

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205555Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205555	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: STERITALC® Established/Proper Name: Talc Dosage Form: Powder Strengths: 2g, 3g, and 4g		
Applicant: Novatech S.A.		
Date of Receipt: April 14, 2016		
PDUFA Goal Date: May 14, 2017		Action Goal Date (if different):
RPM: Elleni Alebachew		
Proposed Indication(s): STERITALC® is a sclerosing agent indicated: • STERITALC is indicated to decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. • STERITALC is indicated in adults to decrease the recurrence of pneumothorax.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If “YES” contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Clinical and nonclinical
NDA 20587 (SCLEROSOL®)	FDA's previous finding of safety and effectiveness (clinical pharmacology and biopharmaceutics)
NDA 21388 (Sterile Talc Powder)	FDA's previous finding of safety and effectiveness (clinical pharmacology and biopharmaceutics)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Steritalc has been available on the European market as a medical device for over 20 years. NDA 205555 for Steritalc relies for approval on the Agency's findings of safety and effectiveness for two listed drugs: Sclerosol (NDA 20587) and Sterile Talc Powder (NDA 021388). The proposed Steritalc product has the same chemical formula as both listed drugs, though the formulation/dosage form is different compared to Sclerosol, which contains an aerosol propellant. The particle sizes of the listed drugs are smaller than the proposed Steritalc product; literature reports suggest that the adverse events (e.g., incidence of acute respiratory distress syndrome or ARDS) of talc for pleurodesis is potentially correlated with smaller talc particle size. Thus, the expectation is that Steritalc may result in a lower incidence of ARDS given that its particle size is larger than those of the listed drugs. Consistent with 21 CFR 320.24(b)(6), FDA determined that in vivo bioavailability studies were unnecessary because talc is well-controlled in terms of the amount administered and direct localization into the pleural cavity, thus bioavailability at the site of action is self-evident. Talc is not expected to leave the pleural surfaces to enter any other body system and then only in small amounts. Moreover, following intrapleural administration, measurements of blood levels of talc would be difficult if not impossible.

The application also relies for approval on published literature describing nonclinical and clinical safety and effectiveness data using products with various formulations of talc, such as slurry and powder, including the European marketed Steritalc product. Published reports indicate that talc (both powder and slurry formulations) have been used successfully in the

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

treatment of pleural effusion for many years. The local exposure of powder and slurry formulations are not expected to differ because talc is introduced directly into the site of action via intrapleural administration, and therefore it is scientifically appropriate to rely for approval on published literature describing both powder and slurry formulations of talc.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☒

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

If “NO,” proceed to question #5.

If “YES,” list the listed drug(s) identified by name and answer question #4(c).

NDA 20587 (SCLEROSOL®)

NDA 21388 (Sterile Talc Powder)

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
SCLEROSOL [®]	NDA 20587	Y
Sterile Talc Powder	NDA 21388	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: **NDA 21388**

- b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

- This application provides for a new indication “For the treatment of pneumothorax”.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☒ NO ☐

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

The pharmaceutical equivalent product is approved for malignant pleural effusion, however the 505(b)(2) application is also seeking approval for an additional indication of pneumothorax which is not currently approved for the RLDs.

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): NDA 021388

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

The pharmaceutical alternative product is approved for malignant pleural effusion, however the 505(b)(2) application is also seeking approval for an additional indication of pneumothorax which is not currently approved for the RLDs.

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 020587

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

ELLENI K ALEBACHEW
05/01/2017

CHRISTY L COTTRELL
05/01/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: February 08, 2017

To: Elleni Alebachew, MS, RAC
Senior Regulatory Health Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **STERITALC® (talco) Powder, for intrapleural use
NDA 205555**

Office of Prescription Drug Promotion comments on proposed
prescribing information (PI)

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) for STERITALC® (talco) powder (STERITALC) as requested by Division of Oncology Products (DOP1) in the consult dated April 20, 2016.

OPDP's review of the proposed PI is based on the draft PI titled, "NDA 205555 proposed PI FDA Revised-1.25.17_clean with comments_Novatech_20170125" sent by electronic mail on January 25, 2017, to OPDP (Nazia Fatima) from DOP1(Elleni Alebachew). OPDP comments are listed on the attached PI.

If you have any questions, please feel free to contact, Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on this PI. Thank you!

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/s/

NAZIA FATIMA
02/08/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 13, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 205555
Product Name and Strength:	Steritalc (talco) Powder, 2 g, 3 g, and 4 g
Submission Date:	January 6, 2017
Applicant/Sponsor Name:	Novatech S.A. c/o Boston Medical Products Inc.
OSE RCM #:	2016-951-1
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Oncology Products 1 (DOP1) requested that we review the revised container labels and carton labeling for Steritalc (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 DISCUSSION

Novatech S.A. submitted the initial revisions for Steritalc container labels and carton labeling in response to our previous label and labeling review via email on December 28, 2016 (see Appendix A) but did not submit as an official electronic submission to the NDA. We reviewed the initial revised Steritalc container labels and carton labeling and found they are unacceptable from a medication error perspective. As presented in the December 28, 2016 email, the strength statement only indicates the amount of the drug, but does not indicate whether this is the total strength of the drug in the vial. Therefore, we recommend revising the strength

^a Gao T. Label and Labeling Review for Steritalc (NDA 205555). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 DEC 13. 16 p. OSE RCM No.: 2016-951.

presentation to express the strength in terms of the total amount of drug per vial as “# g/vial” or “# g per vial”. Additionally, the blue wave-like graphic across the top half of the carton labeling is prominent and may distract readers from important product information. We provided the following recommendations to Novatech S.A. via email on January 4, 2017:

A. General recommendations

1. Since your product is available as a dry powder, revise the strength presentation to express the strength in terms of the total amount of drug per vial as follows: “# g/vial” or “# g per vial”.^b

B. Carton labeling

1. As currently presented, the blue wave-like graphic has more prominence than the proprietary name. Reduce the size of the graphic to ensure that the graphic does not compete in prominence with important product information.^b

Novatech submitted second revisions of the Steritalc container labels and carton labeling on January 6, 2017 (see Appendix B).

3 CONCLUSION

The revised Steritalc container label and carton labeling in the January 6, 2017 submission are acceptable from a medication error perspective. We have no further recommendations at this time.

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immediately following this page

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

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/s/

TINGTING N GAO
01/13/2017

CHI-MING TU
01/13/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 13, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 205555
Product Name and Strength:	Steritalc (talco) Powder, 2 g, 3 g, and 4 g
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novatech S.A. c/o Boston Medical Products Inc.
Submission Date:	April 15, 2016 and August 19, 2016
OSE RCM #:	2016-951
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Novatech S.A. submitted container labels, carton labeling, and prescribing information for Steritalc (talco) Powder. This NDA is being submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act referencing NDA 020587, Sclerosol Intrapleural Aerosol (sterile talc powder), approved December 24, 1997 and NDA 021388, Sterile Talc Powder, approved December 15, 2003.

The Division of Oncology Products 1 (DOP1) requested that we review the submitted Steritalc container labels, carton labeling, and prescribing information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

In this submission, the Applicant submitted the proposed Steritalc container labels for the vial, a “cardboard box label” for the box of 4 vials, (b) (4) Upon review, we realized all the proposed container labels and carton labeling look identical except for the net quantity statement (see Appendix G). Therefore, we requested the Applicant to submit representative samples of a vial labeled with the proposed Steritalc container labels, and a carton labeled with the proposed carton labeling to aid in visualizing how the proposed product is packaged, and to clarify how the “cardboard box label” will be packaged in the “carton label” as part of the 74-day letter^a dated June 23, 2016.

^a Ibrahim, A. Filing Communication – No Filing Review Issues Identified for STERITALC® (Talc) Powder. Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2016 June 23. NDA 205555.

The Applicant provided the requested samples for each strength (2 g, 3 g, and 4 g) on August 25, 2016, which clarified that the “cardboard box label” is the carton labeling for the box of 4 vials (see Figures 1 to 3 below). [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

(b) (4)

Since the (b) (4) we will only evaluate and provide recommendations for the container labels for the vial and the carton labeling for the box of 4 vials in this review.

We evaluated the proposed Steritalc container labels and carton labeling and determined that several areas of the container labels and carton labeling could be improved to ensure safe use of the product:

- Information presented on the container labels and carton labeling appears to be crowded and visually cluttered, making important information difficult to read and/or easily overlooked.
- The critical information (e.g., established name, strength, route of administration) wasn't prominently displayed. Other information such as NDC number, lot number, expiration date, manufacturer information were presented below the proprietary name, thus making it difficult for healthcare professionals to readily locate and understand critical safety information.

Additionally, based on the provided product samples, it appears that in addition to the carton labeling for the box of 4 vials submitted to FDA, there is additional information on the company Novatech on the box containing the 4 vials. As currently presents, the Novatech logo is present on all panels (except the bottom panel) and has more prominence than the product's proprietary name (see Figures 4 and 5), and could be mistaken as the drug name instead of Steritalc. Furthermore, the submitted carton labeling for the box of 4 vials appears to be a sticker that is meant to be affixed to the box of 4 vials rather than the usual carton labeling where critical product information is printed directly on the carton. We recommend Novatech to redesign the carton labeling so drug information are prominently presented and adequately printed directly on the carton labeling.

We evaluated the proposed prescribing information and recommend to combining Section 2.3 Required Equipment and Materials, Section 2.4 Product Preparation and Section 2.5 Administration into one section titled “Product Preparation and Administration” and organize the instructions based on preparation method (slurry or poudrage) rather than based on product strength.

4 CONCLUSION & RECOMMENDATIONS

The proposed Steritalc container labels, carton labeling, and prescribing information can be improved to ensure safe use of the product. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

a. General recommendation

- i. Since the conditionally approved proprietary name for this product is “Steritalc”, remove the (b) (4) from all labels and labeling.

b. Dosage and Administration Section, Full PI

- i. Replace the “hyphen” with the word “to”, and add the corresponding dosage unit after each dosage strength for clarity. For example, replace the statement “2 – 5 grams” with “2 grams to 5 grams”.
- ii. Consider combining Section 2.3 Required Equipment and Materials, Section 2.4 Product Preparation and Section 2.5 Administration into one section titled “Product Preparation and Administration”, and organizing the product preparation and administration instructions based on preparation and administration method (slurry or poudrage) rather than based on product strength.

c. How Supplied/Storage and Handling Section, Full PI

(b) (4)

4.2 RECOMMENDATIONS FOR NOVATECH S.A.

We recommend the following be implemented prior to approval of this NDA:

The submitted (b) (4). Please note that the recommendations we provide below are only pertinent to the container labels for the vial and the carton labeling for the box of 4 vials.

A. General recommendations

1. Since the conditionally approved proprietary name for this product is “Steritalc”, remove the words “(b) (4)” from all container labels and carton labeling.
2. As currently present, the vials are (b) (4)
3. As currently presented, the NDC numbers are presented as a placeholder “XXX-XXX-XX”. Ensure that the product codes (the middle 3 digits -XXX-) in the NDC

numbers are non-sequential between the product strengths. Assignment of sequential numbers for product codes is not an effective differentiating feature (e.g. -666-, -667-, and -668-), which may lead to selecting and dispensing of wrong drug.

4. The container label for 1 vial and the carton labeling of 4 vials should have different NDC numbers. Ensure that the commercial package size codes (the last 2 digits -XX) of the NDC numbers are different for these two package sizes.

5.  (b) (4)

6. Principal display panel (PDP)

- i. Ensure that the PDP contains the most critical information to ensure safe product use, which includes proprietary name, established name, product strength, and route of administration. Other information such as lot number, expiration date, and manufacturer information should be moved to the side panel to ensure that these statements do not complete in size and prominence with the most critical information such as proprietary name, established name, product strength and route of administration.^b

1. Relocate the established name “(Talc) Powder” to the PDP directly under the proprietary name “STERITALC®”.
2. Add the strength statement to the PDP. For example “2 grams/vial”.
3. Relocate the route of administration statement “For Intrapleural Administration” to the PDP and bold this statement to minimize the risk of wrong route of administration errors.
4. Relocate the lot number, expiration date, and manufacturer information to the side panel.
5. Relocate the NDC number to above the proprietary name “STERITALC®”.

7. Side panel

- ii. Add the statement “protect against sunlight” to the storage information on the side panel if space permits.

- B. Carton labeling (box of 4 vials)

1. Based on the provided product samples, it appears that in addition to the “carton labeling” submitted to FDA, there is additional information on Novatech on the box of 4 vials. As currently presents, the Novatech logo has more prominence than the product’s proprietary name, and could be mistaken as the

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

drug name instead of Steritalc. Furthermore, the submitted carton labeling for the box of 4 vials appears to be a sticker that is meant to be affixed to the box of 4 vials rather than the usual carton labeling where critical product information is printed directly on the carton. Redesign the carton labeling so that critical drug information are prominently presented and adequately printed directly on the carton labeling.

2. In the product sample you provided for the carton labeling for Steritalc 3 gram product, it appears that this carton contains 4 vials (b) (4) as stated in the carton labeling image submitted on April 15, 2016. Therefore, revise the net quantity for the carton labeling for Steritalc 3 gram strength product to “4 vials”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Steritalc Talc Powder that Novatech S.A. submitted on April 15, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Steritalc Talc Powder and the Listed Drug			
NDA	20587	21388	205555
Company	Bryan	Bryan	Novatech S.A.
Product Name	SCLEROSOL	Talc	Steritalc Talc Powder
Initial Approval Date	December 24, 1997	December 15, 2003	N/A
Active Ingredient	sterile talc powder	Talc	Talc
Indication	To prevent recurrence of malignant pleural effusions in symptomatic patients.	To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion.	For (b) (4) malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. For (b) (4) pneumothorax.
Route of Administration	Intrapleural	Intrapleural	Intrapleural
Dosage Form	Spray	Powder	Powder
Strength	4 g	5 g	2 g, 3 g, and 4 g
Dose and Frequency	A single 4-8 g dose delivered intrapleurally from the spray canister (1-2 cans), which delivers talc at a rate of 1.2 g per second.	The recommended dose is 5 g, dissolved in 50 ml to 100 ml 0.9% Sodium Chloride Injection, USP, administered intrapleurally.	Malignant Pleural Effusion: 2 g to 5 g Pneumothorax: (b) (4) 2 g

Table 2. Relevant Product Information for Steritalc Talc Powder and the Listed Drug			
NDA	20587	21388	205555
Company	Bryan	Bryan	Novatech S.A.
Product Name	SCLEROSOL	Talc	Steritalc Talc Powder
How Supplied	a single-use aluminum canister contains 4 g of talc suspended in 25 g of inert propellant.	Supplied as a 5 gram bottle packaged in a pouch. A carton contains ten 5-gram bottles.	STERITALC® (b) (4) is supplied as two grams of talc in a single use 50 mL (b) (4) vial (Type III) and closed by a (b) (4) stopper and crimped with an aluminum cap; (b) (4) STERITALC® (b) (4) is supplied as four grams of talc in a single use 50 mL (b) (4) vial (Type III) and closed by a (b) (4) stopper and crimped with an aluminum cap (b) (4) STERITALC® (b) (4) is supplied as three grams of talc in a 10 mL brown glass (Type I) vial, (b) (4) stopper and crimped with an aluminum cap; (b) (4)
Storage	Store between 20°C - 25°C (68°F - 77°F). Protect against sunlight and do not expose to a temperature above 49° C (120° F), or the canister may rupture. Avoid freezing. Shake well before using.	Store the powder at 25°C (77°F). Protect against sunlight.	Store the powder at 20-25°C (68-77°F). Protect against sunlight.
Container Closure	single-use aluminum canister	single use 100 ml brown glass bottle, sealed with a gray, 20 mm stopper and covered with a flip-off seal.	Single use vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 11, 2016, we searched the L:drive and AIMS using the term, talc, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews for Novatech S.A.'s Steritalc Talc Powder product. However, we reviewed our previous recommendations for the listed drug, Sclerosol Intrapleural Aerosol and Sterile Talc Powder, products to ensure our recommendations for Novatech S.A. product are consistent with our previous recommendations for other Sterile Talc Powder products.

Sterile talc powder products				
Application	Applicant	Strength	Status	OSE Review
NDA 020587 Sclerosol Intrapleural Aerosol (sterile talc powder) RLD	Bryan	4 g	Approved: December 24, 1997	None found
NDA 021388 Sterile Talc Powder RLD	Bryan	5 g	Approved: December 24, 1997	2013-1979 ^c 2013-1979-1 ^d
NDA 205555 Steritalc Talc Powder	Novatech S.A.	2 g, 3 g, and 4 g	Subject of this review	2016-951

^c Townsend, O. Label, Labeling, and Packaging Review for Sterile Talc Powder (Talc) (NDA 021388/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 OCT 3. RCM No.: 2013-1979.

^d Townsend, O. Label, Labeling, and Packaging Review for Sterile Talc Powder (Talc) (NDA 021388/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAY 12. RCM No.: 2013-1979-1.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 19, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community
Search Strategy and Terms	Match Exact Word or Phrase: talc

D.2 Results

Our search identified 2 articles that contain the word “talc” that we evaluated further for medication errors possibly associated with label and labeling.

Newsletter	Date	Issue	Relevance
Acute Care	August 23, 2007 ^e	Talc was given intravenously instead of via chest tube	Not related to label or labeling
Acute Care	February 12, 2004 ^f	Talc vial from Bryan looks like Biotrace (sterile barium sulfate) from Bryan.	No error occurred. Not applicable to this product.

^e Institute for Safe Medication Practices. Safety briefs: Talc given IV. ISMP Med Saf Alert Acute Care. August 2007;12(17):1-2.

^f Institute for Safe Medication Practices. Safety briefs: Barium and talc vials. ISMP Med Saf Alert Acute Care. 2004;9(3):1-3.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^g along with postmarket medication error data, we reviewed the following Steritalc Talc Powder labels and labeling submitted by Novatech S.A. on April 15, 2016.

- Container labels
- Carton labeling
- Prescribing Information (not shown)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

^g Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

TINGTING N GAO
12/13/2016

CHI-MING TU
12/13/2016

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205555

Application Type: NEW NDA

Drug Name(s)/Dosage Form(s): STERITALC® Talc Powder, 2g, 3g, and 4g

Applicant: Novatech S.A.

Receipt Date: April 15, 2016

Goal Date: February 15, 2017

1. Regulatory History and Applicant's Main Proposals

STERITALC® is a sclerosing agent indicated:

- For [REDACTED] (b) (4) malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion.
- For [REDACTED] (b) (4) pneumothorax.

BACKGROUND:

Novatech S.A. initially submitted a New Drug Application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for sterile talc on March 1, 2013, received by FDA on March 5, 2013. After a preliminary review, the application was found to be insufficiently complete to permit a substantive review. Therefore, on May 3, 2013, a Refuse-to-File letter was sent to the Applicant. On April 15, 2016, the Applicant re-submitted the NDA for review.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: Margins are not correct and columns are not even. To correct these formatting issues, we recommend using the sample PLR template located at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM340915.docx>

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit** year.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the

Selected Requirements of Prescribing Information

BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

YES

Selected Requirements of Prescribing Information

21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELLENI K ALEBACHEW
07/21/2016

CHRISTY L COTTRELL
08/04/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205555 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: STERITALC® Established/Proper Name: Talc Dosage Form: Powder Strengths: 2g, 3g, and 4g		
Applicant: Novatech S.A. Agent for Applicant (if applicable): Boston Medical Products Inc.		
Date of Application: April 14, 2016 Date of Receipt: April 15, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: February 15, 2017		Action Goal Date (if different):
Filing Date: June 14, 2016		Date of Filing Meeting: May 31, 2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): STERITALC® is a sclerosing agent indicated: - For (b) (4) malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. - For (b) (4) pneumothorax.		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement:	☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2) NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499	

Type of BLA	☐ 351(a) ☐ 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	☒ Standard ☐ Priority
<i>The application will be a priority review if:</i> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☒
Part 3 Combination Product? ☒ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): PIND 104068				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	☒	☐		

<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in electronic archive?	☒	☐		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm	☒	☐	☐	
<i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission?	☐	☐	N/A	
If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>): ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			

User Fee Bundling Policy Refer to the guidance for industry, <i>Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No																			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:		☒	☐																		
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>		☐	☒																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		☐	☒																		
If yes, please list below: <table border="1" style="width: 100%;"> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																					
Exclusivity		YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm		☐	☒		Bryan Corporation's Sclerosol Intrapleural Aerosol had orphan designation for (b) (4)																

				malignant pleural effusion (designation dated 9/18/1995). Exclusivity end date 12/24/2004.
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☒	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☐	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD

	☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: ☒ legible ☐ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no , explain.	☐	☒		Parts of Module 3 are not in English and have not been translated.
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	☐	☐	☐	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☐	☐	N/A	No clinical studies were conducted by the Applicant.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☐	☐	N/A	No clinical data was submitted. The Applicant is pursuing approval under 505b2 pathway
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☒	☒		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☒	☐	Orphan designation
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	☐	☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☐	☒	☐	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☒	☐	☐	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐	☐	☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☐	☒	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	PI and carton and immediate container labeling consulted/sent to OSE/DMEPA
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
All labeling/package sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	☒	☐	☐	CDRH OSE/DVP
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	☐	☒		
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 31, 2016

NDA #: 205555

PROPRIETARY NAME: Steritalc

ESTABLISHED/PROPER NAME: talc

DOSAGE FORM/STRENGTH: powder for intrapleural administration, 2g, 3g and 4g

APPLICANT: Novatech, Inc.

PROPOSED INDICATIONS:

STERITALC® is a sclerosing agent indicated:

- For (b) (4) malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion.
- For (b) (4) pneumothorax.

BACKGROUND:

Novatech S.A. initially submitted a New Drug Application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for sterile talc on March 5, 2013. After a preliminary review, the application was found to be insufficiently complete to permit a substantive review. Therefore, on May 3, 2013, a refuse-to-file letter was sent to the Applicant. On April 15, 2016, the Applicant re-submitted the NDA for review.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elleni Alebachew	Y
	CPMS/TL:	Christy Cottrell	N
Cross-Discipline Team Leader (CDTL)	Xiao Chen		
Division Director/Deputy			
Office Director/Deputy			
Clinical	Reviewer:	Nancy Scher	Y

	TL:	Laleh Amiri Kordestani	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Xianhua Cao	Y
	TL:	Runyan Jin	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	N/A	
	TL:	N/A	

Nonclinical (Pharmacology/Toxicology)	Reviewer:	George Chang	N
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Xiao H.Chen	
	RBPM:	Kristine Leahy	Y
• Drug Substance	Reviewer:	Hari Sarker	Y
• Drug Product	Reviewer:	Nina Ni	Y
• Process	Reviewer:	Peter Guerrieri	Y
• Microbiology	Reviewer:	Yarery Smith	Y
• Facility	Reviewer:	Marion Michaelis	Y
• Biopharmaceutics	Reviewer:	Gerlie Gieser	Y
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Branch Chief: Anamitro Banerjee		Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	N/A	
	TL:	N/A	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Tingting Gao	Y
	TL:	Chi-Ming (Alice) Tu	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	N/A	
	TL:	N/A	
Other attendees	William Pierce,		
	Frances Fahnbulleh		
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL 505 b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO Applicant requested a bioavailability waiver, but provided published literature references
Per reviewers, are all parts in English or English translation? If no, explain: Parts of Module 3 are not in English and are not translated	☐ YES ☒ NO	
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments	

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain: No clinical sites. 505(b)(2) application	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: <i>this drug/biologic is not the first in its class</i>
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

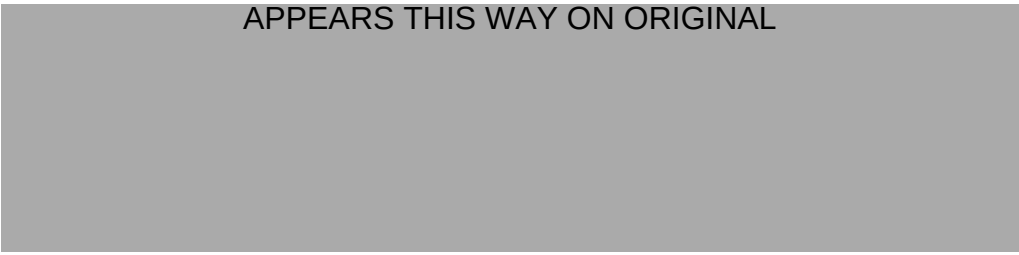
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	N/A ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Amna Ibrahim, MD, Deputy Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): September 7, 2016 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Mid Cycle Mtg: Sept 7, 2016 Wrap Up mtg: Jan 10, 2017	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

APPEARS THIS WAY ON ORIGINAL



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/s/

ELLENI K ALEBACHEW
07/21/2016

CHRISTY L COTTRELL
07/22/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Pharmacovigilance Memorandum

Date: June 8, 2016

Reviewer: Regina Lee, PharmD, Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Team Leader (Acting): Afrouz Nayernama, PharmD
DPV II

Deputy Division Director: S. Christopher Jones PharmD, MPH, MS
DPV II

Product Name(s): Sclerosol Intrapleural Aerosol (sterile talc powder)
Sterile Talc Powder (talc)

Subject: Summary of post-marketing adverse events

Application Type/Number: NDA 020587, 021388

Applicant/Sponsor: Bryan Corporation

OSE RCM #: 2016-1265

1 INTRODUCTION

This memorandum provides a high-level analysis of post-marketing reports of all adverse events from the FDA Adverse Event Reporting System (FAERS) associated with the talc products manufactured by Bryan Corporation, Sterile talc powder (NDA 021388) and Sclerosol Intrapleural Aerosol (NDA 020587), since each product approval date to June 1, 2016. The Division of Oncology Products 1 (DOP1) consulted the Division of Pharmacovigilance II (DPV II) to provide a high-level analysis of all FAERS data, in particular acute respiratory distress syndrome (ARDS) potentially due to particle size, for the current available Talc products manufactured by Bryan from 2010 to the present date. In order to capture all cases of concern, DPV II expanded the search date from the product approval dates to June 1, 2016.

DOP 1 is in the process of reviewing the 505(b)(2) NDA 205555 application for Steritalc (talc) powder manufactured by Nova tech S.A. The sponsor, Nova tech S.A., is seeking approval to market this product for intrapleural administration for (b) (4) malignant pleural effusion and (b) (4) pneumothorax.¹ DOP 1 requested FAERS data in order to determine whether a clinical trial is warranted for the approval of Steritalc. Of note, the Bryan products were approved based on published literature review. DOP 1 is also inquiring whether there is a difference in the adverse event profile between the two talc products manufactured by Bryan.

Talc powder is in many cosmetics, baby powder, and other personal care products. Talc is also found in certain food products, such as rice and chewing gum, and in the manufacture of tablets. In recent years, there has been a concern regarding the association of talc products with carcinogenicity, including ovarian cancer.² It is noteworthy that in 2014, multiple lawsuits were filed against Johnson & Johnson, the manufacturer of Johnson's baby powder (made from cosmetic talc), alleging deliberate disregard for scientific evidence linking the use of talcum powder around the female genital area with an increased risk for ovarian cancer.³ This is relevant, because many of the reports in FAERS make reference to the presence of talc in baby powder as the source of exposure.

2 REGULATORY HISTORY

Sterile talc powder (NDA 021388) was approved by the FDA on December 15, 2003. It is a sclerosing agent indicated to decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion.⁴

Sclerosol Intrapleural Aerosol (NDA 020587) was approved by the FDA on December 24, 1997. It is indicated to prevent recurrence of malignant pleural effusions in symptomatic patients and administered by aerosol during thoracoscopy or open thoracotomy.⁵

2.1 PRODUCT LABELING

ARDS and respiratory failure are labeled events for both talc products as described below.

Sterile talc powder (NDA 021388)⁴

5.1 Warnings and Precautions

Pneumonitis and Acute Respiratory Distress Syndrome (ARDS): Acute Pneumonitis and ARDS, including fatal cases, occur with intrapleural talc administration.

6 Adverse Reactions

Other adverse reactions include dyspnea, arrhythmia, empyema, and acute respiratory distress syndrome.

Sclerosol (NDA 020587)⁵

Precautions

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.*

Adverse Reactions

Respiratory: *Rare instances of pneumonia, ARDS, dyspnea, bronchopleural fistula, hemoptysis, and pulmonary emboli have been reported.*

3 METHODS AND MATERIALS

The FAERS database was searched with the strategies described in Tables 1 and 2.

Table 1. FAERS Search Strategy*	
Date of search	June 1, 2016
Time period of search	December 15, 2003 [†] – June 1, 2016
Product terms	Product Active Ingredient: Talc
MedDRA Search Terms (Version 19)	All
* See Appendix A for a description of the FAERS database.	
[†] FDA approval date	

Table 2. FAERS Search Strategy*	
Date of search	June 1, 2016
Time period of search	December 24, 1997 [†] – June 1, 2016
Product Terms	Product Name: Sclerosol
MedDRA Search Terms (Version 19)	All
Additional criteria	NDA 020587
* See Appendix A for a description of the FAERS database.	
[†] FDA approval date	

4 RESULTS

4.1 FAERS Search 1

FAERS search 1, as described in table 1, yielded 285 reports for Sterile talc powder. DPV II identified that 258 of these FAERS reports were reports of carcinogenicity associated with cosmetic talc products use e.g. Johnson's baby powder. The preferred terms associated with these 258 FAERS litigation reports are listed in Table 3. We do not consider these as reports of interest for the purposes of this document, and do not review them in further detail.

Table 3. FAERS Reported PTs describing Sterile talc powder carcinogenicity association, received by FDA from December 15, 2003 – June 1, 2016, sorted by decreasing number of FAERS reports per PT (N=258)	
Ovarian Cancer	246
Ovarian Cancer Stage IV	4
Uterine Cancer	4
Ovarian Cancer Stage I	1
Ovarian Cancer Stage II	1
Ovarian Cancer Stage III	1
Cervix Carcinoma	1

The remaining 27 FAERS cases for Sterile talc powder were assessed further. The most frequently reported PTs are described in **Table 4**. The narratives of the 27 FAERS cases are embedded in this document (see **Appendix B**). The data included in table 4 are crude and may include duplicates. A detailed case review was not performed for these reports; therefore, a drug-event causal association cannot be assessed based on these data (See **Appendix A** for FAERS limitations).

Table 4. Reported MedDRA PTs*$\geq$2 of all adverse events associated with Sterile Talc Powder received by FDA from December 15, 2003 to June 1, 2016 (N=27)**		
	MedDRA PT	Number of FAERS Reports
1	Drug hypersensitivity	4
2	Incorrect route of drug administration	3
3	Accidental exposure to product	2
4	Diarrhea	2
5	Dyspnea	2
6	Interstitial lung disease	2
7	Lymphadenopathy	2
8	Nephrolithiasis	2
9	Paresthesia	2
10	Pneumonia	2
11	Post procedural complication	2
12	Product quality issue	2
13	Rash	2
14	Shock	2
* May include duplicates. A report may contain more than one preferred term.		
** Excluding the outlier stimulating ligation reports of ovarian cancer associated with cosmetic talc product e.g. Johnson's baby powder.		

We identified one report of interest for acute respiratory distress syndrome (ARDS). The narrative of this case is described below:

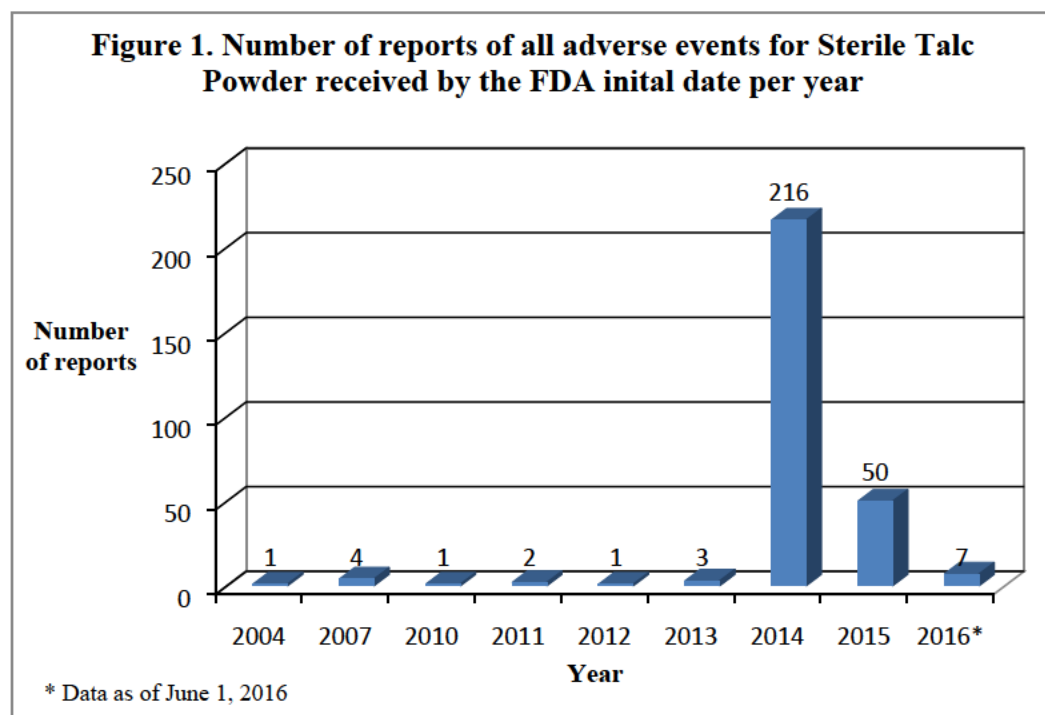
FAERS Case#8744813, U.S.A.

A 65-year-old female with pneumothorax received talc 2g for pleurodesis. After the procedure, the patient had a presumed allergic reaction in the form of systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome. The patient required mechanical ventilation and was started on methylprednisolone 60mg IV q 8 hours. Tracheostomy was placed seven days later. Her past medical history included esophageal reflux, peptic ulcer disease, tardive dyskinesia, chronic obstructive pulmonary disease, bipolar disorder, non-cardiac chest pain, atrial fibrillation, hypertension, and possible congestive heart failure. Concomitant medications included albuterol, atenolol, cefuroxime, docusate-senna, enoxaparin, ezetimibe, famotidine, fenofibrate, guaifenesin, heparin flush, lamotrigine, lidocaine patch, lorazepam, milk of magnesia, metoclopramide, midazolam, multivitamin with iron, pantoprazole, pramipexole, simvastatin, sodium bicarbonate, sucralfate, and trazodone. The outcome of this case was hospitalization.

Reviewer's Comments:

Based on the temporal relationship, and short onset latency, the drug-event association is plausible. Although the patient received multiple concomitant medications, none of them are labeled for ARDS.

Figure 1 shows the number of FAERS reports of all adverse events associated with Sterile talc powder received by the FDA per year since product approval. This figure shows that there is a noticeable increase in the reported adverse events associated with talc since January 1, 2014. However, 258 (91%) of these FAERS reports are described by carcinogenicity PTs, including 202 of 216 reports (94%) in 2014 and 46 of 50 reports (92%) in 2015. These reports appear to be stimulated by recent litigation against the manufacturers of talc containing baby powder products.



4.2 FAERS Search 2

FAERS search 2, as described in table 2, yielded 13 reports associated with Sclerosol (NDA 020587). The narratives of the 13 FAERS cases are embedded in this document (see **Appendix B**).

Table 5 summarizes the reported MedDRA PTs ≥ 2 of all adverse events retrieved from our FAERS search with Sclerosol (NDA 020587), received by FDA from December 24, 1997 – June 1, 2016.

Table 5. Reported MedDRA PTs*$\geq$2 of all adverse events associated with Sclerosol (NDA 020587) received by FDA from December 24, 1997 to June 1, 2016 (N=13)		
	MedDRA PT	Number of FAERS Reports
1	Pain	3
2	Cardio-respiratory arrest	2
3	Hemorrhage	2
4	Medication error	2
5	Pregnancy	2
6	Product quality issue	2
7	Syncope	2
* May include duplicates. A report may contain more than one preferred term.		

We identified one report of ARDS and one report of respiratory failure with FAERS search 2. The narratives of these cases are described below:

FAERS Case#3337746, U.S.A.

A 44-year-old female was administered 4 grams of Sclerosol via the chest tube for pleurodesis of a left-sided malignant pleural effusion. Later in the evening, the patient developed a fever, dyspnea, hypoxia, and tachycardia; she was placed on 100% oxygen with improvement. However, the next day, the patient's O₂ saturation decreased again and she was intubated and transferred to the intensive care unit (ICU). No further information was provided regarding the remainder of the patient's hospital course. According to the reporting physician, the patient died of ARDS and disease progression.

Reviewer's comments:

Based on the temporal relationship, and short onset latency, the drug-event association is plausible. The case is confounded by underlying comorbidities e.g. malignant pleural effusion.

FAERS Case#11211212, U.S.A.

A 66- year-old female with diagnosis of hypoxia and dyspnea on exertion in the hospital underwent a right video assisted thorascopic drainage pleural effusion with pleurodesis. She developed acute hypoxic respiratory failure, a productive cough, shortness of breath, chest tightness, labored breathing, a red tongue with mild swelling, and garbled speech. The physician's assessment was acute hypoxic respiratory failure most likely due to an allergic reaction to clindamycin versus inflammatory reaction with pleurodesis. Clindamycin was discontinued and she was treated with intravenous diphenhydramine and methylprednisolone. The patient was transferred to the ICU and placed on 2L oxygen, which was increased to 4L. She recovered from the event in the ICU after 48 hours and was transferred back to the floor. Past medical history includes DM, HTN, paroxysmal atrial fibrillation, hyperthyroidism, renal failure, carotid artery stenosis, basal cell carcinoma, pneumonia, and pleural effusion. The patient's

history of allergy includes hives from cephalosporins, rash from quinolones, and itchiness from quinine.

Reviewer's Comments:

This case is confounded by the concomitant use of clindamycin. However, based on the temporal relationship, and short onset latency, the drug-event association is possible.

5 REVIEWER'S COMMENTS

Sterile Talc Powder

A high-level analysis of the FAERS database identified 285 reports of all adverse events associated with Sterile talc powder (NDA 021388). The FAERS data for Sterile talc powder was skewed by the stimulating litigation reports of ovarian cancer since January 2014. For the purpose of this high-level FAERS analysis, we excluded reports (n=258) associated with cosmetic talc products. We further assessed the remaining 27 FAERS reports associated with the medical use of Sterile talc powder. DPV concludes the FAERS adverse event profile for sterile talc powder is consistent with known events identified in current product labeling. Several events could also be related to the indication for which the drug is used or are too infrequently reported to make inference. The top three reported events for Sterile talc powder include drug hypersensitivity, incorrect route of drug administration, and accidental exposure to product. Preliminary review of the most frequently reported event, drug hypersensitivity, indicates that reports were confounded by multiple concomitant medications.

Sclerosol

A high-level analysis of the FAERS data identified 13 reports of all adverse events associated with Sclerosol (NDA 020587). The top three reported events with Sclerosol are pain, cardio-respiratory arrest, and hemorrhage, which are all labeled events.

Aggregated FAERS Safety Information Across Both Products

Overall, we retrieved two reports of ARDS and one report of respiratory failure with two FAERS searches. Acute respiratory distress syndrome is currently labeled for both talc products as described under the Product Labeling section of this memo.^{4,5} ARDS is a known event associated with talc poudrage and slurry.⁶ According to the literature, acute respiratory failure associated with talc pleurodesis could potentially be caused by sepsis due to unsterile or endotoxin-containing talc, excessive talc dosing, active air leak, excessive peri-procedure medications, severe underlying lung disease, and re-expansion pulmonary edema.⁶

Based on our high-level FAERS data, the adverse event profiles of Sterile talc powder and Sclerosol are similar. We identified several unlabeled events for both products, which were non-serious, disease-related, secondary to medication error or comorbidities, confounded by concomitant medications, or lacked sufficient information. Our high-level evaluation of the FAERS data did not identify any new safety concerns.

We have attached the 40 FAERS reports for Sterile talc powder (n=27) and Sclerosol (n=13) to this review.

APPENDICES

6 APPENDICES

6.1 Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

(b) (4)



REFERENCES

¹ Novatech S.A. Steritalc NDA 205555 Application. April 14, 2016. Accessed on June 2, 2016 at <\\cdsesub1\evsprod\nda205555\0000\m1\us\12-cover-letters\cover-letter-nda-april-14-2016.pdf>.

² FDA, Cosmetics: Talc. March 19, 2014. Accessed on June 2, 2016 at <http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm293184.htm>

³ Morran C. Jury Awards \$72 Million In Johnson & Johnson Talcum Powder Cancer Lawsuit. February 24, 2016. Accessed on June 2, 2016 at <https://consumerist.com/2016/02/24/jury-awards-72-million-in-johnson-johnson-talcum-powder-cancer-lawsuit/>

⁴ Sterile Talc Powder [Package Insert]. Woburn, MA: Bryan Corporation; June 2014.

⁵ Sclerosol [Package Insert]. Woburn, MA: Bryan Corporation; October 2012.

⁶ American Thoracic Society. Management of malignant pleural effusions. Am J Respir Crit Care Med. 2000 Nov;162(5):1987-2001.

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/s/

REGINA LEE

06/09/2016

AFROUZ R NAYERNAMA

06/09/2016

STEVEN C JONES

06/10/2016

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Project Manager, DSD/ODE/CDRH

From: LCDR Jitendra Virani, MS
Lead Reviewer
General Surgery Devices Branch 2 (GSDB2)
DSD/ODE/CDRH

Subject: NDA 205555 (505b2)
STERITALC Talc Powder

Sponsor: Novatech S.A.

Date: May 6, 2016

Reason for Consult:

We have received re-submission after RTF letter of a 505(b)(2) NDA for Steritalc (Novatech S.A.). They reference Bryan's Sterile Talc Powder and Sclerosol Aerosol. There are 3 presentations for the new product. Regarding one of these, the proposed label says: Section 2.3 and 3. STERITALC® (b)(4) talc in glass vial, 3 g; to be used with Novatech S.A.'s TALCAIR® pulverization kit.

Has this device been submitted to or reviewed by CDRH? Please advise as the sponsor says in response to RTF letter, "this submission is only for the drug component." The division would like to have your comments a week by the filing date.

Indications and Usage:

"STERITALC ® is a sclerosing agent indicated:

- For (b)(4) malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion.

- For (b) (4) pneumothorax.”

Device Information:

The sponsor did not provide device information in the NDA submission and stated, “this submission is only for the drug component.”

The sponsor was sent the following request, via CDER, interactively on April 27, 2016.

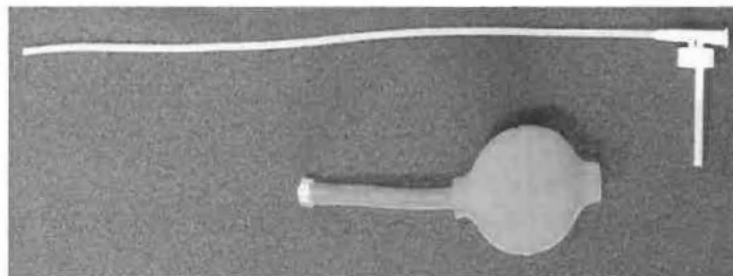
“In response to the RTF letter, you state, “this submission is only for the drug component.” The following is from your proposed labeling (Section 2.3 and 3) “STERITALC® (b) (4) talc in glass vial, 3 g; to be used with Novatech S.A.’s TALCAIR® pulverization kit.” In the submission, we cannot find more information for TALCAIR pulverization kit which appears to be a medical device. Please provide more information on the TALCAIR pulverization kit. If this has already been reviewed and cleared or approved by other centers (CDRH or CBER) of the FDA, please provide submission number (PMA or 510(k) notification) under which it is cleared/approved.”

The sponsor provided the following response, via CDER, on April 28, 2016: “The 510(k) clearance of the NOVATECH TALCAIR has just been received when the NDA preparation was finalized. Therefore, no 510(k) number has been included in the NDA re-submission. However, the 510(k) number of the NOVATECH TALCAIR is K151832. Please find the FDA approval, the 510(k) Summary and the Indication for Use attached.”

The have confirmed that the device, Novatech Talcair, is cleared under K151832. The following is cleared indications for use for this device: **“Treatment of malignant pleural effusion by insufflation of medical grade talc following drainage of pleural fluid.”**

The following is brief information, as reported under K151832, about this device:
NOVATECH® TALCAIR™ is a powder blower comprised of an insufflation cannula, an insufflation bulb and its connecting pieces (a coupling, and a luer connector). The coupling, which is made of polypropylene, is used to attach the device to a vial. The device is a sterile, single use medical device which is sterilized by gamma sterilization.

The following are the pictures of this device.





Consult Discussion:

CDER Consult Question: Has this device been submitted to or reviewed by CDRH?

CDRH Answer: Yes the device, NOVATECH® TALCAIR™, has been reviewed under a 510(k) notification, K151832, and cleared. However, as listed in below table, there are differences in the indications for use for which the device is cleared and the indications for use the sponsor is requesting for the drug under the NDA 205555 (i.e., “For the treatment of pneumothorax”).

Device Indications for Use (Cleared by CDRH), K151832	Drug Indications for Use (Requested from CDER), NDA 205555
“Treatment of malignant pleural effusion by insufflation of medical grade talc following drainage of pleural fluid.”	“For (b) (4) malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. For (b) (4) pneumothorax”

I discussed this issue with CDRH product jurisdiction officer, Dr. James Bertram. We both agreed the firm would need to submit a 510(k) to include the added Indications they are requesting for the Drug (i.e., (b) (4) pneumothorax). Otherwise, there is technically no device to deliver this drug on-label for that indication.

The firms could submit a 510(k) concomitant to this NDA. The firm potentially can submit a 510(k) requesting a generic tool indication or the same additional indication that is being sought under NDA. For example, the firm may use the following language as a generic tool indications for use: ‘*The device is intended for manual insufflation of medical grade talc into the pleural cavity during pleurodesis. The device is indicated for use according to the approved indication for use of the medical grade talc.*’ This will allow for the specific treatment indication to be dependent on the drug component and the firm will be able to use the device for various treatment indications, as approved by the CDER, in which manual insufflation of the drug is a clinically appropriate treatment method. CDER can suggest the firm to contact CDRH for further discussion on the submission of a 510(k).

Alternatively, the firm can either convert this submission into a combination product submission or revise the requested indication under the NDA to align it with the indications for use cleared under the 510(k) K151832.

Jitendra V. Virani -S
2016.05.10 12:25:54 -04'00'

Reviewer
Jitendra V. Virani, MS
Acting Sr. Reviewer\Biomedical Engineer
General and Surgical Devices Branch 2
Division of Surgical Devices

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