of the control of recurrent pleural fluid was similar with the two talc preparations (79% vs. 85%) used in the second trial. This study was not adequately powered to define efficacy accurately, but these results suggest that there is not a large difference in treatment efficacy between the two preparations.

In conclusion, we have shown that pleurodesis with mixed talc causes a greater systemic inflammatory response than graded talc and tetracycline. This is associated with greater hypoxemia and a fall in the clearance half time of inhaled DTPA from the contralateral lung, demonstrating significant lung inflammation. These results suggest that the severe hypoxemia and adult respiratory distress syndrome described after talc pleurodesis are probably the severe ends of a widely detectable spectrum of toxicity and are likely to be minimized by using graded talc (with its smallest particles removed). We conclude that talc from which most particles of less than 15 µm have been removed is probably a safer agent for pleurodesis than standard mixed talc.

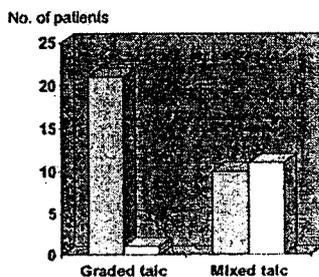


Figure 5. The proportion of individuals who remained pyrexial (> 37.5, open bars) and afebrile (gray bars) 48 hours after pleurodesis in the second trial (mixed talc vs. graded talc; p < 0.001, χ^2).

TABLE 3. TUMOR TYPES IN TRIAL 2: MIXED VERSUS GRADED TALC

	Mixed Talc (n = 24)	Graded Talc (n = 24)
Primary tumor type, n		
Breast	8	6
Lung	7	6
Pleura (mesothelioma)	3	2
Ovary	2	3
Sarcoma	1	1
Bladder	1	-
Renal	-	1
Non-Hodgkins lymphoma	-	1
Bowel (metastatic carcinoma)	-	1
Unknown (adenocarcinoma)	2	3
Unknown (squamous cell)	1	-

Conflict of Interest Statement: N.A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; Y.C.G.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.V.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.L.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.J.O.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Exhibit 9

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Chest 1997;111:442-448

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A M E R I C A N C O L L E G E O F
 **C H E S T**
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laboratory and animal investigations

A Comparison of Thoracoscopic Talc Insufflation, Slurry, and Mechanical Abrasion Pleurodesis*

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Ronald G. Konopka, BS; Peter G. Chiles, BA; Craig A. Pedersen; and
David Kapelanski, MD

The purpose of this study was to compare the anatomic and histopathologic results of four different methods of pleurodesis in 10 dogs. Each animal was randomly assigned to receive two of the following methods of pleurodesis: thoracoscopic talc insufflation (poudrage), talc slurry administration, focal gauze abrasion by limited thoracotomy, and mechanical abrasion by thoracoscopy using a commercially available pleural abrader. Animals were killed 30 days after pleurodesis. At autopsy, the efficacy of pleurodesis was graded by evaluating the gross appearance of each pleural cavity and lung (pleurodesis score), and by determining the extent of adhesion formation (obliteration grade). Pleural and lung biopsy specimens were obtained from the areas most representative of adhesion formation for histopathologic evaluation. Pleurodesis scores (on a scale of 0 to 4) were 3.0 ± 0.7 for talc poudrage ($p < 0.05$ when compared with talc slurry), 2.2 ± 1.7 for thoracotomy, and 1.6 ± 1.1 for talc slurry. Adhesions produced by gauze abrasion during thoracotomy were mostly peri-incisional. Thoracoscopic pleural abrasion using the pleural abrader was uniformly unsatisfactory. Granulation tissue formation was greatest in both talc models. The degree of parietal pleural thickening was greatest in the talc slurry model, but fibrosis and inflammation occurred mostly in gravity-dependent areas within the pleural cavity. Although differences were not statistically significant, thoracoscopic talc insufflation consistently produced the most widespread, firm fibrotic adhesions as evidenced by higher obliteration grades. (CHEST 1997; 111:442-48)

Key words: abrasion; pleurodesis; talc; thoracoscopy

Abbreviations: TTI=thoracoscopic talc insufflation

Pleurodesis usually involves the introduction of sclerosing agents into the pleural space to relieve dyspnea in patients with recurrent pleural effusions. This palliative technique is particularly useful for patients with malignancy because their short life expectancy requires successful, palliative intervention to improve quality of life.¹ Pleurodesis may also prevent recurrent pneumothorax in patients with

spontaneous or secondary pneumothorax.² All sclerosing agents can be introduced through indwelling chest tubes. Pleurodesis can also be performed thoracoscopically or during open thoracotomy. Indeed, open pleural abrasion, usually using a folded gauze, has been the gold standard for pleurodesis in patients with pneumothorax. In patients with malignant pleural effusions, however, introduction of a chemical sclerosing agent into the pleural space has been advocated most frequently. Success rates depend on the agent used, and potentially, on the dose, frequency, and therapeutic modality employed.³ Increasingly, it appears that pleurodesis using sterile, asbestos-free talc powder is more frequently effective than either tetracycline derivatives or antineoplastic agents.⁴ Talc can be administered thoraco-

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scopically, which also allows diagnostic tissue sampling, evacuation of loculated pleural fluid collections, lysis of adhesions, evaluation of lung entrapment, and cauterization or resection of blebs and bullae.⁵ Potential disadvantages of thoracoscopy are increased costs related to instrumentation purchase, operating room or endoscopy suite use, and a preference toward using general anesthesia in many institutions. In patients who do not require thoracoscopy, are unable to tolerate the procedure, or in patients first seen with an indwelling chest tube, talc can be administered as a slurry; it is diluted in normal saline solution and delivered through the chest tube.⁶ This technique may be less effective than thoracoscopic talc insufflation (TTI), and hospitalization can be prolonged 2 to 3 days while pleural fluid drainage decreases sufficiently to allow effective sclerosis (often <100 mL/d).⁷

Although multiple studies of sclerosing agents in small animal models are available, to our knowledge none have compared both talc slurry and thoracoscopic talc insufflation to pleural abrasion, particularly in a large animal model. The purpose of this controlled, comparative study, therefore, was to examine the macroscopic and histopathologic consequences of pleurodesis 30 days after TTI, talc slurry administration, thoracoscopic mechanical abrasion using a commercially available "pleural abrader," and focal mechanical gauze abrasion through a limited thoracotomy.

MATERIALS AND METHODS

Animal Subjects

The protocol was approved by the Institution's Committee on Investigations Involving Animal Subjects. All animals were housed and procedures were performed in the facilities of the University of California San Diego. Humane care was provided in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH publication No. 86-23, revised, 1985).

General Design

Ten conditioned mongrel dogs (weight, 25 to 35 kg) were randomly assigned to undergo sequential bilateral pleurodesis during the same general anesthetic. The randomization procedure precluded utilization of the same pleurodesis method in both hemithoraces. The following pleurodesis techniques were evaluated: (1) dry gauze abrasion through a limited thoracotomy; (2) thoracoscopic mechanical abrasion using a commercially available 5-mm stainless-steel grooved burr abrader (Richard Wolf Co; Vernon Hills, Ill); (3) TTI using 4 g of asbestos-free United States Pharmacopocia (USP)-approved sterile talc powder administered by pneumatic atomizer (Richard Wolf Co.); and (4) instillation of talc slurry comprising 5 g of USP approved sterile, asbestos-free talc powder suspended in 100 mL of sterile saline solution.

Operative Techniques

General anesthesia was induced with propofol (6 to 10 mg/kg) IV. Following induction and endotracheal intubation, a surgical plane of anesthesia was maintained using halothane (1 to 1.5%). Penicillin G benzathine (Bicillin), 40,000 U/kg IM, was administered prophylactically. Arterial BP was continuously monitored after percutaneous placement of a femoral arterial catheter. The surface ECG was continuously monitored using standard limb leads. Variation in core temperature was minimized by employment of a circulating water blanket. An antimicrobial skin preparation (povidone-iodine) was employed prior to all invasive procedures, each of which was performed using aseptic surgical technique.

For thoracoscopic pleurodesis, 5- and 7-mm pleural trocars were introduced through lateral 1-cm incisions overlying the fourth and sixth intercostal spaces. Visual examination of the hemithorax was performed using a 7-mm diameter rigid telescope and single-chip videocamera (Richard Wolf Co). Following TTI, the uniform distribution of insufflated talc over all visceral and parietal pleural surfaces was verified by thoracoscopic inspection. Widespread thoracoscopic mechanical abrasion was performed by rubbing the parietal pleura with the grooved burr of the pleural abrader until punctate hemorrhages were observed, taking care to avoid full-thickness disruption of the pleural lining (Fig 1). Talc slurry was administered through the pleural trocars, simulating the clinical technique of blind administration through an indwelling chest tube.

Prior to thoracotomy, neuromuscular relaxation was achieved by administration of succinylcholine (0.2 mg/kg) IV single injection. The span of the lateral cutaneous incision was limited to 6 cm by direct measurement. A muscle-dividing fifth intercostal space approach provided access to the entire hemithorax. Focal abrasion of the visceral and parietal pleura was performed using a dry gauze until punctate hemorrhages were evident. Disruption of the pleural surface in areas remote from the operative incision was scrupulously avoided.

At the conclusion of each thoracoscopic procedure, a chest tube was inserted through one of the trocar insertion sites. After thoracotomy, a separate caudal stab incision was employed. The pleural drain was attached to a reservoir (Pleur-evac; Deknatel;



FIGURE 1. Curved, 5-mm stainless-steel, commercially available pleural abrader (Richard Wolf Co) with grooved-burr distal extremity rubbed gently on parietal pleural surface to cause punctate, subpleural hemorrhage during thoracoscopy.

Fall River, Mass) and negative suction was applied (-20 cm H₂O). The cutaneous trocar incisions were closed with running nylon; thoracotomy wounds were repaired in layered fashion using absorbable suture. After radiographic verification of complete lung reexpansion, the chest tube was removed while positive airway pressure was sustained. The animal was then repositioned, and the designated contralateral procedure was performed.

Following completion of both procedures and anesthetic emergence, animals were allowed to recover and returned to quarters. Buprenorphine hydrochloride (Buprenex) (0.02 to 0.05 mg/kg IM) was given every 8 h or as needed if animals demonstrated signs of pain or discomfort (hesitancy in movement, vocalizing, or withdrawal from attendants). Wound integrity and vital signs (temperature, pulse, body weight, and respiration) were carefully monitored for the initial 3 days following the procedure and weekly thereafter. All animals survived the procedures and the designated observation period, providing 20 hemithoraces for analysis.

Macroscopic Evaluation

Thirty days after pleurodesis, each animal was killed by administration of pentobarbital sodium (Nembutal) (120 mg/kg IV). A median sternotomy was performed, and both pleural cavities were carefully inspected and graded by investigators blinded to the method of pleurodesis. A five-point pleurodesis score^{8,9} was employed to characterize the aggregate response to pleurodesis, where 0=normal pleural space and lung; 1=no adhesions but pleural space inflamed as evidenced by redness and fibrin deposition; 2=few scattered adhesions; 3=generalized scattered adhesions; and 4=complete obliteration of the pleural space by adhesions. The extent of adhesions within the pleural cavity was measured using an obliteration grade¹⁰ where one point each was attributed for adhesions between the lower lobe and diaphragm; between the lower lobe and chest wall; between the upper lobe and chest wall; between the upper lobe and mediastinum; between different lobes and the pericardium; and obliteration of the main fissure. One-half point was awarded for filamentous adhesions involving only a portion of a lobe. Using this scale, the maximum attainable grade was six.

Histopathologic Evaluation

In the areas of greatest adhesion formation, a 2-cm wedge of lung parenchyma was removed with a corresponding 1-cm portion of attached parietal pleura. Specimens were placed in 10% neutral buffered formaldehyde solution and labeled for subsequent identification. After fixation for a minimum of 12 h, biopsy specimens were processed routinely in the histology laboratory. Specimens received no special handling and were processed identically to human surgical pathology specimens. Smaller biopsy specimens were submitted intact; larger specimens were sectioned and representative portions were submitted. Paraffin sections were stained with hematoxylin-eosin and trichrome stains. Histologic features of each of the sections were reviewed by a pathologist (V.R.) blinded to the method of pleurodesis. The extent of fibrosis, granulation tissue formation, foreign body granulomas, mesothelial cell proliferation, and pleural thickening were individually graded on a four-point scale where 0=not present, 1=mild, 2=moderate, and 3=marked. Fibrotic pleural plaques and nodules were noted separately, as was loss or absence of the submesothelial elastic layer.

Statistical Analysis

Summary data were expressed as mean ± SD. Numeric scores for each macroscopic and histologic feature were pooled and

ranked in ascending order. A nonparametric one-way analysis of variance (Kruskal-Wallis) was used for statistical comparisons.¹¹ Statistical significance was determined from a standard set of χ^2 tables (*p* value <0.05 considered statistically significant).

RESULTS

The macroscopic features of each of the four pleurodesis techniques are summarized in Table 1. TTI produced widespread, dense adhesions requiring sharp dissection for lysis. Adhesions following talc slurry were most prominent in dependent regions of the hemithorax, but were generally less dense than those caused by talc insufflation. Mechanical abrasion by limited thoracotomy produced firm adhesions in the area surrounding the incision. Not surprisingly, overall adhesion distribution was less uniform than that achieved after TTI, and the extent of pleural obliteration was less than obtained with either method of talc administration. The pleural abrader was ineffective as demonstrated by inferior results using either grading system (*p*<0.05) (Fig 2, 3).

The pleurodesis scores of TTI and gauze abrasion by thoracotomy were similar but TTI was better than talc slurry (*p*<0.05). No differences in obliteration grade were demonstrated between talc administration techniques and mechanical gauze abrasion.

The summary histologic scores for parietal and visceral pleural are shown in Tables 2 and 3. Although differences were not always statistically significant, certain trends were observed. Granulation tissue formation (and its accompanying histologic alterations of inflammation and increased capillaries) was exuberant in both talc models, but was less prominent in the abrasion models. As anticipated, foreign body granulomas were identified only following talc administration (*p*<0.05). In the parietal pleura, fibrosis developed between the mesothelial and elastic layers. Granulomas were confined between the fibrotic layer and the elastic tissue of the chest wall.

In the visceral pleura, fibrosis was seen either

Table 1—Macroscopic Examination of Pleural Cavities After Pleurodesis*

Method of Pleurodesis	Pleurodesis Score	Obliteration Grade
Mechanical abrasion by thoracotomy	2.2 (1.0)	1.7 (1.7)
Thoracoscopic abrasion	0.2 (0.4) [†]	0 [†]
Talc poudrage	3.0 (0.7) [‡]	4.1 (0.7)
Talc slurry	1.6 (1.1)	2.0 (1.5)

*Values are shown as mean ± SD.

[†]*p*<0.05 when compared with each of the other techniques.

[‡]*p*<0.05 when compared with talc slurry.

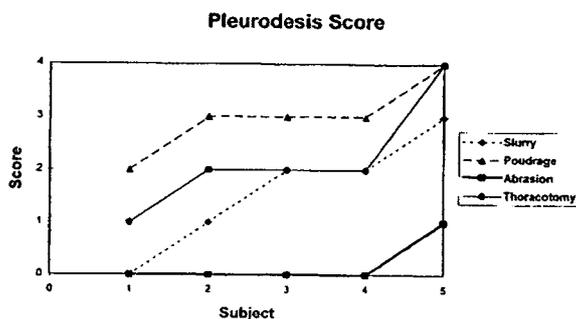


FIGURE 2. Pleurodesis score for each of five hemithoraces treated by each pleurodesis modality.

below or between the mesothelial and elastic layers. When present, foreign body giant cell reaction was consistently observed between these two layers (Fig 4). None of the pleurodesis techniques resulted in histologic alterations of subadjacent pulmonary parenchyma or elicited significant mesothelial cell proliferation. Fibrosis scores were highest after gauze abrasion, although the analysis failed to confirm a statistical advantage. When TTI and talc slurry were compared, fibrotic reactions in both pleural layers were greatest after TTI ($p < 0.05$). The degree of visceral pleural thickening was also greatest in the TTI group ($p < 0.05$), whereas parietal pleural thickening was greatest in the talc slurry group ($p < 0.05$).

DISCUSSION

Most investigators agree that rupture of the integrity of pleural tissues should prompt a tissue repair process comprised of an ingrowth of capillaries, an influx of inflammatory cells, activation of fibroblasts, and production of collagen (granulation tissue). Mesothelial cell injury results in fibronectin production, which also plays an important role in the pathogenesis of fibrin formation and eventual pleural fibrosis.^{12,13} The time course of these events, and partic-

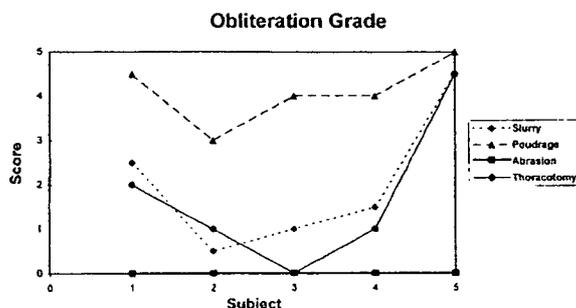


FIGURE 3. Obliteration grade for each of five hemithoraces treated by each pleurodesis modality.

ularly of the histopathologic changes caused by intrapleural talc administration, however, is still uncertain.

In our study, fibrosis without significant granulation tissue formation was seen in both abrasion models,¹⁴ whereas fibrosis with foreign body giant cell reactions and active granulation tissue formation was noted 30 days after talc pleurodesis. Despite these parietal pleural changes, we found no significant histologic alterations within the subjacent lung parenchyma. McGahren et al¹⁵ described marked adhesions with visceral and parietal pleural thickening in a porcine model 5 weeks after TTI: histologic sections of lung parenchyma also showed no inflammatory changes. Pleural thickening, fibrin deposition in areas of mesothelial denudement, and a transient mononuclear vasculitis have been noted in rabbit lungs 7 days after talc slurry (70 mg/kg) administration.¹⁶ Contrary to a previous study,¹⁷ however, only a few, thin adhesions were found at autopsy, and pathologic findings did not support the belief that adhesion strength and number increased because of persistent chronic inflammation.

To facilitate comparisons with other experimental studies, we intentionally used both a previously published pleurodesis score⁸ and obliteration grade¹⁰ to assess outcome. The obliteration grade is a measure of the extent of adhesions between the lungs, mediastinum, diaphragm, and chest wall. Originally described in a canine study of the effects of pleural symphysis on lung mechanics, Deschamps and Rodarte¹⁰ reported a mean grade of 4.6, five weeks after simultaneous thoracotomy, pleurectomy, talc insufflation, and electrocauterization of the parietal pleura. Not surprisingly, the combination of all these techniques surpasses the mean obliteration grade achieved by any single method used in our study.

The pleurodesis score is a measure of the macroscopic appearance of the pleural space.¹⁸ In one previously published rabbit study, the highest mean score after talc slurry pleurodesis (using 400 mg/kg) was 3.36.⁹ Authors concluded that response to talc slurry was dose-dependent. This score is clearly higher than those noted after talc slurry using only 142 mg/kg (5 g of talc for each dog weighing 35 kg) in our study. We chose this amount, however, because of concerns about potential toxicity of higher doses and because this amount was recommended for use in humans.⁴

It is still unclear whether differences in adhesion formation after talc are dose-dependent or can be explained by differences in animal size or species. In the canine model, the dose-response relationship of TTI was previously explored by Mathlouti et al.¹⁹ Killing animals between 1 and 30 days after thoracotomy, authors noted that pleural symphysis was

Table 2—Results of Microscopic Examination of Parietal Pleural Changes*

Technique of Pleurodesis	Granulation		Chronic		Foreign Body	Mesothelial Cell	Degree of Pleural Thickening
	Fibrosis	Tissue	Inflammation	Capillaries	Granulomas	Proliferation	
Mechanical abrasion by thoracotomy	2.2 (1.6)	0.4 (0.5)	1.4 (0.8)	0.4 (0.5)	0 ^{††}	0	2.2 (1.6)
Thoracoscopic abrasion	1.0 (0.7)	0	0.2 (0.4) ^{‡§}	0.4 (0.8)	0 ^{††}	0.2 (0.4)	1.2 (1.3)
Talc poudrage	1.8 (0.4) [†]	1.2 (0.4) ^{§§}	1.4 (0.5)	1.4 (0.5) [§]	2.0 (1.0)	0.8 (0.8)	1.8 (0.4)
Talc slurry	1.4 (1.1)	1.0 (1.0)	1.2 (0.8)	1.0 (0.7)	1.8 (1.3)	1.0 (0.7)	2.8 (0.4) ^{¶¶}

*Values are shown as mean ± SD.

[†]p < 0.05 when compared with talc slurry.

[‡]p < 0.05 when compared with talc poudrage.

[§]p < 0.05 when compared with thoracotomy.

[¶]p < 0.05 when compared with thoracoscopic abrasion using pleural abrader.

progressive and occurred in stages. Pleural congestion and inflammation were followed rapidly by fibrin deposition and granuloma formation by day 7. Contrary to the study by Kennedy et al,¹⁶ firm fibrotic adhesions had formed by day 30, and neither the granulomatous reaction nor the extent of adhesions appeared dose-dependent.

While designing our study protocol, we were concerned about using the pleural abrader rather than thoracoscopic mechanical abrasion with a folded gauze for comparison with an open surgical technique. We were impressed, however, by verbal reports of the efficacy of this commercially available instrument, and believed that a study of its effect in an experimental model was warranted. To our surprise, the instrument was unsatisfactory. Although laceration of the parietal pleura was avoided by gently rubbing the instrument along the ribs rather than along the intercostal pleural surfaces, abrasion of the visceral pleura could not be performed without risk of lung perforation. Because this study convincingly demonstrates that the 5-mm grooved-burr pleural abrader does not promote satisfactory pleurodesis, we do not recommend its use. We are not suggesting, of course, that thoracoscopic abrasion is unwarranted. The ideal abrader should easily preserve the integrity of both pleural surfaces and result in satisfactory sclerosis and adhesion formation.

Demonstrating statistically significant differences in a study this size is difficult, and our conclusions are limited by the overall power of this investigation. Ideally, the subject size should be increased. We do not believe, however, that this particular investigation justifies the sacrifice of additional animals. The evidence against using the currently marketed pleural abrader is sufficiently strong to warrant its abandonment, and the similarity between talc and dry gauze abrasion confirms the findings of previous investigators. For example, Bresticker et al²⁰ demonstrated in the canine model that pleurodesis by talc instillation during thoracotomy was comparable to dry gauze mechanical abrasion, and better than laser photocoagulation, argon beam coagulation, or tetracycline administration. Although abrasion appears to be inferior to talc in our study, differences are not statistically significant, and are probably related to our technique. Only the area surrounding the incision site was treated to simulate focal abrasion through a limited thoracotomy.²¹ The good response to local abrasion as manifested by the pleurodesis score supports the use of this technique in selected individuals. We are certain that pleurodesis and obliteration scores would have been higher had a larger pleural surface been treated. However, the trend toward a higher obliteration grade in animals undergoing TTI compared with thoracotomy could suggest that TTI is particularly useful when

Table 3—Results of Microscopic Examination of Visceral Pleural Changes*

Technique of Pleurodesis	Granulation		Chronic		Foreign Body	Mesothelial Cell	Degree of Pleural Thickening
	Fibrosis	Tissue	Inflammation	Capillaries	Granulomas	Proliferation	
Mechanical abrasion by thoracotomy	0.8 (0.4)	1.0 (1.0)	0.8 (0.8) ^{††}	0.8 (0.8) [‡]	0 ^{††}	0.6 (0.8)	1.2 (0.8)
Thoracoscopic abrasion	0.8 (0.4)	0	0.2 (0.4)	0 ^{††}	0 ^{††}	0	0.6 (0.5)
Talc poudrage	1.8 (0.4) ^{‡§}	2.2 (0.8)	1.8 (0.4)	2.0 (0.7)	2.8 (0.4)	0.6 (0.5)	2.8 (0.4) ^{¶§¶}
Talc slurry	1.4 (0.5)	2.0 (0)	1.2 (0.4)	1.6 (0.5)	2.2 (0.8)	0.6 (0.8)	1.8 (0.4)

* Values are shown as mean ± SD.

[†]p < 0.05 when compared with talc slurry.

[‡]p < 0.05 when compared with talc poudrage.

[§]p < 0.05 when compared with thoracoscopic abrasion using pleural abrader.

[¶]p < 0.05 when compared with thoracotomy.

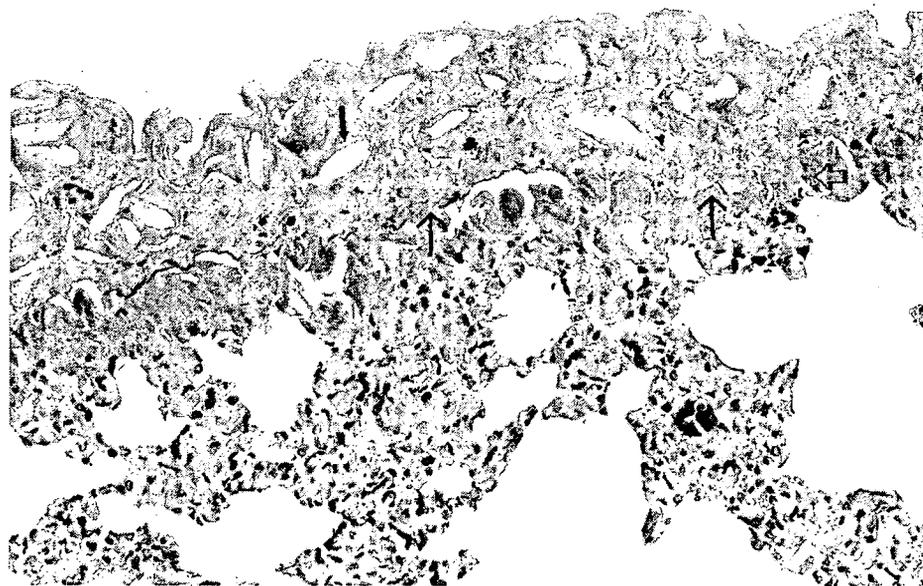


FIGURE 4. Photomicrograph of visceral pleural changes after talc slurry pleurodesis. Note elastic layer (long arrows) with foreign body reaction to talc particles (short bold arrow) between elastic layer and mesothelium, and a dense band of fibrosis (hollow arrow) between elastic layer and pulmonary parenchyma (trichrome/elastic stain, original $\times 200$).

diffuse, dense adhesions are desirable, as in patients with malignant effusions or persistent airleaks from nonresectable blebs or bullae.

In conclusion, TTI is a consistently effective method of pleurodesis, causing a greater degree of parietal and visceral pleural fibrosis than mechanical abrasion in the canine model. At the interval studied, intrapleural talc administration did not cause fibrothorax or hemothorax. The distribution and differences in parietal and visceral pleural thickening between the talc models are readily attributable to localized pooling of slurry in gravity-dependent areas, while insufflation allowed uniform application of talc powder on all visualized pleural surfaces. Clinical applications based on results of this study may be better suited to patients with pneumothorax than to those with malignant pleural diseases because factors such as trapped lung or pleural tumor burden were not accounted for. Additional experimentation and new study design will be necessary to further explore potential differences between slurry and TTI techniques.

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A comparison of thoracoscopic talc insufflation, slurry, and mechanical abrasion pleurodesis

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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S

Exhibit 10

Thoracoscopic Talc Poudrage Pleurodesis for Malignant Effusions*

A Review of 360 Cases

Jean-Regis Viallat, MD, PhD; Françoise Rey, MD, PhD;
Philippe Astoul, MD, FCCP; and Christian Boutin, MD, FCCP

Objective: To assess the efficacy, permanence, and safety of thoracoscopic talc poudrage (TTP) for pleurodesis in malignant effusions.

Design: Retrospective.

Participants: Patients with lifetime follow-up who received TTP in two related centers in Marseilles, France.

Results: Three hundred sixty patients were included in this study: 88 had mesothelioma and 272 had pleural metastases. The mean follow-up time was 12 months (2 to 120). Of the 327 patients whose response could be evaluated, 90.2% had a successful pleurodesis at 1 month, and 82.1% had a life-long pleural symphysis. Adverse effects included 1 death 3 days after the procedure in a patient with end-stage disease, fever (9.8%), empyema (2.5%), pulmonary infection (0.8%), and malignant invasion of the scar (1 patient).

Conclusions: TTP is an effective and safe method of lifelong pleurodesis. It should be performed early on in the history of malignant effusions to avoid the risk of respiratory failure, this being directly linked to the general and respiratory status of the patients at the time of the procedure.

(CHEST 1996; 110:1387-93)

Key words: malignant effusions; mesothelioma; pleurodesis; talc poudrage; thoracoscopy

About 50% of pleural effusions are malignant,^{1,2} and only a minority benefit from suitable systemic treatment. Pulmonologists thus frequently have to treat these chronic pleural effusions, which recur rapidly³ and are disabling for the patient. When thoracentesis is repeated frequently over a number of months to treat dyspnea, the resulting depletion in ions, fluid, and proteins contributes to the deterioration in the patient's general condition. Pleurodesis is therefore the symptomatic treatment of choice^{2,4} and should be considered as early as possible in the course of chronic malignant pleural effusions.

Among the various sclerosing agents used to induce pleurodesis,⁵ thoracoscopic talc poudrage is a widely used and valued medical technique in Europe and its neighboring countries.⁶⁻¹⁴ In North America, the standard pleurodesis method, chosen mainly for the sake of simplicity, is administration of tetracycline via a chest tube.¹⁵⁻¹⁸ However, reports of experience with tetracycline (actually no longer available¹⁹) over the past decade show that this pleurodesis technique has

associated complications^{5,20} and causes a significant percentage of early and late failures.^{16,21,22}

There has been a recent renewal in interest for talc pleurodesis in North America, whichever method is used to administer the talc, namely thoracoscopic poudrage²³⁻²⁶ or talc slurry.²⁷⁻³⁰ However, reappraisal of the various pleurodesis agents is often based only on the English-language literature,⁵ thus omitting part of the wide and well-established European experience that followed the work of Bethune³¹ and subsequent early medical applications.^{6,32-36} We therefore considered it useful to present our experience on thoracoscopic talc poudrage for malignant pleural effusions and to compare it with the largest series reported in the literature, irrespective of which language in which they were published.

MATERIALS AND METHODS

Patients

Three hundred sixty patients were included, their clinical and radiologic history required for this study having been recorded on computer.

Thoracoscopy was performed for diagnosis and subsequent talc pleurodesis in 215 patients, or just for pleurodesis in 145 patients. In the latter group, the diagnosis had been obtained previously by conventional techniques (cytology, blind needle biopsy) or by thoracoscopy.

Patients with known pleural malignancy underwent thoraco-

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Table 1—Diagnoses of 360 Patients Who Underwent Talc Pleurodesis

	No.	%
Malignant mesothelioma	88	24.4
Pleural metastases	272	
Breast		32.8
Unknown (adenocarcinoma)		15
Lymphoma		9.4
Genito-urinary		5.8
Lung		3.9
Various		8.7
Overall	360	100

scopic talc pleurodesis if they met the following criteria: (1) failure or unavailability of specific treatments (chemotherapy, hormone treatment); (2) dyspnea that improved after large-volume thoracentesis with subsequent rapid recurrence of the pleural effusion; (3) total amount of fluid drawn off of more than 3 L; and (4) absence of trapped lung, as evidenced by previous thoracenteses and control of intrapleural pressures.³⁷

In patients whose malignancy was diagnosed at thoracoscopy, the criteria for subsequent immediate talc poudrage were the following: (1) macroscopic or extemporaneous histopathologic evidence of malignancy; (2) history of chronic pleural effusion lasting over 3 weeks; and (3) ineligibility of the patient for trials of intrapleural treatment.^{38,39}

Technique

Our rigid thoroscopic procedure has been described previously²² and was performed in an endoscopy suite for patients treated at the Conception Hospital or in a surgical room for those treated at the Paoli-Calmettes Institute. In most patients, a large volume of fluid had been removed by thoracentesis the day before thoracoscopy to relieve the dyspnea, estimate the potential for lung reexpansion, and induce a pneumothorax with about 300 mL of air. The pneumothorax was produced and subsequent radiographs helped the optimal entry site for thoracoscopy to be chosen. However, when thoracoscopy was required for talc pleurodesis alone, thoracentesis and subsequent pneumothorax induction were frequently performed on the operating table, through the cannula of the thoracoscope. Indeed, a large amount of pleural fluid can be aspirated through a thin catheter in just a few minutes without any complication, provided that the cannula is not airtight, thus allowing air to enter the pleural cavity freely and to replace the fluid drawn off.

Patients were placed in the lateral decubitus position. The BP, pulse rate, and oxygen saturation were monitored continuously.

Table 2—Results of Talc Pleurodesis at 1 Month*

	Mesotheliomas ¹ (n=85) [†]	Pleural Metastases ¹ (n=242) [†]	Overall (n=327) [‡]
Complete response, %	78.8	88.5	85.9
Partial response, %	5.9	3.7	4.3
Failure, %	15.3	7.8	9.8
Total, %	100	100	100

*Complete response: normal or subnormal radiograph; partial response: residual pleural fluid (<500 mL), not requiring further tapping; failure: all other cases.

[†]p=0.085. Comparison of mesotheliomas and pleural metastases did not show any significant difference.

[‡]No. of evaluable patients.

Supplemental oxygen was given to maintain the oxygen saturation above 90%. Anesthesia was achieved by a combination of local anesthetics plus IV administration of midazolam and meperidine at the Conception Hospital (240 patients) and by general anesthesia with simple-lumen endotracheal intubation at the Paoli-Calmettes Institute (120 patients).

We used a rigid thoracoscope (Wolf), connected to a video camera, with a 7-mm diameter trocar and cannula.²² The entry site was chosen as low as possible in the midaxillary line (usually between the sixth and eighth intercostal spaces) for the reasons explained later. After all the remaining fluid had been aspirated, a thorough inspection of the whole of the pleural surfaces and the mediastinum was made. Any loculations resulting from repeated thoracenteses were divided. As many biopsies as necessary were performed, under visual control, for the various examinations (histopathology, hormone receptors, mineralogic analyses).

At the end of the diagnostic stage of the procedure, asbestos-free talc from Luzenac (France) was used as the sclerosing agent. For this purpose, 3-g aliquots of pure talc are heat sterilized at 160° for 2 h at our centers. An average of 3 to 4.5 g of talc powder was distributed uniformly onto the pleural surface using a pneumatic atomizer (Wolf Medical). After removal of the cannula, a 28 to 32F chest tube was inserted through the same incision and placed in the costovertebral gutter, as high as possible in the direction of the apex. Good positioning of the tube and additional holes facilitated fluid drainage. The chest tube was connected to an underwater sealed chamber with a wall suction of 30 to 50 cm H₂O, and it was left in place until less than 100 mL of fluid was drained in 24 h.

The above-described video-assisted thoroscopic procedure was performed by pulmonologists, and should thus be considered as a medical technique. Indeed, it is at the hand of several pulmonologists in most French university medical centers, because they are trained early to perform pleural procedures, including chest tube placement and medical thoracoscopy.

Assessment of the Response

One of the main objectives of the study was to confirm the permanence of the talc pleurodesis and to determine if there were any relapses, or if further thoracenteses were necessary to relieve dyspnea during the patient's lifetime.

Assessment of the response was based on clinical and radiologic parameters. Patients with normal or subnormal radiographs were considered as having a complete response. Those with residual pleural liquid (usually <500 mL) that did not require further tapping during the patient's lifetime were said to have a partial response. The failures were all the other cases.

Statistics

The results were expressed as mean values ± SEM. Discrete variables and percentages were compared by χ^2 analysis. Survivals were assessed from the time of thoracoscopy according to the Kaplan-Meier method and were compared using the log-rank test.

RESULTS

Three hundred sixty patients aged 60 ± 0.7 years were selected for the study; 161 (44.7%) patients were men. The etiology of the malignant effusions is noted in Table 1: 88 patients had malignant mesothelioma and 272 had pleural metastases, 15% of these being adenocarcinomas of unknown origin.

Immediate Results

Thirty-three critically ill patients died within the first month, and so could not be evaluated. Of the 327 re-

maining patients, 295 (90.2%) had a complete or partial response at 1 month, which meant that further tapping was not necessary over this 1-month period (Table 2). The results were slightly better for the patients with metastases than those with mesothelioma, although the difference was not statistically significant ($p < 0.09$).

Long-term Results

Of the 327 patients who could be assessed at 1 month, 295 had an immediate response. It was possible to follow up 265 of them until their death, the mean follow-up period being 12 months (2 to 120 months). Twenty-one relapses (7.9%) occurred at a mean time of 10.2 ± 2.2 months (2 to 45 months) after talc pleurodesis. Finally, taking in account the immediate failures and the observed relapses, 82.1% of patients had a lifelong pleural symphysis, including, respectively, 74.1% of the patients having mesothelioma and 85.4% of those having pleural metastases ($p < 0.001$) (Fig 1).

The median survival of the whole cohort was 6.4 months, with, respectively, 9 months for patients with mesothelioma and 5.2 months for those having metastases. The median survival also depended on the initial response to the procedure, and was 7.6 months for responders and 2.6 months in nonresponders, the difference being statistically significant ($p < 0.001$).

The main causes of failure of thoroscopic talc poudrage were (1) trapped lung and (2) massive cancerous invasion of the pleura. Both usually resulted from delayed indication of talc pleurodesis, as developed in the "Discussion" section.

Complications

None of our patients developed talc-induced acute respiratory failure. One patient with end-stage disease died from respiratory failure 3 days after the procedure, but she had a huge mediastinal lymphoma resistant to chemotherapy, which had invaded half of the right hemithorax and was associated with a right pleural effusion. For weeks this had caused severe respiratory failure despite pleural tapings. Another 32 deaths (9.2%) occurred within 4 weeks after talc poudrage. All were caused by critical illnesses that were present before the procedure and which should actually have contraindicated it.

The mean drainage time was 5.3 ± 0.2 days; 6.1% of patients had a drainage time of longer than 7 days, and in 1 patient the chest tube had to be replaced. Two patients had significant subcutaneous emphysema that resolved spontaneously, and 4.3% had a residual pleural effusion after removal of the chest tube (between 100 and 500 mL) and were considered as having a partial response.

Pain was almost invariably present during the first 24

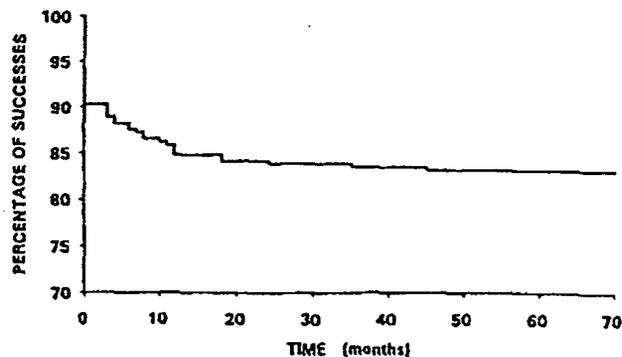


FIGURE 1. Lifetime outcome of pleural symphysis obtained with thoroscopic talc poudrage in 295 patients.

h after the procedure, though it was much less severe than after talc poudrage for pneumothorax. This pain was systematically treated with drugs ranging from acetaminophen (paracetamol) to morphine sulfate, depending on the individual patient's needs.

Temperature greater than 38.5°C was observed in 9.8% of patients and lasted, on average, for 1 day, acetaminophen being the only treatment required. An infection of the pleural space developed in 2.5% of patients and 0.8% had a pulmonary infection; all of them were treated successfully with parenteral antibiotics.

In 1 patient with advanced mesothelioma that invaded the chest wall, the thoracoscopy scar still had not healed when he died 2 months after the procedure.

DISCUSSION

Immediate pleurodesis was achieved in 90.2% of our patients by thoroscopic talc poudrage. Our results are similar to those of the largest series reported by Boniface and Guerin⁷ (270 patients, 93% response), Ladjimi et al¹² (218 patients, 78% response), Weissberg and Ben-Zeev¹⁴ (169 patients, 92.2% response), Canto et al¹⁰ (128 patients, 86% response), or Sánchez-Armengol and Rodríguez-Panadero¹³ (119 patients, 87% response). Recent reviews of the English-language literature also confirmed the superiority of talc when compared to other pleurodesis agents, including cyclines and bleomycin.^{5,26} The same conclusions can be drawn from the randomized controlled trials, despite the frequent limited number of patients included.^{24,40-42} Experimental studies like that of Brester et al⁴³ also concluded that talc was superior to tetracycline and as effective as mechanical abrasion.

Doxycycline and minocycline, however, are still proposed as substitutes for tetracycline, and thus as standard agents by Walker-Renard et al,⁵ despite the very small number of patients included in a limited number of reported series.^{44,45} We believe that the absence of an adequate definition of what constitutes successful pleurodesis is responsible for the persistent

Table 3—Long-term Response After Pleurodesis for Malignant Effusions

Technique	Series	No. of Patients	% Positive Response at			
			0-1 mo	3 mo	6 mo	12 mo
Talc poudrage (691 patients)	Fentiman et al ⁴⁶	12	92
	Boniface and Guerin ⁷	270	93			80
	Marchandise et al ⁴⁷	33	87		76	
	Hartman et al ²⁴	33	97	95		
	Our series	327	90.2	88.9	87.5	84.8
Bleomycine (69 patients)	Ostrowski ⁴⁹	32	69	54
	Hartman et al ²⁴	37	64	70		
Cyclines (212 patients)	Fentiman et al ⁴⁶	21	48
	Boutin et al ⁴⁹	20	80	75	50	
	Sherman et al ¹⁵	108	94	49		
	Hartman et al ²⁴	36	33	47		
	Heffner et al ⁴⁵	27	78	65		

use of cyclines. Both Fentiman¹ and ourselves consider that a positive response (whether complete or partial) should mean that the pleurodesis lasts until the patient's death. We observed 8.4% of patients to have late relapses between 2 and 45 months after talc pleurodesis, leaving 84.8% with a positive response at 12 months, and 83.1% with a positive response at the patient's death. Our results are quite similar to those of Boniface and Guerin⁷ and should be compared with those obtained with bleomycine, tetracycline, or other cyclines: Table 3 clearly shows that contrary to what is obtained with talc, the percentage of relapses observed with cyclines increases rapidly with time.^{7,15,24,45-49}

In a previous randomized study,⁴⁹ we compared the results of 40 consecutive patients with malignant pleural effusions, in whom talc (4.5 g) and tetracycline powder (20 mg/kg) were insufflated through the thoracoscope. The long-term success rate remained at 90% in the talc group, while it dropped to 50% at 6 months in the tetracycline group (Table 3). The observed differences in the results may be due to the fact that tetracycline, being soluble, gradually disappears from the pleural cavity,⁵⁰ while talc remains in place indefinitely, thus producing a permanent pleurodesis.^{51,52}

The finding that 9.2% of the patients in our series died within a month of the pleurodesis reflects our initial policy of attempting talc poudrage in patients with much more advanced disease than those referred to us more recently. This is particularly true for the patient who died 3 days after the procedure: she already had severe respiratory failure at the time of talc poudrage, this being performed only as a last resort in an attempt to save the patient's life. This led us to define the following guidelines for patient selection²²: (1) PO_2 greater than 60 mm Hg while breathing room air; (2) prothrombin time greater than 60%; (3) cephalin-kaolin greater than 70%; and (4) platelet count greater than 60,000/mm³.

A temperature greater than 38.5°C lasting for about 24 h was the most frequently observed complication (9.8%), but it was easily controlled with acetaminophen. Our 2.5% with infection of the pleural space plus 0.8% with pulmonary infection, all successfully treated by systemic antibiotherapy, are no more frequent than the infectious complications encountered routinely with any pleural procedure.^{53,54}

Pain observed was due to chest tubing rather than talc poudrage, and was lower than that observed with tetracycline or talc slurry. This is the opposite to what we have observed in pneumothorax, where the pleura is normal and so is much more sensitive to talc poudrage. Analgesics, prescribed in general for 24 h, easily overcame this problem.

Malignant seeding of the scar, a well-described complication of mesothelioma, was successfully prevented by systematic electron therapy of the scars (3 daily doses of 7 Gy), delivered 2 weeks after the procedure.⁵⁵

The type of anesthesia used differed between the Conception Hospital (local anesthesia plus neuroleptics) and the Paoli-Calmettes Institute (general anesthesia plus simple-lumen endotracheal intubation), although the thoroscopic and talc poudrage procedures were similar. Even though we, at the Paoli-Calmettes Institute, do in fact prefer local anesthesia, we believed it to be unnecessary to fight against the wishes of anesthesiologists, who are convinced that single-lumen endotracheal intubation (and thus general anesthesia) is safer than spontaneous ventilation, in case acute cardiac or respiratory failure occurs. The complications were, in fact, equally distributed between the two hospitals.

The quality of pleurodesis largely depends on a perfect drainage technique being employed. First, the chest tube should be large enough (28 to 32F), and inserted as low as possible in the thorax: that is why we chose the entry site for thoracoscopy as low as the sixth

to eighth intercostal spaces. The chest tube is then directed posteriorly toward the costovertebral gutter and as close to the apex as possible. Additional holes made in the lower part of the tube will help drainage of most of the pleural cavity. Incorrect positioning of the chest tube resulted in some liquid being left when the drain was removed and in subsequent radiologic sequelae in 4.7% of our cases (referred to as partial responses).

The drainage time was 5.3 ± 0.2 days in this series, slightly longer than in our previous experience,²² but still shorter than for tetracycline pleurodesis^{56,57} or talc slurry.²⁸ Hartman et al²⁴ reported a mean drainage time of 4.0 ± 1.2 days for talc poudrage, 6.6 ± 1.6 days for bleomycin, and 6.5 ± 2.1 days for tetracycline. In our series, drainage was complicated in about 10% of cases, either by a drainage time longer than 7 days or by some pleural fluid left in place after removal of the chest tube. These were either the result of "trapped" lung, which had not been sufficiently well recognized before thoracoscopy, or because of incorrect positioning of the chest tube. We consider trapped lung to be a contraindication to thoroscopic talc poudrage, because pleurodesis gives only satisfactory results in 50% of cases. Boniface and Guerin⁷ obtained the same results but considered it worthwhile to attempt thoroscopic talc poudrage, in view of the lack of alternative treatment available. Sanchez-Armengol and Rodriguez-Panadero¹³ also obtained 50% positive results in 22 patients with massive lesions invading the visceral pleura.

Waiting too long for pleurodesis is detrimental to the patient: we observed a median survival of 2.6 months in the patients who suffered a relapse after pleurodesis; these relapses did not occur because the procedure had been performed incorrectly, but as a result of spread of the cancer. In fact, huge parietal nodules and/or cancerous thickening of the visceral pleura, that increase with time, can prevent adhesion of the lung to the chest wall, this being a prerequisite for pleurodesis. Also, as more and more pleural taps are performed with time, the creation of multiple loculations is favored, these hindering further pleural drainage. Our policy is now to carry out pleurodesis as early as possible, when the patient meets the criteria developed in the "Materials and Methods" section.²² Some concern has been raised about the availability of sterilized talc in certain hospitals.⁵⁸ Although we prefer using talc that has been heat sterilized at 150°C for 2 h by our hospital staff, we have successfully tested a disposable commercial gas-propelled atomizer containing 2 g of sterile talc powder that is available in Europe for a reasonable price.

Talc pleurodesis has been associated with cases of acute respiratory failure.^{28,59,60} Most of the reported

observations were the result of talc slurry, in which high doses (10 g) of talc had been administered.

We are not in favor of talc slurry, because it does not allow the talc to be evenly distributed over the pleural surfaces (most of the talc, in fact, is eventually eliminated through the chest tube with saline solution). Talc poudrage, performed after thorough aspiration of any remaining pleural effusion, gives much better results with limited quantities of talc and a shorter drainage time.⁶¹

We actually recommend the use of no more than 5 g of talc for malignant effusions, and 1 to 2 g for pneumothoraces. We investigated the possibility of talc migration into the lung in patients treated by talc poudrage for pneumothorax. No significant increase in the permeability of the alveolar membrane was measured by ⁹⁹Te diethylene triamine penta acetate pulmonary scintigraphy, and no talc was found in BAL specimens.⁶²

The main reason why talc poudrage is not currently accepted as a standard procedure in North America, despite its long-term efficacy, is obviously because of the lack of experience of most pulmonologists at thoracoscopy. We and other authors have shown that medical thoracoscopy is a simple and safe technique that has many useful diagnostic and therapeutic indications.^{8,22,53,63} It does not require more skill or training than does bronchoscopy, which is currently learned by pulmonologists. In our series, thoroscopic talc poudrage proved to be a safe, efficient medical technique for treating symptomatic malignant pleural effusions. It is cost-effective, well-tolerated by patients when performed under local anesthesia supplemented with IV sedation, and can be done easily by trained physicians. A growing number of reports and reviews from North-American physicians confirm our experience.^{23,24,26,64}

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Exhibit 11

Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study

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Summary

Background Talc is the most effective chemical pleurodesis agent for patients with malignant pleural effusion. However, concerns have arisen about the safety of intrapleural application of talc, after reports of development of acute respiratory distress syndrome in 1–9% of treated patients. Our aim was to establish whether use of large-particle-size talc is safe in patients with malignant pleural effusion.

Methods We did a multicentre, open-label, prospective cohort study of 558 patients with malignant pleural effusion who underwent thoracoscopy and talc poudrage with 4 g of calibrated French large-particle talc in 13 European hospitals, and one in South Africa. The primary endpoint was the occurrence of acute respiratory distress syndrome after talc pleurodesis.

Findings No patients developed acute respiratory distress syndrome (frequency 0%, one-sided 95% CI 0–0.54%). 11 (2%) patients died within 30 days. Additionally, seven patients had non-fatal post-thoracoscopy complications (1.2%), including one case of respiratory failure due to unexplained bilateral pneumothorax.

Interpretation Use of large-particle talc for pleurodesis in malignant pleural effusion is safe, and not associated with the development of acute respiratory distress syndrome.

Introduction

Talc is hydrated magnesium silicate, and was first used for pleurodesis in 1935 by the surgeon Norman Bethune.¹ In the second half of the 20th century, talc became increasingly popular for induction of pleurodesis in many pleural diseases—eg, spontaneous pneumothorax, benign pleural effusion, and malignant pleural effusion.^{2–6} Compared with other agents for chemical pleurodesis, talc seemed to give the best results in terms of effectiveness, with least recurrence of effusion, after both talc poudrage, and instillation of talc slurry through a chest tube.⁷ The effectiveness of talc pleurodesis compared with other forms of pleurodesis has also been supported by animal studies.⁸ Additionally, talc is inexpensive and widely available.

However, the safety of intrapleural application of talc has been debated since cases of respiratory failure and acute respiratory distress syndrome after talc pleurodesis were reported.^{9–11} Other authors noted no complications at all, even in large series of patients.^{6,12,13} The occurrence of acute respiratory distress syndrome in some series and its absence in others was independent of the underlying disease (malignant pulmonary effusion or pneumothorax),^{6,10,11} the quantity of talc used (2–10 g),^{4,6,10–12} or the technique of talc instillation (slurry or poudrage).^{4,6,10–12} Several researchers have reported results that suggest that acute respiratory distress syndrome after talc pleurodesis is mainly related to the particle size of the talc used.^{14,15}

Our aim was to assess the safety of large-particle talc applied as poudrage for pleurodesis in patients with malignant pleural effusion.

Methods

Patients

We did a prospective cohort study to measure the side-effects of thoracoscopy and pleurodesis by poudrage with large-particle talc for treatment of recurrent malignant pleural effusions. 14 centres (all departments of pulmonary diseases) participated in the study, 13 in Europe and one in South Africa, between Oct 1, 2002, and Oct 31, 2005. Our primary endpoint was the occurrence of acute respiratory distress syndrome after talc pleurodesis. Secondary endpoints were other side-effects (eg, fever, hypoxaemia, and respiratory failure without acute respiratory distress syndrome) and death within 30 days.

Patients were included if they had malignant pleural effusion for which the treating physician thought pleurodesis to be appropriate. Patients in whom malignant pleural effusion was strongly suspected during thoracoscopy, and in whom retrospective histological examination of pleural biopsies confirmed malignancy, were also included. We excluded patients who had pulmonary infection, unstable respiratory status, fever of more than 38°C, cardiac failure, myocardial infarction within the past 30 days, bleeding disorders, previous or concomitant ipsilateral mechanical pleurodesis, previous or concomitant ipsilateral chemical pleurodesis, life expectancy of less than 30 days, pregnancy, or performance status of ECOG 4 (Karnofsky score 30 or lower). The study was approved by the ethics committee of each participating hospital. Written informed consent was obtained according to local protocol.

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	Baseline value
Number of patients	558
Number of centres	14
Age (years)	64.37 (30–96)
Sex	
Female	284 (51%)
Male	274 (49%)
Primary cancer causing pleural metastasis	
Non-small cell lung cancer	230 (41%)
Breast cancer	120 (22%)
Mesothelioma	85 (15%)
Urogenital tract	35 (6%)
Lymphoma	17 (3%)
Colon	14 (3%)
Melanoma	13 (2%)
Small cell lung cancer	11 (2%)
Unknown primary	19 (3%)
Other	14 (3%)
Patients per institution	
Marseille, France	85 (15%)
Brescia, Italy	66 (12%)
Brussels, Belgium	66 (12%)
Berlin, Germany	52 (9%)
Seville, Spain	52 (9%)
Heidelberg, Germany	47 (8%)
Ancona, Italy	38 (7%)
Lille, France	36 (6%)
Treuenbrietzen, Germany	33 (6%)
Nijmegen, Netherlands	32 (6%)
Heraklion, Greece	27 (5%)
Montana, Switzerland	17 (3%)
Turnhout, Belgium	4 (1%)
Cape Town, South Africa	3 (1%)

Data are n (%) or mean (range).

Table 1: Patient characteristics

Procedures

Our null hypothesis was that use of graded large-particle talc would result in no cases of acute respiratory distress syndrome. Steritalc (Novatec, La Ciotat, France) was chosen as the standard talc to be used in this study. The mean particle size of this talc preparation is 24.5 µm. The concentration of small particles (<5 µm) in Steritalc is 11% by volume, compared with up to 82% in some Brazilian talcs analysed, and 54% in a sample of talc from the USA.¹⁶

Thoracoscopy was done by pulmonologists in accordance with a standard technique.¹⁷ Physicians had free choice of which medications to use before, during, and after thoracoscopy, which could be done under local or general anaesthesia. Parietal and visceral pleural biopsies were allowed during the procedure. The pleurodesis technique, however, was standardised: only talc poudrage with 4 g of sterile graded talc was allowed. The talc powder was

	Number of patients (%)
Local anaesthesia	436 (78%)
General anaesthesia	122 (22%)
Number of entry points	
1	428 (77%)
2	129 (23%)
3	1 (0.2%)
Day of drain removal*	
1	29 (5%)
2	76 (14%)
3	150 (27%)
4	132 (24%)
5	96 (17%)
6–10	19 (3%)
>10	4 (1%)

All patients received 4 g Steritalc (Novatec, La Ciotat, France). Data missing for 29 patients. *Range 1–14 days, mode=day 3.

Table 2: Details of thoracoscopy procedure

administered by a pneumatic atomiser. After thoracoscopy, a chest tube (size 20–28 French) was inserted.

A chest radiograph was taken at baseline and within 24 h of thoracoscopy. Additional chest radiographs were done according to local treatment protocol. Daily chest radiographs were taken to monitor for severe complications. A normal postoperative chest radiograph was classified as no clinically significant additional pulmonary infiltrate. Acute respiratory distress syndrome was defined according to the American-European consensus:¹⁸ acute onset of symptoms, partial arterial pressure of oxygen/concentration of oxygen in inspired air of less than 200 mm Hg, bilateral infiltrates on frontal view of chest radiograph, pulmonary artery pressure less than 18 mm Hg when measured, or no clinical evidence of left atrial hypertension. Patients had their temperature recorded twice daily before thoracoscopy and on days 1–5 after the procedure. The amount of supplementary oxygen (L/min) and oxygen saturation were recorded. To guard against hypoxaemia (oxygen saturation <90%) an arterial blood gas measurement was taken.

Statistical analysis

We estimated a maximum frequency of acute respiratory distress syndrome of 1%. To show the risk of acute respiratory distress syndrome to be less than 1% with a one-sided 95% CI, we needed to include at least 300 patients. Statistical analyses were done with SPSS version 12.0.1. We used the paired *t* test to compare patient's temperature, oxygen saturation, and oxygen supplementation at baseline with days 1–5 post-procedure.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Julius Janssen and Gareth Collier had access to all the

data and Julius Janssen had final responsibility for the decision to submit for publication.

Results

558 patients aged 30–96 years, (mean 64.4 years) were recruited. Table 1 shows the patients' baseline characteristics and the contribution of each institution. Table 2 shows details of the thorascopic procedures. Non-steroidal anti-inflammatory drugs were used in 178 (32%) patients. Parietal pleural biopsies were obtained in 475 (85%) patients (range 1–30, mean 6.3, mode 5 per patient). Visceral biopsies (range 1–10, average 3.7, mode 3) were obtained in 23 (4%) patients. If no biopsy sample was taken, the diagnosis had been established before thoracoscopy. Table 3 shows details of the side-effects reported after thoracoscopy. No patients developed acute respiratory distress syndrome.

Chest radiography showed that seven patients had a new infiltration after thoracoscopy; one developed because of transient cardiogenic pulmonary oedema. In two patients the infiltrates resolved. Chest radiographs also showed that two patients had re-expansion oedema that resolved after treatment with oxygen and diuretic drugs. No intensive care was necessary. One patient developed respiratory failure not caused by acute respiratory distress syndrome, for which treatment in the intensive care unit was necessary. This patient had an unexplained contralateral pneumothorax on the day of the thoracoscopy, which was discovered after the procedure. After bilateral pleural drainage, the patient recovered without mechanical ventilation. One patient had a pulmonary embolism on day 8, which resolved after treatment. One patient, who was on chemotherapy, developed non-pulmonary sepsis 48 h after thoracoscopy. She was monitored in the intensive care unit for 2 days, but recovered. One patient with new infiltrates developed high fever, and was given antibiotic drugs, resulting in resolution of infiltration. One patient developed pericardial effusion and congestive heart failure on day 2 after thoracoscopy, and was given diuretic drugs. 11 (2%) patients died within 30 days (2–29 days after thoracoscopy, mean 11.8 days). Table 4 shows details of causes of death.

A significant increase in mean temperature was seen on days 1–4 after thoracoscopy compared with baseline (figure 1). No significant difference in oxygen saturation was seen after procedure (data not shown). A significant rise in the volume of supplemental oxygen used was recorded on days 1 and 2 post-thoracoscopy compared with baseline (0.25 L/min increase on day 1 in the 339 patients using supplemental oxygen [$p=0.001$]; 0.21 L/min increase on day 2 in the 317 using supplemental oxygen [$p=0.025$]; figure 2).

Discussion

The absence of acute respiratory distress syndrome in patients with malignant pulmonary effusion supports our hypothesis that pleurodesis with large-particle talc is

safe. Side-effects from thorascopic pleurodesis were mild in our study. The small increases in temperature and oxygen use after talc pleurodesis were not clinically significant, and might be due to mild systemic and lung inflammation caused by talc.^{14,19} Our results also accord with the hypothesis that acute respiratory distress syndrome and severe hypoxaemia are caused by talc toxicity, which can be avoided by the use of large-particle talc.¹⁴

About 2% of our patients died within 30 days of thoracoscopy. However, in such patients, who had a limited life expectancy and serious comorbidity, postoperative complications and mortality within 30 days can be expected in a small proportion. None of our patients had serious pulmonary complications within 48 h of procedure, which provides further evidence of the safety of this procedure.

At present there is no consensus about the safety of talc for pleurodesis.^{20,21} Sahn²² reviewed publications about the development of acute respiratory distress syndrome in talc pleurodesis. Of the 4030 patients with malignant pleural effusion who were treated with talc pleurodesis that he identified, 41 (1%) patients had acute respiratory failure after administration of talc. However, almost all

	Number of patients
Acute respiratory distress syndrome	0 (0%; 0–0.54*)
Death within 30 days	11 (1.97%; 0.8–3.1)
Respiratory failure not due to acute respiratory distress syndrome	1 (0.17%; 0–0.53)
Other serious adverse event	6 (1.07%; 0.24–1.9)

Data are n (%; 95% CI). *One-sided 95% CI.

Table 3: Side-effects of thoracoscopy

	Age (years)	Sex	Time from procedure to death (days)
Acute gastrointestinal bleeding on day 6, family requested no further intervention, palliative care only	82	Female	8
Massive pericardial effusion and cardiac failure on day 2	67	Male	2
Pleural empyema on day 8, operation for intrathoracic bleeding on day 14, ICU treatment afterwards, death due to respiratory and cardiovascular failure	63	Male	29
Tumour progression, malignant pericardial effusion, tachyarrhythmia, circulatory failure	64	Male	13
Disease progression, brain metastasis	61	Male	18
Sudden death, suspected massive pulmonary embolism	46	Female	8
Progressive disease, carcinomatous lymphangitis	79	Female	20
Progressive disease, carcinomatous lymphangitis	64	Male	14
Progressive disease	51	Male	10
Sepsis	78	Male	5
Infected peritoneal carcinomatosis, died from sepsis, no ICU care, but palliative treatment given	54	Female	3

ICU=Intensive care unit.

Table 4: Causes of death within 30 days of thoracoscopy

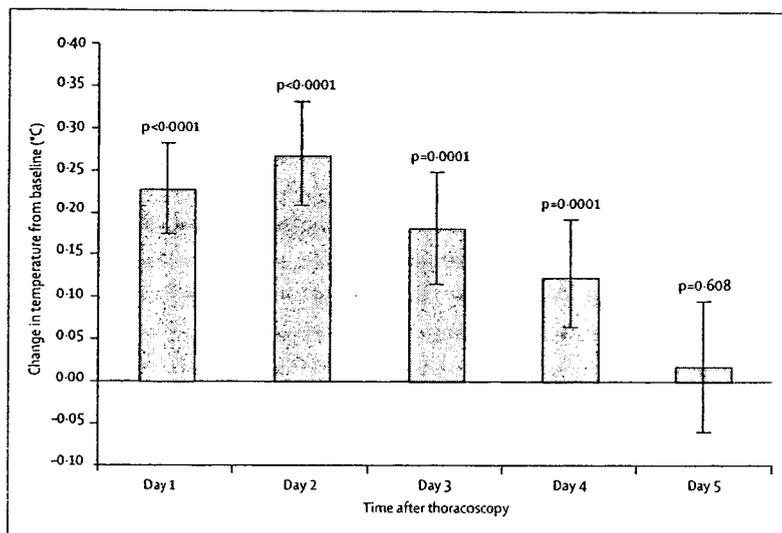


Figure 1: Mean temperature increase from baseline
Bars show 95% CI.

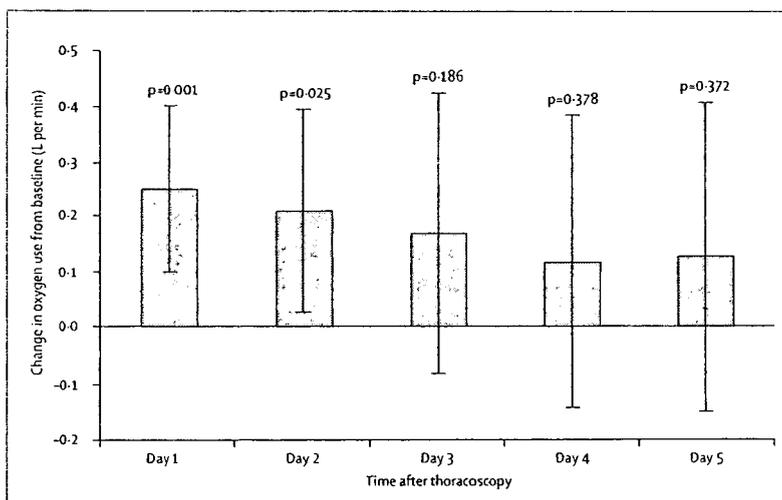


Figure 2: Mean increase in supplemental oxygen use from baseline
Bars show 95% CI.

the data was retrospective, without detailed documentation of the clinical course of disease and outcome. He questioned whether there was a causal association between respiratory failure and talc pleurodesis, since no important side-effects were reported in more than 5000 patients who underwent talc pleurodesis between 1958 and 2001.

Researchers in the USA and Brazil have described cases of acute respiratory distress syndrome after talc pleurodesis; by contrast, no such cases have been recorded in large review series in Europe and Israel. Animal studies in the USA and Brazil showed deposition of talc in the lung parenchyma and other organs,^{24,25} whereas such deposition in other organs was absent in a European study.²⁶ In animal studies in

Wistar rats, talc was seen in 100% of organs of all animals in a Brazilian study, versus 2% in a European study.^{25,26} In the European study, the researchers proposed that the talc seen in four of 198 assessed organs was probably caused by contamination during storage of the organs.²⁷

This geographic discrepancy is probably due to the size of the particles of talc. Ferrer and colleagues²⁸ showed that talc preparations for pleurodesis varied greatly. They also showed that damage to the lung parenchyma took place after pleurodesis with small-particle talc in rabbits, but not when large-particle talc was used.¹⁵ In human beings, Maskell and colleagues¹⁴ showed that pleurodesis with mixed talc, including small particles, worsened gas exchange, and induced more systemic inflammation than did graded talc, from which most particles less than 10 µm were removed.

Indeed, of the publications that described acute respiratory distress syndrome after talc pleurodesis, details of the particle size of the talc were given only in one.¹¹ Thus the causal role of particle size in the side-effects associated with talc pleurodesis was overlooked, and talc, in general, was thought to be dangerous as a pleurodesis agent by some investigators.²⁰

In view of growing evidence to suggest that talc particle size is the main cause of side-effects, we did not think comparing small and large-particle talc in a prospective randomised way in human beings was ethical. We therefore chose to do a prospective cohort study to test our hypothesis that pleurodesis with large-particle talc would not cause acute respiratory distress syndrome. Our results suggest that acute respiratory distress syndrome after pleurodesis with large-particle talc would happen in six patients in every thousand, which is well below the 1% estimated from a review of the retrospective studies.²²

Our results are limited to the side-effects of talc poudrage, we therefore cannot draw any conclusions about the safety of talc applied as slurry. Additionally, our study did not assess the efficacy of talc pleurodesis.

The most important clinical implication of our study is that large-particle talc can safely be used for pleurodesis. Other talc preparations should not be used for this indication.

Contributors

JJ, PA, GT, MN, FR-P, KL, SG, CHM, MF, CB, and JMT designed the study protocol. All authors enrolled patients. JJ and GC collected the data. The spreadsheet for data collection was developed by JMT. GC did the statistical analysis, with external consultation. JJ drafted the manuscript, which was contributed to by all authors, and all authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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Exhibit 12



U.S. Food and Drug Administration • Center for Drug Evaluation and Research
FDA Oncology Tools Product Label Details in Conventional Order for talc

Select Prescribe for how someone prescribing a medication such as a physician may view the product label section order. Select Prepare for how someone preparing a medication such as a pharmacist or nurse may view the sections. Select Administer for how someone administering a medication such as a nurse or patient may view the sections. Please send any errors, omissions, and comments to [Send Comment](#).

Prescribe

Prepare

Administer

Application	
Supplement Number	020587
Complete Label	
Formatted in PDF	SCLEROSOL INTRAPLEURAL AEROSOL
Description	
Mechanism of Action	<p>Sclerosol Intrapleural Aerosol (sterile talc powder 4 g) is a sclerosing agent for intrapleural administration supplied as a single-use, pressurized spray canister with two delivery tubes of 15 cm and 25 cm in length. Each canister contains 4 g of talc, either white or off-white to light grey, asbestos-free, and brucite-free grade of talc of controlled granulometry. The composition of the talc is ≈95% talc as hydrated magnesium silicate. The empirical formula is Mg₃ Si₄ O₁₀ (OH)₂ with molecular weight of 379.3. Associated naturally occurring minerals include chlorite (hydrated aluminum and magnesium silicate), dolomite (calcium and magnesium carbonate), calcite (calcium carbonate) and quartz. Talc is practically insoluble in water, and in dilute solutions of acids and alkali hydroxides. The canister and delivery tubes have been sterilized by gamma irradiation. The aerosol propellant contained in Sclerosol Intrapleural Aerosol is dichlorodifluoromethane (CFC-12) with 26 g present per canister. The canister delivers 0.4 g of talc per second through the valve and the product contains no other excipients.</p>
Generic Drug Name	sterile talc powder
Distributor	
Distributor	BRYAN CORPORATION, WOBURN, MA 01801.
Actions	
Summary	<p>The therapeutic action of talc instilled into the pleural cavity is believed to result from induction of an inflammatory reaction. This reaction promotes adherence of the visceral to the parietal pleura, obliterating the pleural space and preventing reaccumulation of pleural fluid. The extent of talc systemically absorbed after intrapleural administration has not been adequately studied. Systemic exposure could be affected by the integrity of the visceral pleura, and therefore could be increased if talc is administered immediately following lung resection or biopsy.</p>
Clinical	

Studies	
Summary	The data demonstrating safety and efficacy of talc in the treatment of malignant pleural effusions are derived from the published medical literature. The following four trials were prospective, randomized studies of talc vs. a concurrent control, and provide sufficient detail for evaluation, including a clear, readily determined definition of response (no fluid reaccumulation by chest roentgenogram at one month or greater) and information allowing an analysis of all patients randomized. Talc was statistically significantly superior to the control arms in evaluable patients across the studies. (table) *p values are two-sided In other studies, greater than 1000 patients with malignant pleural effusions have been reported (with varying degrees of detail and durations of response) to have had successful pleurodesis with talc.
Indications and Usage	
Summary	Sclerosol Intrapleural Aerosol, administered by aerosol during thoracoscopy or open thoracotomy, is indicated to prevent recurrence of malignant pleural effusions in symptomatic patients.
Precautions	
Summary	<p>1) Future procedures. The possibility of future diagnostic and therapeutic procedures involving the hemithorax to be treated must be considered prior to administering Sclerosol Intrapleural Aerosol. Sclerosis of the pleural space may preclude subsequent diagnostic procedures of the pleura on the treated side. Talc sclerosis may complicate or preclude future ipsilateral lung resective surgery, including pneumonectomy for transplantation purposes. 2) Use in potentially curable disease. Talc has no known antineoplastic activity and should not be used for potentially curable malignancies where systemic therapy would be more appropriate, e.g., a malignant effusion secondary to a potentially curable lymphoma. 3) Potential pulmonary complications. Acute pneumonitis or acute respiratory distress syndrome (ARDS) have rarely been reported in association with intrapleural talc administration. Whether these were causally related to talc is unclear. In none of the reported cases was talc applied thoracoscopically or by insufflation. Three of four case reports of ARDS have occurred after treatment with 10 g of talc administered via intrapleural chest tube instillation. One patient died one month post treatment and two patients recovered without further sequelae. Intravenous administration of talc is a well-recognized cause of pulmonary hypertension and pulmonary lung parenchymal disease, but these complications have not been reported after intrapleural administration. Pulmonary diseases, e.g., silicosis or asbestosis-like diseases, chronic bronchitis, bronchogenic carcinoma, and pleural plaques have been reported in association with inhaled talc. 4) Contents under pressure. The contents of the Sclerosol Intrapleural Aerosol (sterile talc powder) canister are under pressure. The canister must not be punctured and should not be used or stored near heat or open flame.</p> <p>Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies on the carcinogenicity of talc have been performed using non-standard designs, which prevent firm conclusions on its carcinogenicity. With single intraperitoneal administration to mice at 20 mg and observation for at least</p>

	<p>6 months, or 4 weekly doses administered intraperitoneally at 25 mg/dose to rats with observation for at least 84 weeks, tumor incidence was not increased. In these studies, the talc and its asbestos content were not characterized. Genotoxicity was assessed in cultures of rat pleural mesothelial cells (RPMC), as unscheduled DNA syntheses (UDS) and sister chromatid exchanges (SCEs). None of the talc samples (which were asbestos free) enhanced UDS or SCEs in treated cultures. No information is available on impairment of fertility in animals by talc. Pregnancy: Pregnancy category B. An oral administration study has been performed in the rabbit at 900 mg/kg, approximately 5-fold higher than the human dose on mg/m² basis, and has revealed no evidence of teratogenicity due to talc. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless it is clearly needed. Pediatric Use: The safety and efficacy of Sclerosol Intrapleural Aerosol (sterile talc powder) in pediatric patients has not been established. Geriatric Use: The mean and median ages of patients treated with talc in the clinical studies table were 50-62 years. No analyses to specifically evaluate the safety and efficacy in the geriatric population have been reported.</p>
<p>Drug Interactions</p>	
<p>Summary</p>	<p>Drug Interactions: It is not known whether the effectiveness of a second sclerosing agent after prior talc pleurodesis would be diminished by the absorptive properties of talc.</p>
<p>Adverse Reactions</p>	
<p>Summary</p>	<p>Talc administration has been described in more than 1500 patients reported in the medical literature. Patients with malignant pleural effusions were treated with talc via poudrage or slurry. In general, with respect to reported adverse experiences, it is difficult to distinguish the effects of talc from the effects of the procedure(s) associated with its administration. The most reported common adverse experiences were fever and pain. Almost all of the cases of fever, and over half of the cases of pain, were in patients who received diagnostic biopsies at the time of talc administration. Infections: Empyema was a rare complication of talc administration and/or the procedure. Biopsies had been obtained prior to onset in over half the reported cases. Respiratory: Rare instances of pneumonia, ARDS, dyspnea, bronchopleural fistula, hemoptysis, and pulmonary emboli have been reported. Cardiovascular: Tachycardia, myocardial infarction, hypotension, hypovolemia, and asystolic arrest associated with surgery and/or anesthesia have been rarely reported. Delivery Procedure: Adverse reactions due to the delivery procedure and the chest tube may include: infection at the site of thoracostomy or thoracoscopy, localized bleeding, and subcutaneous emphysema. Chronic Toxicity: Lange et al. (Thorax 1988;43:559) reported on 114 consecutive cases of idiopathic spontaneous pneumothorax treated with talc poudrage (60 patients), or simple drainage (54 patients) via an intercostal tube. Pulmonary function tests (FEV₁, VC, TLC, and RV) 22 to 35 years after treatment, showed no significant differences in the incidence of pleural changes between the two groups. Two patients treated with talc</p>

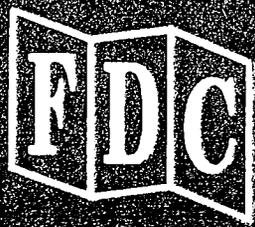
	<p>poudrage had more extensive pleural thickening with calcification. The mean total lung capacities were 89% of predicted in the talc group and 96% in the drainage only group. Fourteen patients (12 lifelong heavy smokers, 2 non-smokers) had airflow limitation (5 severe). Source and purity of the talc used was not reported. No cases of mesothelioma were reported. One case report noted the occurrence of adenocarcinoma of the chest wall two years after pleurodesis following 10 g of 1% iodized talc (administered for recurrent pneumothorax).</p>
Overdosage	
Summary	Overdosages have not been reported. (See PRECAUTIONS: 3) Potential pulmonary complications.
Dosage and Administration	
Summary	<p>Sclerosol Intrapleural Aerosol (sterile talc powder) is administered after adequate drainage of the effusion. It has been suggested that success of the pleurodesis is related to the completeness of the drainage of the pleural fluid, as well as full reexpansion of the lung, both of which will promote symphysis of the pleural surfaces. The usual dosage of Sclerosol Intrapleural Aerosol (sterile talc powder) is a single 4-8 g dose delivered intrapleurally from the spray canister (1-2 cans), which delivers talc at a rate of 0.4 g per second. ADMINISTRATION PROCEDURE Shake canister well before usage. Remove protective cap and securely attach actuator button with its delivery tube (either 15 cm or 25 cm) to the valve stem of canister. Insert delivery tube through pleural trocar, taking care not to place the distal end of the delivery tube adjacent to the lung parenchyma or directly against the chest wall. While firmly holding the delivery tube and pleural trocar together in one hand, gently apply pressure to the actuator button on the canister. Sclerosol Intrapleural Aerosol is not delivered by metered dose, but depends on the extent and duration of manual compression of the actuator button on the canister. The distal end of the delivery tube should be pointed in several different directions, while short bursts are administered in order to distribute the talc powder equally and extensively on all visceral and parietal pleural surfaces. For optimal distribution, always maintain the Sclerosol Intrapleural Aerosol (sterile talc powder) canister in the upright position. After application, discard the canister and delivery tube. The duration of chest tube drainage following talc sclerosis is dictated by the clinical situation.</p>
How Supplied	
Summary	<p>NDC 63256-0100-30: Sclerosol Intrapleural Aerosol (sterile talc powder) contains 4 g of talc suspended in 26 g of inert propellant in a single-use aluminum canister. The canister is fitted with a continuous spray valve which delivers approximately 0.4 g of talc per second. This canister, attached to an actuator button, and two delivery tubes of 15 cm and 25 cm length, are supplied in a sterile, flexible plastic peel pack. STORAGE: Warning: Contents under pressure. Do not puncture or incinerate container. Store between 59°F - 86°F (15°C - 30°C). Protect against sunlight and do not expose to a temperature above 120° F (49° C), or the canister may rupture. Avoid freezing. Shake well before using. NOTE: The indented statement below is required by the Federal Government's Clean Air Act for</p>

	all products containing or manufactured with chlorofluorocarbons (CFCs).
NDC	
NDC	63256-0100-30
Contact	
Contact	Toll Free: 800.343.7711 Fax: 781.935.7602 Email: sales@bryancorp.com www.bryancorp.com

Exhibit 13

THE NDA PIPELINE — 1998

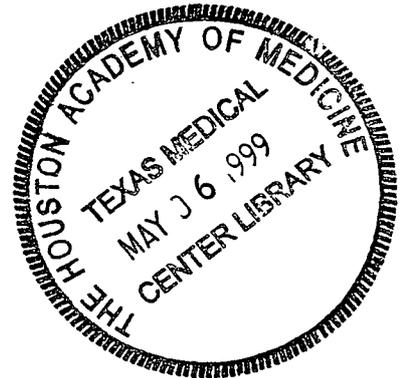
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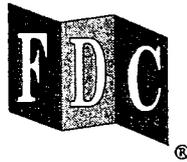
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INTRODUCTION

Welcome to *The NDA Pipeline —1998*, a complete reference guide to 1998 drug and biological product approvals and research activity in the United States. Information contained in the 17th edition of *The NDA Pipeline* is drawn from a variety of sources, including the Food & Drug Administration (FDA); industry resources; pharmaceutical companies (which are provided the opportunity to review their R&D lists each year prior to publication); *"The Pink Sheet"*, an F-D-C Reports weekly publication specializing in coverage of the pharmaceutical industry; and *Pharmaceutical Approvals Monthly*, an F-D-C Reports publication focusing on the NDA approval process. *The NDA Pipeline —1998* contains detailed information on drugs and biological products from the earliest stages of research through approval — everything you want to know about industry activity during 1998.

What does *The NDA Pipeline — 1998* include?

- Comprehensive list of U.S. research and development activity during 1998.
- Complete list of drugs and biological products approved by FDA during 1998.
- Reports from *"The Pink Sheet"* and *Pharmaceutical Approvals Monthly* on drugs and biological products approved and under development in the U.S.
- Complete coverage of FDA advisory committee activity as originally reported in *"The Pink Sheet"*.
- A cumulative list of FDA designated orphan products.
- A list of active ANDA suitability petitions.
- Directory information for all companies featured in this edition.

Where do you find information among the eight sections?

- **Section I** provides an in-depth company-by-company picture of new drug and biological product activity during 1998, including lists of new drug and selected biological approvals, comprehensive lists of products in research, and related stories from *"The Pink Sheet"* and *Pharmaceutical Approvals Monthly*. Companies are listed alphabetically by *parent* with subsidiaries listed under the parent.
- **Section II** contains a list of all original NDAs approved in 1998. The list is arranged according to FDA's IND/NDA classification system for chemical types and therapeutic potential.
- **Section III** contains an alphabetical list by generic name of all drugs and biological products approved during 1998.
- **Section IV** provides an alphabetical list of all drugs and biologics in research and development given in Section I. The products are ordered by generic name and cross-referenced by brand name or code name. In cases where there is only a description of the product in development, a name has been assigned based on the use or action of the drug or biological product.
- **Section V** reviews the 1998 activities of FDA's prescription drug and biological products advisory committees. Committee membership rosters, meeting agendas and stories providing complete meeting coverage and committee actions, as originally published in *"The Pink Sheet"*, are provided. An index to all products discussed by the committees appears at the end of the section.
- **Section VI** contains a cumulative list, arranged alphabetically by generic name, of all FDA designated orphan drugs and biologics through December 1998, including products previously approved. Each orphan designation, which is granted for rare conditions affecting less than 200,000 Americans, gives sponsors certain advantages following approval. The most important gain is seven years of marketing exclusivity.
- **Section VII** charts all 1998 ANDA Suitability Petition activity, including petitions filed during the year and those filed prior to 1998 which were still pending at the end of the year. The information is arranged alphabetically by generic name.
- **Section VIII** provides current directory information, including a corporate headquarters address and telephone number, for companies covered in the 1998 edition.

SECTION VI

FDA ORPHAN DRUGS/BIOLOGICS DESIGNATIONS, 1983-1998

This section contains a cumulative list of FDA designated orphan products through year-end 1998. The list, arranged alphabetically by generic name, includes both approved and unapproved products. The section is reproduced from information contained in FDA's cumulative list of orphan drugs. In cases where sponsors have changed since FDA orphan status was sought or granted, the orphan designated product is listed with the current sponsor's name.

FDA ORPHAN DRUG AND BIOLOGICAL DESIGNATIONS THROUGH 1998

GENERIC NAME TRADE NAME	SPONSOR	PROPOSED USE	DESIGNATION DATE DATE APPROVED
1,5-(Butylimino)-1,5 dideoxy, D-glucitol	Oxford GlycoSciences	Treatment of Fabry's disease.	5/12/1998
		Treatment of Gaucher's disease.	5/29/1998
15AU81	Lung Rx	Treatment of primary pulmonary hypertension.	6/4/1997
2'-deoxycytidine	Steven Grant, MD, Massey Cancer Center, VCU	As a host-protective agent in the treatment of acute myelogenous leukemia.	9/9/1996
2-O-desulfated heparin Aeropin	University of Utah Health Sciences Center	Treatment of cystic fibrosis.	9/17/1993
24,25 dihydroxycholecalciferol	Teva	Treatment of uremic osteodystrophy.	2/27/1987
3-(3,5-dimethyl-1H-2ylmethylene)- 1,3-dihydro-indol-2-one	Sugen	Treatment of Kaposi's sarcoma.	9/11/1998
3,4-diaminopyridine	Jacobus Pharmaceutical Company	Treatment of Lambert-Eaton myasthenic syndrome.	12/18/1990
4-aminosalicylic acid Pamisyl (Parke-Davis) Rezipas (Squibb)	Warren Beeken, MD, Uni- versity of Vermont	Treatment of mild to moderate ulcerative colitis in patients intolerant to sulfasalazine.	12/13/1989
40SD02	Biomedical Frontiers	Treatment of chronic iron overload resulting from conventional transfusional treatment of beta-thalassemia major and sickle cell anemia.	12/21/1998
5,6-dihydro-5-azacytidine	ILEX Oncology	Treatment of malignant mesothelioma.	5/11/1992
5-aza-2'-deoxycytidine	Pharmachemie	Treatment of acute leukemia.	8/3/1987
5a8, monoclonal antibody to CD4	Biogen	For use in post-exposure prophylaxis for occupational exposure to human immunodeficiency virus.	12/20/1993
8 Cyclopentyl 1,3-dipropylxanthine	SciClone Pharmaceuticals	Treatment of cystic fibrosis.	3/24/1997
8-methoxsalen Uvadex	Therakos	For use in conjunction with the UVAR photopheresis to treat diffuse systemic sclerosis.	6/22/1993
		For the prevention of acute rejection of cardiac allografts.	5/12/1994
9-cis retinoic acid Panretin	Ligand Pharmaceuticals	Treatment of acute promyelocytic leukemia.	4/10/1992
		For the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.	3/24/1998
9-nitro-20-(S)-camptothecin (9-NC)	Stehlin Foundation for Cancer Research	Treatment of pancreatic cancer.	9/16/1996
Acetylcysteine Mucomyst/ Mucomyst 10 IV	Apothecon	Intravenous treatment of patients presenting with moderate to severe acetaminophen overdose.	8/13/1987
Aconiazide	Lincoln Diagnostics	Treatment of tuberculosis.	6/20/1988
Adeno-associated viral-based vector cystic fibrosis gene therapy	Targeted Genetics	Treatment of cystic fibrosis.	2/15/1995
AI-RSA	AutoImmune	Treatment of autoimmune uveitis.	10/8/1992
Albendazole Albenza	SmithKline Beecham	Treatment of hydatid disease (cystic echinococcosis due to <i>E. granulosus</i> larvae or alveolar echinococcosis due to <i>E. multilocularis</i> larvae).	1/17/1996 6/11/1996
		Treatment of neurocysticercosis due to <i>Taenia solium</i> as: 1) chemotherapy of parenchymal, subarachnoidal and racemose (cysts in spinal fluid) neurocysticercosis in symptomatic cases and 2) prophylaxis of epilepsy and other sequelae in asymptomatic neurocysticercosis.	1/18/1996 6/11/1996
Aldesleukin Proleukin	Chiron	Treatment of metastatic renal cell carcinoma.	9/14/1988 5/5/1992
		Treatment of acute myelogenous leukemia.	7/31/1998
		Treatment of non-Hodgkin's lymphoma.	11/24/1998

GENERIC NAME TRADE NAME	SPONSOR	PROPOSED USE	DESIGNATION DATE DATE APPROVED
Sotalol HCl Betapace	Berlex Laboratories	Treatment of life-threatening ventricular tachy-arrhythmias.	9/23/1988 10/30/1992
		Prevention of life-threatening ventricular tachy-arrhythmias.	9/23/1988
ST1-RTA immunotoxin (SR 44163)	Sanofi	Treatment of patients with B-chronic lymphocytic leukemia.	8/12/1987
		Prevention of acute graft versus host disease (GVHD) in allogeneic bone marrow transplantation.	8/12/1987
Sterile talc powder Sclerosol Intrapleural aerosol	Bryan Corporation	Treatment of malignant pleural effusion.	9/18/1995 12/24/1997
Sterile talc Steritalc	Novatech SA	Treatment of malignant pleural effusion.	12/8/1997
		Treatment of pneumothorax.	12/8/1997
SU101	Sugen	Treatment of ovarian cancer.	3/12/1996
		Treatment of malignant glioma.	5/25/1995
Succimer Chemet capsules	Bock Pharnacal	Prevention of cystine kidney stone formation in patients with homozygous cystinuria who are prone to stone development.	11/5/1990
		Treatment of mercury intoxication.	3/22/1991
		Treatment of lead poisoning in children.	5/9/1984 1/30/1991
Sucralfate	Fuisz Technologies, Ltd.	Treatment of oral mucositis and stomatitis following radiation therapy for head and neck cancer.	7/15/1993
Sucralfate suspension	Darby Pharmaceuticals	Treatment of oral complications of chemotherapy in bone marrow transplant patients.	3/12/1990
		Treatment of oral ulcerations and dysphagia in patients with epidermolysis bullosa.	3/4/1991
Sulfadiazine	Eon Labs Manufacturing	For use in combination with pyrimethamine for the treatment of toxoplasma gondii encephalitis in patients with and without acquired immunodeficiency syndrome (AIDS).	3/14/1994 7/29/1994
Sulfapyridine	Jacobus Pharmaceutical	Treatment of dermatitis herpetiformis.	9/10/1990
Superoxide dismutase (human)	Pharmacia & Upjohn and Chiron	Protection of donor organ tissue from damage or injury mediated by oxygen-derived free radicals that are generated during the necessary periods of ischemia (hypoxia, anoxia), and especially reperfusion, associated with the operative procedure.	3/6/1985
Superoxide dismutase (recombinant human)	Bio-Technology General	Prevention of reperfusion injury to donor organ tissue.	5/17/1988
Suramin Metaret	Parke-Davis	Treatment of metastatic hormone-refractory prostate cancer.	5/6/1997
Surface active extract of saline lavage of bovine lungs Infasurf	ONY	Treatment and prevention of respiratory failure due to pulmonary surfactant deficiency in preterm infants.	6/7/1985
Synsorb Pk	Synsorb Biotech	Treatment of verocytotoxigenic <i>E. coli</i> infections.	7/17/1995
T4 endonuclease V, liposome encapsulated	AGI	To prevent cutaneous neoplasms and other skin abnormalities in xeroderma pigmentosum.	6/27/1989
Tacrolimus Prograf	Fujisawa USA	Prophylaxis of graft-versus-host disease.	4/6/1998
TAK-603	TAP Holdings	Treatment of Crohn's disease.	5/13/1998
Technetium Tc-99m antimelanoma murine monoclonal antibody Oncotrac Melanoma Imaging Kit	NeoRx	For use in detecting, by imaging, metastases of malignant melanoma.	6/2/1987

Exhibit 14

Center for Drug Evaluation and Research **2003**

Report to the Nation

*Improving
Public Health
Through
Human Drugs*

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

MISSION

The Center for Drug Evaluation and Research promotes and protects public health by assuring that safe and effective drugs are available to Americans. The *Food and Drug Administration Modernization Act of 1997* affirmed the center's public health protection role, clarified the FDA's mission and called for the FDA to:

- 1** Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner.
- 2** Protect the public health by ensuring that human drugs are safe and effective.
- 3** Participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.
- 4** Carry out its mission in consultation with experts in science, medicine and public health and in cooperation with consumers, users, manufacturers, importers, packers, distributors and retailers of human drugs.

This report is available on the Internet in Adobe Acrobat Portable Document Format and in hypertext markup language. The charts and graphs are available as Microsoft PowerPoint slides. The locations are:

PDF: <http://www.fda.gov/cder/reports/rtn/2003/rtn2003.pdf>

HTML: <http://www.fda.gov/cder/reports/rtn/2003/rtn2003.htm>

Slides: <http://www.fda.gov/cder/reports/rtn/2003/rtn2003.ppt>

Suggested citation: Food and Drug Administration. *CDER 2003 Report to the Nation: Improving Public Health Through Human Drugs*. Rockville, Maryland, 20857.

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1

DRUG REVIEW

Drug approvals for 2003

- 72 new drugs
- 21 new molecular entities
- 6 orphan new drugs
- 2 orphan new uses for existing drugs
- 131 new or expanded uses for already approved drugs
- 3 over-the-counter drugs or Rx-to OTC switches
- 263 generic equivalents for prescription and over-the counter drugs

Many Americans benefited from last year's timely reviews of new prescription medicines, over-the-counter medicines and the generic equivalents for both.

We approved 21 new medicines that have never been marketed before in this country, known as new molecular entities. We approved 263 generic versions of existing drugs. We authorized three medicines to be sold over the counter without a prescription, and one of them can be used by children.

We met or exceeded all 10 performance goals for the fiscal year 2002 receipt cohort, the latest year for which we have full statistics. These are goals we agreed to under legislation authorizing us to collect user fees for drug reviews. In addition to surpassing all goals for original new drug applications, we exceeded both goals for new molecular entities.

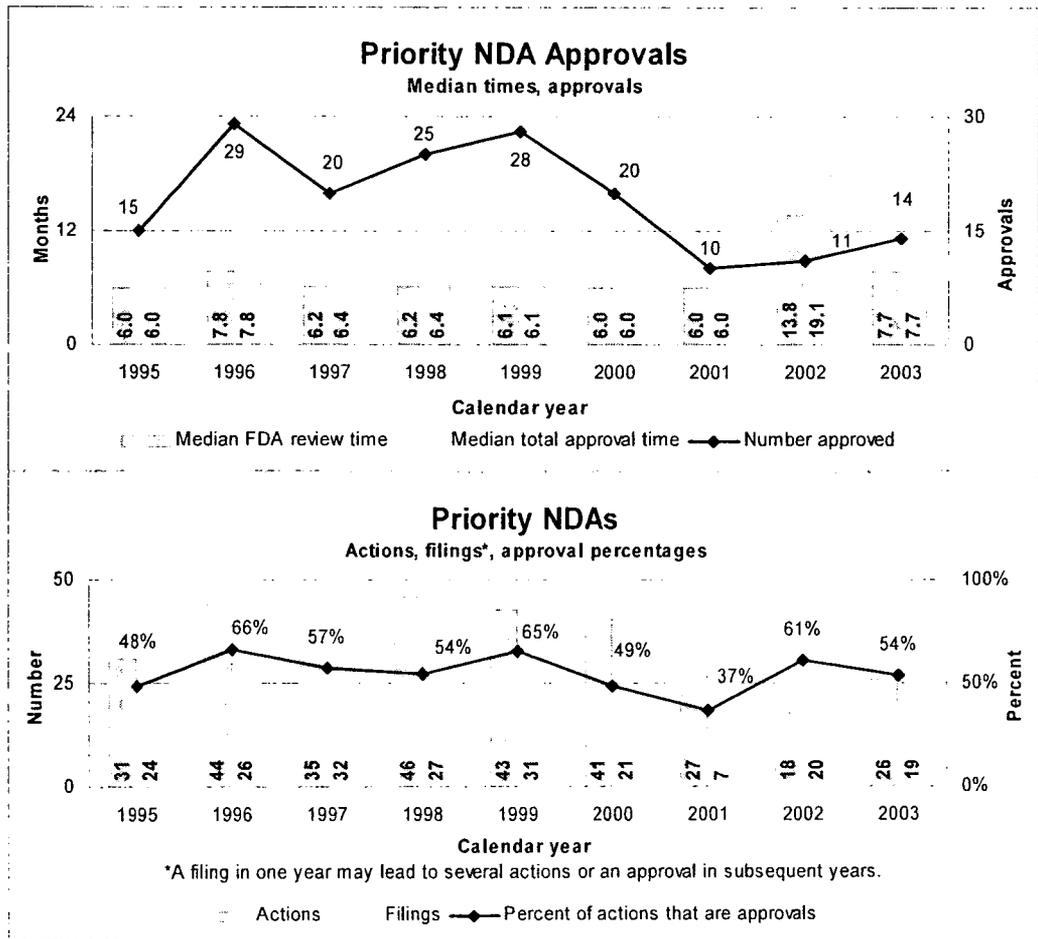
We conducted 728 foreign and domestic inspections that help protect volunteers for clinical trials from research risks and validate the quality and integrity of data submitted to us.

Highlights of new medication options for American consumers include:

- Five cancer treatments.
- Three new drugs for HIV infection, including the first in a class of antiretroviral drugs known as fusion inhibitors.
- Three treatments for infections, including the first in a new class of antibiotics.
- Six orphan new drugs and two orphan new uses to treat patient populations of fewer than 200,000.
- One new drug for treating hepatitis in children and 15 labels with information for treating children.
- Lower doses of estrogen-containing drugs for treating symptoms of menopause.
- Expanded treatment options for children with depression and obsessive compulsive disorder.
- New options for oral contraceptives, including a chewable version and one that reduces menstruations to once every three months.
- The first over-the-counter treatment for frequent heartburn.

Mission

We promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner.



- Priority new drugs**
- 14 approvals (including 9 NMEs)
 - Median review time: 7.7 months
 - Median approval time: 7.7 months
 - 26 actions
 - 19 filings
 - 5 orphan approvals (including 3 NMEs)

- Priority new drugs (N=NME)**
- Abarelix (Plenaxis) (N)
 - Aprepitant (Emend) (N)
 - Atazanavir sulfate (Reyataz) (N)
 - Bortezomib (Velcade) (N)
 - Daptomycin (Cubicin) (N)
 - Enfuvirtide (Fuzeon) (N)
 - Gefitinib (Iressa) (N)
 - Imatinib mesylate (Gleevec)

Priority approval, review times down in 2003

The median total approval and review times for priority NDAs were 7.7 months each, and the times for priority NMEs were 6.7 months each.

The much higher times shown in 2002 were caused by the approval of a number of older applications coupled with a decrease in the number of new applications received.

New Drug Review

Definitions

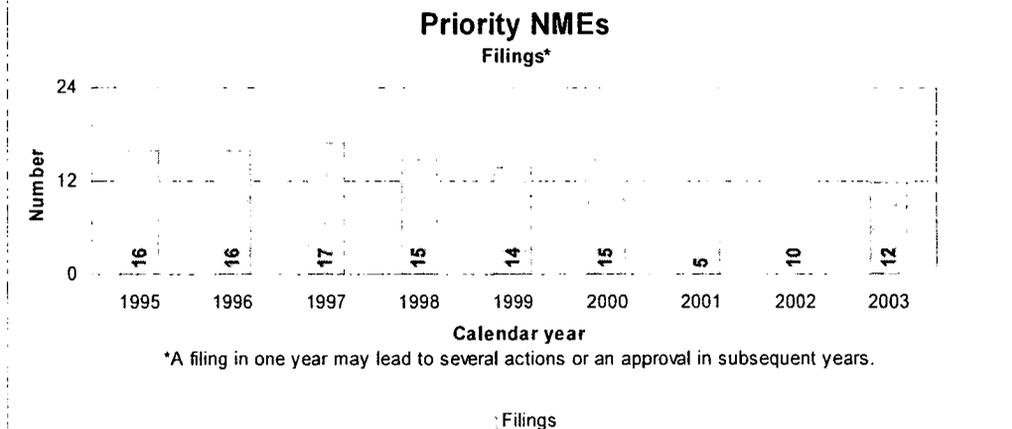
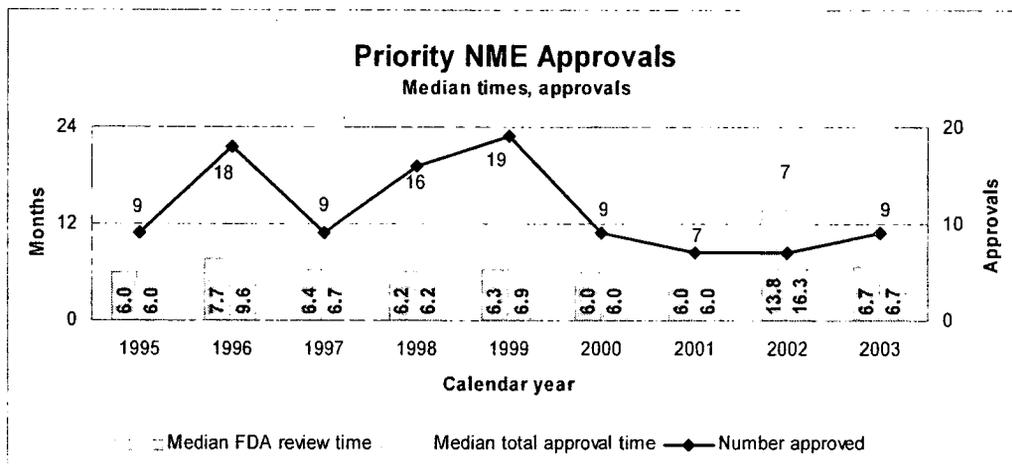
Review and approval times. Review time represents the time that we spend examining the application. Approval time represents our review time plus industry's response time to our requests for additional information.

Median times. Our charts show review and approval times as "medians." The value for the median time is the number that falls in the middle of the group after the numbers are ranked in order. It provides a truer picture of our performance than average time, which can be unduly influenced by a few very long or short times. Our guide to understanding median approval time statistics is available at <http://www.fda.gov/cder/present/MedianAPtime/index.htm>.

New molecular entities. NMEs contain an active substance that has never before been approved for marketing in any form in the United States. Because of high interest in truly new medicines, we report NMEs separately; however, the charts for NDAs include the NMEs as well.

Priority new molecular entities

- 9 approvals
- Median review time: 6.7 months
- Median approval time: 6.7 months
- 12 filings
- 3 orphan approvals



Priority new drugs
(cont.) (N=NME)

- Olanzapine and fluoxetine hydrochloride (Symbyax)
- Pegvisomant (Somavert) (N)
- Prussian blue (Radiogardase) (N)
- Pyridostigmine bromide (Pyridostigmine Bromide)
- Ribavirin (Rebetol)
- Sterile talc powder (Sterile Talc Powder)

Priority new drugs. These drugs represent significant improvements compared with marketed products. We have a goal of reviewing 90 percent of these applications within six months.

Standard new drugs. These drugs have therapeutic qualities similar to those of already marketed products. We have a goal of reviewing 90 percent of these applications within 10 months.

Actions and filings. An application is "filed" when we determine it is complete and accept it for review. We make a filing decision within 60 days of receiving an application. Approval is one of the actions that we can take once an application is filed. Other actions include seeking more information from the sponsor. There is no direct connection between applications filed in one year and actions in the same year. Filings provide an idea of what the workload in subsequent years will be.

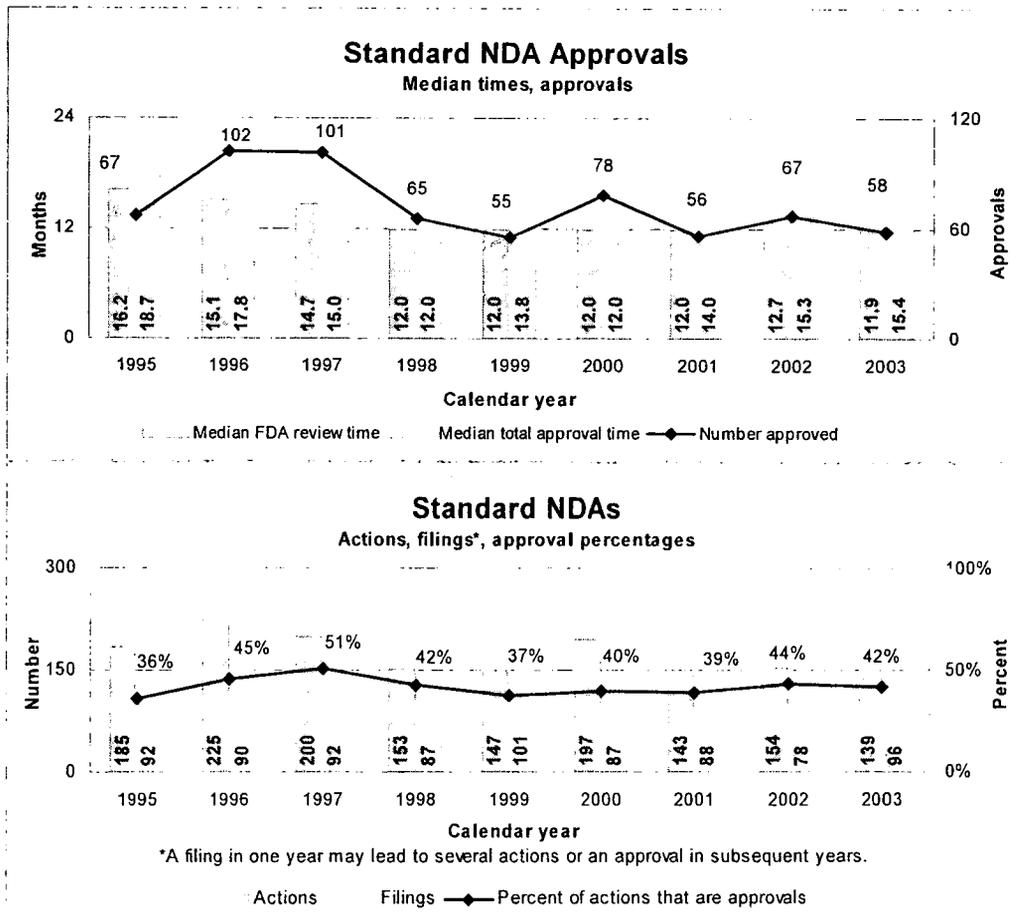
Orphan drugs. We administer a program that provides incentives to develop drugs for use in patient populations of 200,000 or fewer. Sponsors of orphan drugs receive inducements that include seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance from FDA and grants of up to \$200,000 per year.

Accelerated approval

This program helps make products for serious or life-threatening diseases available earlier in the development process.

We base our approval on a promising effect of the drug that can be observed significantly sooner than a long-term clinical benefit.

Sponsors perform additional studies to demonstrate long-term clinical benefit.



Standard new drugs

- 58 approvals (including 12 NMEs)
- Median review time: 11.9 months
- Median approval time: 15.4 months
- 139 actions
- 96 filings
- 1 orphan approval

New molecular entities

- Abarelix (Plenaxis)
- Alfuzosin hydrochloride (Uroxatral)
- Aprepitant (Emend)
- Atazanavir sulfate (Reyataz)
- Bortezomib (Velcade)
- Daptomycin (Cubicin)
- Emtricitabine (Emtriva)
- Enfuvirtide (Fuzeon)
- Epinastine hydrochloride (ELESTAT)
- Gefitinib (Iressa)

Notable 2003 new drug approvals

Last year's approvals benefited people with cancer, HIV infection, heart disease and other disorders.

People with cancer

Abarelix (Plenaxis) is a palliative treatment for advanced prostate cancer for patients who cannot take other hormone therapies and who have refused surgical castration. Abarelix lowers the male hormone testosterone, which is involved in most prostate cancer growth. A study of 81 men showed they could avoid surgical castration by undergoing at least 12 weeks of treatment with the drug. Some also experienced other benefits, including decreased pain and relief from urinary problems. The drug is marketed under a risk management program because of an increased risk of serious and potentially life-threatening allergic reactions. (NME, P)

Aprepitant (Emend) is used in combination with other anti-nausea and anti-vomiting drugs for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. (NME, P)

Internet resources for drug review statistics

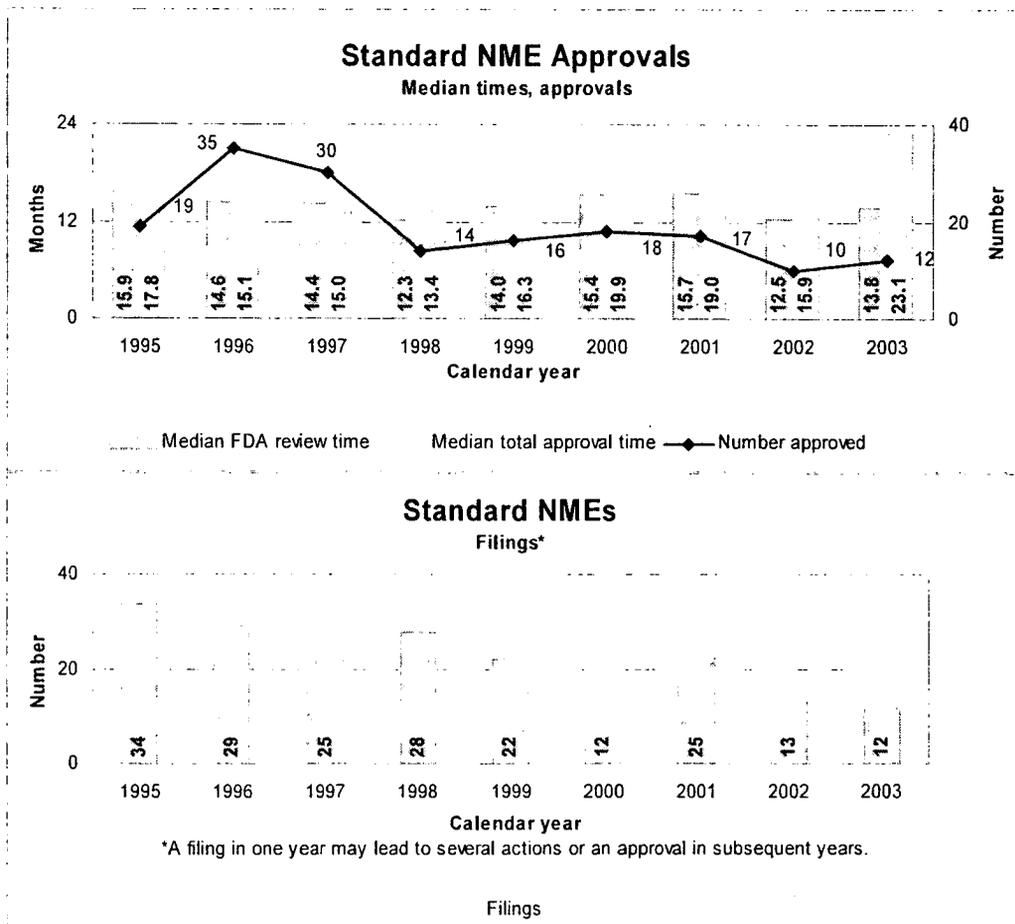
Other drug review statistics are available on our Web site at <http://www.fda.gov/cder/rdmt/default.htm>.

Standard new molecular entities

- 12 approvals
- Median review time: 13.8 months
- Median approval time: 23.1 months
- 13 filings
- 1 orphan approval

New molecular entities (cont.)

- Gemifloxacin mesylate (Factive)
- Ibandronate sodium (Boniva)
- Memantine hydrochloride (Namenda)
- Miglustat (Zavesca)
- Palonosetron hydrochloride (Aloxi)
- Pegvisomant (Somavert)
- Prussian blue (Radiogardase)
- Rosuvastatin calcium (Crestor)
- Sertaconazole nitrate (Ertaczo)
- Tadalafil (Cialis)
- Vardenafil hydrochloride (Levitra)



Notable 2003 new drug approvals (continued)

Gefitinib (Iressa) is a single-agent treatment for patients with advanced non-small cell lung cancer, whose cancer has continued to progress despite treatment with platinum-based chemotherapy and docetaxel. Gefitinib, which received accelerated approval, was developed to block growth stimulatory signals in cancer cells. (NME, P)

Imatinib mesylate (Gleevec) received regular approval as a treatment for refractory chronic myeloid leukemia, a rare life threatening form of cancer-affecting about 40,000 people in the United States. The drug was originally approved under the accelerated approval program in 2001. (NDA, P)

Palonosetron hydrochloride (Aloxi) is an injectable drug for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy and the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. (NME, S)

Orphan new drug approvals (N=NME)

- Bortezomib (Velcade) (N)
- Miglustat (Zavesca) (N)
- Pegvisomant (Somavert) (N)
- Prussian blue (Radiogardase) (N)
- Ribavirin (Rebetol)
- Sterile talc powder (Sterile Talc Powder)

Counterterrorism treatments

Insoluble Prussian blue (Radiogardase), an orphan drug, can be used to treat people exposed to radiation contamination due to harmful levels of cesium-137 or thallium poisoning. The drug works by increasing the rate of elimination of these substances from the body. More information is at http://www.fda.gov/cder/drug/infopage/prussian_blue/. (Orphan, NME, P)

Pyridostigmine bromide tablets (Pyridostigmine Bromide) are used as a pretreatment to increase survival after exposure to Soman "nerve gas" poisoning. The product is approved for combat use by U.S. armed forces. This application, sponsored by the U.S. Army, is the first drug approved under the animal efficacy rule (page 8). That 2002 regulation allows for use of animal data for evidence of a drug's effectiveness when the drug cannot be ethically or feasibly tested in humans. (NDA, P)

Notable 2003 new drug approvals (continued)

Bortezomib (Velcade), an orphan drug, is indicated for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. (Orphan, NME, P)

Sterile talc powder (Sterile Talc Powder), an orphan drug, is indicated for administering intrapleurally via chest-tube as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients. The pleura is a thin, transparent membrane that covers the lungs and also lines the inside of the chest wall. Normally, only a thin layer of fluid separates the two layers of the pleura. An excessive amount of fluid, called pleural effusion, may accumulate for many reasons, including heart failure, cirrhosis, pneumonia and cancer. (Orphan, NDA, P)

People with HIV infection

Atazanavir sulfate (Reyataz) is a protease inhibitor to be used in combination with other anti-retroviral agents for the treatment of adult patients with HIV infection. This drug is the first protease inhibitor that only can be taken once daily. It has a low "pill burden" of two pills each day. Protease inhibitors block the protease enzyme that HIV needs in order to make new viruses. When protease is blocked, HIV makes copies of itself that cannot infect new cells. (NME, P)

Emtricitabine (Emtriva) is indicated for the treatment of HIV infection in adults. The drug belongs to the class of anti-HIV agents known as nucleoside reverse transcriptase inhibitors that, when used in combination with other anti-HIV drugs, can block the replication of HIV in a person's blood. (NME, S)

Enfuvirtide (Fuzeon) is an injectable drug indicated for the use in combination with other antiretroviral agents for the treatment of HIV infection in treatment-experienced patients who show evidence of HIV replication despite ongoing antiretroviral therapy. The first member of a new class of medications called fusion inhibitors, the drug received accelerated approval. Enfuvirtide interferes with the entry of HIV into cells by inhibiting fusion of viral and cellular membranes. (NME, P)

People with heart disease

Rosuvastatin calcium (Crestor) is an adjunct to diet to lower elevated cholesterol levels, a risk factor for heart disease. It belongs to the class of drugs called HMG-CoA reductase inhibitors, also known as statins. (NME, S)

Drugs@FDA

Drugs@FDA is a Web site where you can find official information about FDA approved brand name and generic drugs. Use Drugs@FDA to search for:

- Approved and tentatively approved drug products
- The regulatory history of an approved drug
- Labels for approved drug products
- All drugs with a specific active ingredient
- Generic drug products for a brand-name drug product
- Therapeutically equivalent drug products for a brand-name or generic drug product
- Consumer information for drugs approved after 1998

To use Drugs@FDA, go to our home page (<http://www.fda.gov/cder>) and click on "Drugs@FDA."

Notable 2003 new drug approvals (continued)

Infectious diseases

Daptomycin (Cubicin) injection treats complicated skin and skin structure infections. These are serious infections, usually occurring in hospitalized patients and include major abscesses, post-surgical skin wound infections and infected ulcers. Daptomycin is the first approved product in a new class of antibiotics called cyclic lipopeptide antibacterial agents. The drug binds to bacterial membranes and rapidly upsets electrical balance. This leads to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. (NME, P)

Gemifloxacin mesylate (Factive) is indicated for the treatment of community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis. Gemifloxacin, a synthetic broad-spectrum antibacterial agent for oral administration, is related to the fluoroquinolone class of antibiotics. (NME, S)

Sertaconazole nitrate (Ertaczo) cream is indicated for the topical treatment of athlete's foot (interdigital tinea pedis) in immunocompetent patients 12 years of age and older. Sertaconazole belongs to the imidazole class of antifungals. (NME, S)

People with metabolic disorders

Miglustat (Zavesca), an orphan drug, is indicated for the treatment of mild to moderate Type I Gaucher disease in adults for whom enzyme replacement therapy is not a therapeutic option due to constraints such as allergy, hypersensitivity or poor venous access. Type I Gaucher disease is an inborn error of metabolism that results in disease because of a defect in an enzyme needed to break down the chemical glucocerebroside. The enzyme defect leads to the progressive accumulation of glucocerebroside in the spleen, liver and lymph nodes. Miglustat reduces the body's formation of glucocerebroside to a level that allows the residual activity of the deficient enzyme to be more effective. (Orphan, NME, S)

Pegvisomant (Somavert), an orphan drug, is for the treatment of acromegaly in patients who have an inadequate response to existing therapies or for whom these therapies are not appropriate. Acromegaly is a potentially life-threatening disease caused by an excess of growth hormone. The drug is the first in a new class called growth hormone receptor antagonists. Acromegaly causes changes in facial features and enlarged hands, feet and jaw as well as headaches, profuse sweating, swelling and joint disorders. If untreated, patients with acromegaly often have a shortened life span because of heart and respiratory diseases, diabetes mellitus and cancer. (Orphan, NME, P)

BLA approval statistics

This report will begin incorporating statistics on consolidated therapeutic biologic license approvals (BLAs) in 2004.

The Center for Biologics Evaluation and Research is reporting these statistics for 2003.

During the period Sept. 1 to Dec. 31, 2003, when we had official approval authority for therapeutic biologics, we approved one BLA:

□ *Efalizumab (Raptiva)* is a treatment for adult patients 18 years or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Therapeutic biologic reviews consolidated

The review staff and review of some new biologic products were transferred to our center in 2003.

This will enhance the efficiency and consistency of reviewing clinically similar products.

Medicines transferred include monoclonal antibodies, cytokines, growth factors, enzymes and other therapeutic immunotherapies.

Notable 2003 new drug approvals (continued)

Women

***Ibandronate sodium (Boniva)*, indicated for the treatment and prevention of postmenopausal osteoporosis, is a bisphosphonate that inhibits bone resorption. (NME, S)**

***Estradiol (Estrasorb)* topical emulsion is an estrogen therapy product in a topical form. The drug treats moderate to severe symptoms of hot flashes and night sweats associated with menopause. Current estrogen products available for treatment include oral pills, transdermal patches and a vaginal ring. (NDA, S)**

People with allergic conjunctivitis

Epinastine hydrochloride (ELESTAT) ophthalmic solution is an antihistamine indicated for the prevention of itching associated with allergic conjunctivitis. (NME, S)

People with bipolar disorder

Olanzapine and fluoxetine hydrochloride (Symbyax) is a combination of two psychotropic agents and is indicated for the treatment of depressive episodes associated with bipolar disorder. Olanzapine belongs to the thienobenzodiazepine class of drugs, and fluoxetine hydrochloride is a selective serotonin reuptake inhibitor. (NDA, P)

Older people

Memantine hydrochloride (Namenda) is the first drug approved for the treatment of patients with moderate to severe Alzheimer's disease. Previous treatments have been studied in patients with mild to moderate disease. The drug is an N-methyl-D-aspartate (NMDA) antagonist and is thought to work by blocking the action of the chemical glutamate. Although memantine hydrochloride helps treat the symptoms of Alzheimer's disease, there is no evidence that it modifies the underlying pathology of the disease. (NME, S)

Children

Ribavirin (Rebetol) oral solution, an orphan drug, is to be used as part of combination therapy with interferon alpha-2b recombinant (Intron A) for the treatment of chronic hepatitis C among previously untreated pediatric patients at least 3 years of age or older. The drug, a nucleoside analog, was first approved in capsule form in 1998. (Orphan, NDA, P)

Men

Tadalafil (Cialis) and *vardenafil (Levitra)* are oral medications to treat erectile dysfunction in men. These are the second and third oral products approved for this condition. (Both NME, S)

Alfuzosin hydrochloride (Uroxatral) is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia. The drug is an alpha-blocker and may help to relax the muscles in the prostate and the bladder, which may lessen the symptoms of BPH and improve urine flow. (NME, S)

Women (cont.)

A combination of a progestin (*norethindrone*) and an estrogen (*ethinyl estradiol*) (*Ovcon 35*) is an oral, spearmint-flavored contraceptive tablet that can be chewed or swallowed. This dosage form provides one more alternative to the many types of oral contraceptives currently on the market. (NDA, S)

A combination of a progestin (*levonorgestrel*) and an estrogen (*ethinyl estradiol*) (*Seasonale*) provides a new 91-day oral contraceptive regimen. Tablets containing the active hormones are taken for 12 weeks, followed by one week of inactive tablets. Conventional oral contraceptive use is based on a 28-day regimen (21 days of active tablets followed by seven days of inactive tablets). Under this drug's dosing regimen, the number of expected menstrual periods is reduced from one a month to about one every three months. (NDA, S)

Exhibit 15

LEXSEE 1999 TTAB LEXIS 284

Rudolf Wild GMBH & Co. v. The Coca-Cola Company

Opposition No. 99,709

Trademark Trial and Appeal Board

1999 TTAB LEXIS 284

June 29, 1999, Decided

JUDGES: [*1]

Before Simms, Hohein and Hairston, Administrative Trademark Judges.

OPINION BY: SIMMS

OPINION:

THIS DISPOSITION IS NOT CITABLE AS PRECEDENT OF THE T.T.A.B.

Opinion by Simms, Administrative Trademark Judge:

This case now comes up on a number of matters including opposer's motion to strike parts of applicant's answer, applicant's motion for summary judgment and opposer's attempt to amend the notice of opposition. n1

n1 The delay in acting upon the foregoing matters is regretted.

In the notice of opposition against applicant's intent-to-use application to register the mark MINUTE POUCH for fruit drinks, fruit juices and concentrates ("POUCH" disclaimed), opposer, a German limited partnership, asserts that, through licensees, it has sold juice drinks in single-serving packages unique to the juice and fruit drinks category, which packages it has called "pouches." Opposer asserts that both the package and word "pouch" have come to be associated in the minds of consumers with opposer and its licensed juice drinks. Opposer further asserts that either the term "pouch" is suggestive for the container for its juice drinks or that it is descriptive thereof and has acquired secondary [*2] meaning. In any event, opposer asserts that applicant's mark so resembles opposer's "previously-used mark" as to be likely to cause confusion, to cause mistake or to deceive. As a separate "ground" for opposition, opposer asserts that:

Applicant intends and is attempting to genericize [sic] the word "pouch" in connection with packaging for juice or fruit drinks, causing it no longer to be exclusively associated with Opposer, and thus damaging Opposer and its marketing of its juice drinks in competition with Applicant.

Finally, opposer asserts that applicant has no intention of using the word "pouch" for any of the fruit drink products for which it seeks registration of the mark but instead intends to identify only its packaging for such products with the word "pouch." On this basis, opposer alleges that the application is void *ab initio*.

In its answer to the opposition applicant has denied the essential allegations of the opposition but has admitted that the term "POUCH" is descriptive of containers for fruit juices of the types used by opposer and its licensees. As defenses, applicant asserts that the opposition fails to state a claim upon which relief can [*3] be granted; that the notice of opposition was not timely filed; n2 that opposer lacks standing; that opposer will not be damaged by issuance of a

registration for the mark MINUTE POUCH; that opposer and its licensees have used the word "pouch" as a common descriptive and/or generic term; and that to the extent that opposer has any trademark rights in connection with juice drink products, those trademark rights are not superior to those of applicant.

n2 Applicant has subsequently withdrawn this defense after learning that a second request for an extension of time in which to oppose was granted after the notice of opposition was filed. Such defense is accordingly stricken from applicant's answer.

Turning first to opposer's motion to strike, opposer seeks to strike applicant's first four defenses (that the opposition fails to state a claim, that the notice of opposition was not timely filed, that opposer lacks standing and that opposer will not be damaged by issuance of a registration to applicant). It is opposer's position that it has pleaded its standing and grounds for opposition. More particularly opposer asserts that it has a real interest in the outcome of this proceeding [*4] because it has pleaded that it is engaged in the production and sale of juice drinks which are sold in packages called "pouches." These "pouches" have, according to opposer's pleading, come to be associated in the minds of consumers with opposer and its juice drinks.

When a party moves to strike an affirmative defense, such as that the notice of opposition fails to state a claim, the question to be determined is whether the notice of opposition does indeed set forth facts which, if proved, would entitle opposer to the relief it is seeking. A plaintiff may utilize the defendant's assertion of failure to state a claim to test the sufficiency of its pleading by moving under *Rule 12(f) of the Federal Rules of Civil Procedure* to strike this defense from the answer. *S.C. Johnson & Sons, Inc. v. GAF Corp., 177 USPQ 720 (TTAB 1973)*.

Because the essence of the issues presented by opposer's motion to strike are at the heart of applicant's motion for summary judgment, we shall turn to that motion before resolving the motion to strike.

In its motion for summary judgment, applicant argues that, because opposer has never used "pouch" as a [*5] trademark and because the term is generic, opposer does not have a sufficient commercial interest to demonstrate standing; that opposer's claim that applicant is attempting to "genericize" the term "pouch" is not a recognizable basis for opposing registration; and that the undisputed facts show that applicant is using its asserted mark in commerce for the goods specified in the application, so that opposer's claim that applicant lacks a bona fide intent to use the mark for its goods is without merit.

In particular, applicant maintains that opposer or its licensees have never used the term "pouch" as a trademark but rather have used it in a non-trademark manner. Applicant points to the numerous appearances of this term on the licensee's packaging wherein the term is used generically. See below. For example, "10 POUCHES" and "...frozen Capri Sun(R) All Natural<TM> pouches...", "Fun pouch... Capri Sun(R) All Natural<TM> pouches..." Applicant points out that while the brand name CAPRI SUN appears with the registration symbol, the term "pouch" is generally in lower case lettering without any indication of trademark significance. Applicant argues, therefore, that even opposer uses the [*6] term "pouch" as the name of a type of container.

[SEE ILLUSTRATION IN ORIGINAL]

As further evidence of the generic nature of the term "pouch," applicant points to various third-party uses made of record with its motion for summary judgment (see pages 9 and 10 of applicant's brief), various patents showing pouch technology where the term is used generically, media usage and dictionaries. With respect to opposer's trade dress design, which is the subject of a registration, applicant argues essentially that that trade dress is irrelevant to the issues in this proceeding. (The use of that trade dress is licensed to the maker of the CAPRI SUN fruit juice drink.)

With respect to the "genericization" claim, applicant argues that this is not a recognized ground for opposition. Concerning the last ground for opposition (lack of bona fide intent to use the mark on the goods), applicant asserts that it uses its mark as a mark for the concentrate and that there is no merit to this allegation. n3

n3 The record on summary judgment shows that applicant began selling its goods in July 1995 and that the mark MINUTE POUCH appears on containers of MINUTE MAID brand frozen fruit juice concentrate sold to commercial vendors.

[*7]

Opposer filed a brief in opposition to the motion as well as a proposed amended notice of opposition which pleads that applicant's mark is merely descriptive (in that it may mean "small pouch") of applicant's concentrate packaged in bag-like containers for the food service industry. With respect to the motion for summary judgment, opposer argues that there are several disputes which prevent the entry of summary judgment. These include whether the term "Pouch" is generic, whether the relevant field for consideration is juice beverages, and whether opposer has exclusive rights to use "Pouch" for its goods as a result of long use and ownership of the trade dress of a pouch and its registration for that trade dress. Opposer argues that its licensee is the only entity authorized to use this trade dress for juice beverages; that opposer has substantially exclusive use of this term in connection with its goods and that this term has become distinctive of its goods. With respect to the "genericization" claim, it is opposer's position that this claim is within the scope of a Lanham Act Section 2(d) claim of likelihood of confusion. Finally, opposer argues that it is entitled to Rule 56(f) [*8] discovery concerning applicant's intent to use its asserted mark at the time the application was filed, in view of the evidence submitted by applicant on summary judgment. Opposer also argues that the question of intent is particularly unsuited to disposition by summary judgment.

In reply, applicant argues, among other things, that opposer has offered no evidence of the alleged acquired distinctiveness of the term "Pouch," that applicant submitted its own evidence of use of MINUTE POUCH with its summary judgment motion before it was required to make such use under intent-to-use procedures in order to rebut opposer's claim of lack of intent to use, and that there is no issue of fact concerning applicant's intent to use the mark. Accordingly, applicant argues that opposer is not entitled to Rule 56(f) discovery.

Upon careful consideration of the materials of record and the arguments of the parties, we deny opposer's Rule 56(f) request for discovery for the reasons indicated by applicant. We also agree with applicant that there are no genuine issues of fact in dispute and that summary judgment should be entered in favor of applicant. Specifically, concerning the motion for summary [*9] judgment itself, while opposer has listed what it regards as some alleged issues in dispute, we do not believe that those issues are genuinely in dispute. Although it is a fact that opposer has trade dress rights in a configuration which one may call a "pouch," it does not follow that opposer has rights to the generic term ("pouch") which may be used to describe that trade dress. There is no genuine issue that this term is in fact generic, inasmuch as opposer itself is using this term generically, and other evidence submitted by applicant clearly shows that this term is generic. n4 Suffice it to say that there is no genuine issue concerning opposer's lack of proprietary rights in the term "pouch." Whether one views this case in terms of the lack of standing on the part of opposer (as does applicant) or as a failure to present a claim of likelihood of confusion (there can logically be no likelihood of confusion unless opposer has some rights in an asserted term), applicant's motion is well taken.

n4 The Board may determine that a term is not proprietary on summary judgment. *Teleflora, Inc. v. Florists Transworld Delivery Association*, 217 USPQ 1081 (C.D. Cal. 1981) and *Data National Corporation v. Bell South Corporation*, 18 USPQ2d 1862 (TTAB 1994), *aff'd.*, 60 F.3d 1565 (Fed. Cir. 1995).

[*10]

We also agree with applicant that opposer's "genericization" claim is not a cognizable claim for the Board. Opposer has pointed to no authority recognizing this alleged claim as a ground for opposition. Also, we agree with applicant that there is no genuine issue with respect to applicant's intent to use its mark, for the reasons stated by applicant. Applicant has in fact demonstrated trademark use of its asserted mark for its concentrate. See, for example, Exhibits A and G attached to the Taylor affidavit submitted with applicant's motion.

Finally, opposer's belated attempt to avoid summary judgment by its pleading of mere descriptiveness is of no

avail. We see no reason why this ground could not have been asserted earlier since there was no evidence which applicant submitted on summary judgment which would give rise to this claim. A party should not be able to avoid the entry of summary judgment by an amendment which is asserted after undue delay, as the result of a dilatory motion or because of its futility. See *Moldea v. New York Times Co.*, 793 F. Supp. 338 (D.D.C. 1982), *Waldoboro Bank F.S.B. v. American Casualty Co.*, 775 F. Supp. 432 (D.Me. 1991) [*11] and *Martinez v. Junta de Planificacion*, 736 F. Supp. 413 (D.P.R. 1993).

In sum, opposer's motion to strike is denied, applicant's motion for summary judgment is granted, and opposer's motion to amend is denied. The opposition is dismissed.

R. L. Simms

G. D. Hohein

P. T. Hairston

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Picture 1, no caption