CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205555Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 205555
Review # 1

Drug Name/Dosage Form	STERITALC Powder
Strength	2g, 3g and 4g
Route of Administration	Intrapleural
Rx/OTC Dispensed	Rx
Applicant	Novatech S.A.
US agent, if applicable	Stuart K. Montgomery, President, Boston Medical Products Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	CDER/OPQ/ONDP/DNDAPI
Drug Product	Nina Ni	CDER/OPQ/ONDP/DNDPI/NDPBII
Process	Peter Guerrieri	CDER/OPQ/OPF/DPAI/PAB1
Microbiology	Yarery Smith	CDER/OPQ/OPF/DMA/MAB1
Facility	Marion Michaelis	CDER/OPQ/OPF/DIA/IAB1
Biopharmaceutics	Gerlie Gieser	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/B1
Application Technical Lead	Anamitro Banerjee	CDER/OPQ/ONDP/DNDPI/NDPBII
Laboratory (OTR)	Akhtar Siddiqui	CDER/OPQ/OTR/DPQR/PQBII
ORA Lead	NA	
OPPQ	Brian Hasselbalch	CDER/OPQ/OPPQ
Environmental Analysis (EA)	NA	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)				Adequate		Referred by several NDAs and ANDA. Adequate information provided in the NDA
				Adequate		Referred by several NDAs and ANDA. Adequate information provided in the NDA
				Adequate		Referred by several NDAs and ANDA. Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021388	Sterile Talc Powder (Listed Drug)
NDA	020587	SCLEROSOL® intrapleural Aerosol (Listed Drug)

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The CMC information provided in this application is acceptable. This NDA may be approved from the CMC point of view.

II. Summary of Quality Assessments

A. Product Overview

Steritalc is a white or off-white to gray, asbestos free, sclerosing agent for intrapleural administration available as sterile 2 g, 3g, and 4g single dose glass vials. The applicant lists the two NDAs: 021388 and 020587, and relies on the literature reports for safety and efficacy. This product contains particle size controlled talc, graded to decrease the presence of smaller particles. This product is currently approved for marketing in the EU as a device.

This NDA was originally submitted on March 05, 2013. On May 3, 2013, the applicant was sent a refuse-to-file letter as the application was determined to be incomplete and did not contain information required under 21 CFR 314.50. The NDA was resubmitted April 14, 2016 and filed on June 14, 2016.

Proposed Indication(s) including Intended Patient Population	1. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. 2. In adults to decrease the recurrence of complicated pneumothorax or recurrent pneumothorax.
Duration of Treatment	1. Malignant Pleural Effusion: The recommended dose is (b) (4) to 5 g administered intrapleurally. 2. Recurrent or Complicated Pneumothorax: The recommended dose is 2 g administered intrapleurally.
Maximum Daily Dose	Total cumulative dosage: 10 grams per procedure.
Alternative Methods of Administration	NA

B. Quality Assessment Overview

The finished drug product is a powder with strengths, 2g, 3g and 4g also designated as Steritalc (b) (4) Steritalc (b) (4) and Steritalc (b) (4) respectively. The 3g configuration, (b) (4) can

be delivered with NOVATECH®TALCAIR™ powder blower that is already approved by the FDA. The other two configurations, (b) (4) and (b) (4) may be delivered by any of the approved powder blowers or a catheter. The proposed product, STERITALC®, is composed of (b) (4) asbestos free sterile talc powder ($Mg_3Si_4O_{10}(OH)_2$); hydrated magnesium silicate. In this NDA, the drug substance (Talc, also termed as (b) (4) is sourced from (b) (4) The drug substance is (b) (4) . (b) (4) during the production of the drug substance and no excipients are used in the manufacturing of the STERITALC® drug product.

Designation of starting material and drug substance manufacturer: (b) (4)

(b) (4)

(b) (4)

As this is a unique situation where the drug substance is not expected to be manufactured if the NDA is approved for foreseeable future, the Office of Policy for Pharmaceutical Quality (OPPQ) was requested to advise on the specific sections of the FD&C Act, regulations, and relevant policies to determine if a viable API manufacturer is necessary to support this NDA. The OPPQ memo dated December 29, 2016 by Dr. Brian J. Hasselbalch, Deputy Director (Acting), OPPQ, indicated that no policy appears to prevent the approvability of this NDA even though the API manufacturer listed in this NDA no longer intends to manufacture the API.

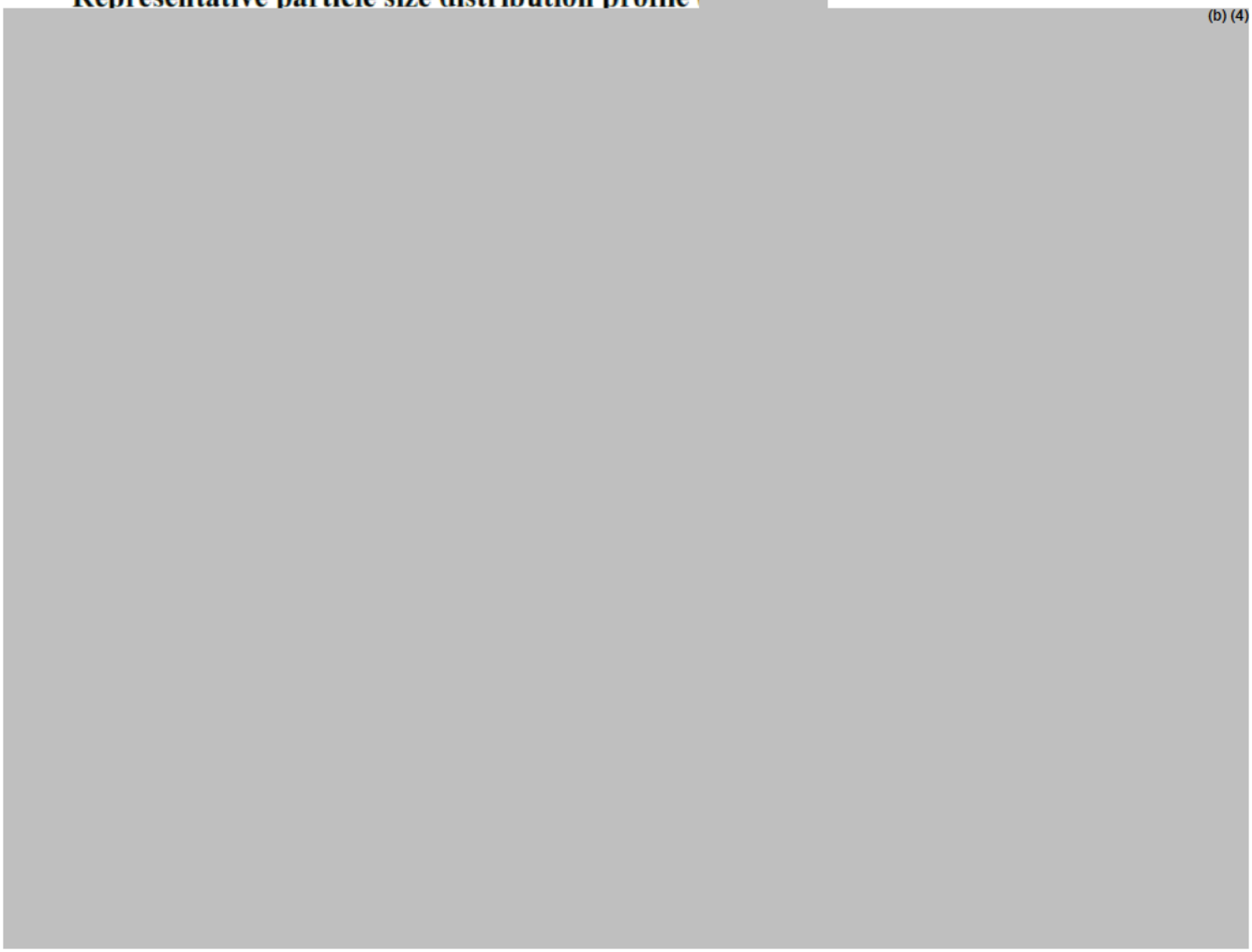
Other sites: [redacted] Bess Pro, GmbH, Berlin, Germany ([redacted], drug product manufacturing and packaging) were inspected and were found to be acceptable. The release testing sites, [redacted] was also found acceptable based on profile. No sites currently have any outstanding issues that may affect the approvability of this NDA.

Particle Size Distribution: This product is graded to remove particles less than [redacted] microns. This product (Steritalc) has a particle size distribution specification to control smaller particles [redacted] µm is included in the drug product specifications) when measured by [redacted] method. Based on the literature reports, this product is safer than the currently approved talc products in the US. Literature reports cite particle size differences responsible for lower side effects (acute respiratory distress syndrome) observed for this product. Literature data and testing by the FDA laboratories indicates that this product has fewer particles less than [redacted] microns, while the currently approved products (listed drugs Sclerosol, NDA 020587 and Sterile Talc Powder, NDA 021388) contains substantially higher proportions of smaller particles. The report dated November 25, 2016 by Dr. Akhtar Siddiqui, OTR, detailing the findings of the FDA is attached in this review. The results indicate that apart from the particle size distribution, the physicochemical properties of the proposed product and the listed drugs have no significant differences. The particle size distribution measured by three different methods indicated that proportion of particles less than [redacted] microns in the proposed product is less than that in the listed drug.

[redacted]

Representative particle size distribution profile (b) (4)

(b) (4)



Drug Product Specifications: The controls for asbestos were found satisfactory by the drug substance reviewer upon review of the documents and procedure during inspection of the (b) (4) site. Hence, additional tests for asbestos were not included in the drug substance or drug product specifications. Upon request, the applicant provided a risk analysis of elemental impurities. Apart from lead, (b) (4) elemental impurities comply with the levels indicated in the ICH Q3D. The risk assessment for these elements was evaluated by the pharm-tox reviewer, who found the proposed controls for these elements acceptable based on the dosage and duration of use. The applicant will test for the levels of (b) (4). Batch data and stability data for the drug product are adequate, and are consistent with drug product specifications.

Biopharmaceutics: The Applicant's biowaiver request was not deemed necessary because the bioavailability of locally (intrapleurally) administered talc for pleurodesis is self-evident and can be established consistent with 21 CFR 320.24(b)(6). In some of the medical literature studies submitted, either STERITALC® itself or comparable sterile

talc products were evaluated for efficacy and/or safety in [redacted] malignant pleural effusions and/or [redacted] pneumothorax.

Microbiology: The drug product is [redacted] of the drug product have been adequately validated. The drug product conformed to the release specification for sterility and endotoxins.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies for Complete Response

None

Application Technical Lead Name and Date:

Anamitro Banerjee, Ph.D. ***April 25, 2017***

LABELING

{For NDA only}

R Regional Information

1.14 Labeling

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

STERITALC® (talc), powder, for intrapleural use
Initial U.S. Approval: 2003

- Powder: 2 grams, in a 50 mL single-dose vial (3)
- Powder: 4 grams, in a 50 mL single-dose vial (3)
- Powder: 3 grams, in a 10 mL single-dose vial (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	STERITALC® (talc)	Adequate.
Dosage form, route of administration	For intrapleural use	Adequate.
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Powder: 2 grams, 3 grams, and 4 grams.	Adequate.

Conclusion: Adequate. See assessment above.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

White or off-white to light gray sterile powder provided in the following strengths:

- Powder, for intrapleural use: STERITALC®, 2 grams in a 50 mL single-dose vial
- Powder, for intrapleural use: STERITALC®, 4 grams in a 50 mL single-dose vial
- Powder, for intrapleural use: STERITALC®, 3 grams in a 10 mL single-dose vial, for use with Novatech® S.A.'s TALCAIR™

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Provided as powder for intrapeural use	Adequate.
Strengths: in metric system	Provided as 2 grams, 3 grams, and 4 grams	Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White or off-white to light gray sterile powder	Adequate.

Conclusion: Adequate. See assessment above.

#11: Description (21CFR 201.57(c)(12))

STERITALC® (talc) is a sclerosing agent for intrapleural administration. The molecular weight is 379.3 g/mole. The chemical name of talc is hydrated magnesium silicate. The talc powder contains ≥ 95% of hydrated magnesium silicate; associated minerals include chlorites (hydrated aluminum and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate). The talc elementary sheet is composed of a layer of magnesium-oxygen/hydroxyl octahedra, sandwiched between two layers of silicon-oxygen tetrahedra. Talc is insoluble in water.

STERITALC® is supplied as 2 grams, 3 grams, and 4 grams white or off-white to light gray, asbestos free, sterile powder. STERITALC contains particle size-controlled talc, graded to decrease the proportion of smaller particles.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	STERITALC® (talc)	Adequate.
Dosage form and route of administration	Powders for intrapleural administration	Adequate.
Active moiety expression of strength with equivalence statement for salt (if applicable)	N/A	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	N/A	N/A
Statement of being sterile (if applicable)	Sterile	Adequate.
Pharmacological/ therapeutic class	Provided	Adequate.
Chemical name, structural formula, molecular weight	Provided	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate.

Conclusion: Adequate. See assessment above.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

STERITALC®, white or off-white to light gray, asbestos-free, sterile powder is supplied as

- two grams of talc powder in a single-dose 50 mL Type III glass vial, closed with a stopper, and crimped with an aluminum cap; with 4 vials packaged in one carton. NDC XXXX-XXXX-XX

- four grams of talc powder in a single-dose 50 mL Type III glass vial, closed by a stopper, and crimped with an aluminum cap; with 4 vials packaged in one carton. NDC XXXX-XXXX-XX

- three grams of talc powder in a single-dose 10 mL Type I brown glass vial, closed by a stopper, and crimped with an aluminum cap; with 4 vials packaged in one carton. NDC XXXX-XXXX-XX

Store at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Protect against sunlight.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Provided	Adequate.
Available units (e.g., bottles of 100 tablets)	Provided	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided Space allocated for NDC number	Adequate.
Special handling (e.g., protect from light, do not freeze)	Protect against sunlight.	Adequate.
Storage conditions	Provided	Adequate.

Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured for: Novatech S.A.
Z.I. Athélia III - 1058, Voie Antiope
13705 La Ciotat CEDEX
France

By: bess pro gmbh
Gustav-Krone-Strasse 7
14167 Berlin
Germany

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Provided.	Adequate.

Conclusion: Adequate. See assessment above.

2. Container and Carton Labeling

(b) (4)

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Provided	Adequate.
Strength (21CFR 201.10(d)(1); 21 CFR 201.100(b)(4))	Provided	Adequate.
Route of administration 21 CFR 201.100(b)(3))	Provided	Adequate.
Net contents* (21 CFR 201.51(a))	Provided	Adequate.
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	N/A	Adequate.
Lot number per 21 CFR 201.18	Space allocated	Adequate.
Expiration date per 21 CFR 201.17	Space allocated	Adequate.
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Adequate.
Storage (not required)	Provided	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or	Provided	Adequate.
Bar Code per 21 CFR	Provided	Adequate.

201.25(c)(2)***		
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate.
Others	Need to add "Single-Dose Vial. Discard unused portion."	Adequate.

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate. See assessment above.

2) Carton Labeling

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Provided	Adequate.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Provided	Adequate.
Net contents (21 CFR 201.51(a))	Provided	Adequate.
Lot number per 21 CFR 201.18	Space allocated	Adequate.
Expiration date per 21 CFR 201.17	Space allocated	Adequate.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	N/A	N/A
Sterility Information (if applicable)	Provided	Adequate.
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate.
Storage Conditions	Provided	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21	Space allocated	Adequate.
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate.
Name of manufacturer/distributor	Provided	Adequate.

"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate.
"Keep out of reach of children" (optional for Rx, required for OTC)	N/A	N/A
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Provided	Adequate.

Conclusion: Adequate. See assessment above.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Adequate. See assessment above.

Nina Ni, Ph. D.

04/20/2017

Secondary Review Comments and Concurrence: I concur.

Anamitro Banerjee, Ph. D.

04/20/2017

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 4/20/2017 09:41:24AM
GUID: 5075764700003844b7bc89632228509f

Nina Ni

Digitally signed by Nina Ni
Date: 4/20/2017 09:43:07AM
GUID: 502d1ab500002afbbe642f8f37136920

25 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 205555-ORIG-1-RESUB-10
Drug Product Name / Strength: STERITALC® (b) (4) (b) (4) and (b) (4) (contains 2, 3, and 4 grams sterile talc powder, respectively) in single dose glass vials
Route of Administration: Sterile Powder for intrapleural use (as powder or slurry)
Applicant Name: Novatech S.A.

Review Summary:

The Applicant requested an *in vivo* bioavailability (BA) biowaiver in connection with the literature-based 505(b)(2) NDA of STERITALC® (talc powder for intrapleural use). This biowaiver request is not deemed necessary because the bioavailability of locally (intrapleurally) administered talc for pleurodesis is self-evident and can be established consistent with 21 CFR 320.24(b)(6). Additionally, adequate bridging was established to the drug products evaluated in some literature studies because either STERITALC® itself or comparable sterile talc products were evaluated for efficacy and/or safety in (b) (4) malignant pleural effusions and/or (b) (4) pneumothorax.

From a Biopharmaceutics perspective, NDA 205-555 for STERITALC® is recommended for APPROVAL.

List Submissions being reviewed:

SDN-10, 4/15/2016 (Original NDA Resubmission)
SDN-11, 6/2/2016 (Quality/Response to Information Request)
SDN-14, 8/19/2016 (Multiple Categories/Subcategories – Response to Clinical Information Request regarding proposed dosage for (b) (4) pneumothorax)
SDN-18, 10/12/2016 (Quality/Response to Information Request regarding Dosing and Administration Instructions in the proposed labeling)
SDN-19 and SDN-20, 10/31/2016 and 11/8/2016 (Multiple Categories/Subcategories regarding Revised Finished Product Specification (inclusion of particle size distribution)

Highlight Key Outstanding Issues from Last Cycle:

Since there was not enough information in the original NDA to discern relationship of the drug product(s) used in the literature studies, the Applicant needed to submit Bioavailability/ Bioequivalence data or a Biowaiver Request.

Concise Description of Outstanding Issues:
None

BCS Designation *- Not Applicable*

Reviewer's Assessment:

Solubility: Insoluble in water
Permeability: Not intended for systemic absorption
Dissolution: Not Applicable

Bridging of Formulations *- ADEQUATE*

Reviewer's Assessment:

From the Biopharmaceutics perspective, it is appropriate to consider the medical literature in NDA 205-555 to evaluate the efficacy and safety of STERITALC® (talc powder for intrapleural use) in pleurodesis for (b) (4) malignant pleural effusion (MPE) and/or (b) (4) pneumothorax (PN), considering the following observations.

1. The proposed drug product (STERITALC®, by Novatech France) was the brand of sterile talc formulation identified to have been used in at least 15 of the 81 literature references provided by the Applicant to support the approval of the two indications sought (see attached Table 1). Of these 15 literature references published in 1999 or later, a total of 7 (4 for MPE and 3 for PN) contributes to the evaluation of STERITALC's efficacy; a total of 9 studies (5 for MPE and 4 for PN), for STERITALC's safety evaluation. Note that a total of 3 literature studies evaluated both efficacy and safety, and some papers reported the results of "pharmacology" studies. Additionally, Table 1A shows two more publications for the efficacy and/or safety of "graded talc" or "French graded talc".
2. Since 1999, STERITALC® (sterile talc powder in vials) has been marketed as a medical device in European and other countries, and used in the clinics for pleurodesis (administered by powder insufflation or slurry) in (b) (4) MPE and PN.
3. In addition to the two publications that evaluated STERITALC® in prospective randomized controlled trials (Maskell 2004 and Mohsen 2011; included in Table 1), 12 other submitted literature references based on adequate well-controlled studies were also reviewed for the characteristics of the talc preparation used (see attached Table 2). The talc preparations evaluated in these 12 other literature studies were described as "sterile, asbestos-free talc" (#5), "asbestos-free talc" (#1), or "pharmacopeial grade talc" (#1); the characteristics of the remaining talc products were not available. There was limited information in these papers to discern comparability to STERITALC® in terms of talc particle size distribution.

4. STERITALC® will be administered as talc poudrage (powder insufflation) or as a slurry ((b) (4)% in sterile isotonic solution) similar to Sterile™ Talc (as (b) (4)% slurry in saline solution). The results of the laboratory testing conducted by the FDA Office of Testing and Research (OTR) showed that the proposed drug product (STERITALC®) has similar physicochemical properties (e.g., pH, viscosity and zeta potential of (b) (4)% suspension in saline, bulk and tapped density of the powder, X-ray diffractograms, elemental composition) as compared to the Listed Drugs (Sterile™ Talc and Sclerosol®), except for the particle size distribution in both the dry and aqueous suspension states (as measured by (b) (4) and other methods). The OTR findings confirmed the relatively lower level of " (b) (4) talc particles (b) (4) µm in STERITALC® samples which is ***(i)*** considered optimal given the pleural stomata diameter (~ 6.2 µm, by SEM) reported by Li (1993) and ***(ii)*** in line with literature reports of a favorable safety profile of graded or large particle talc and the proposed drug product. Per FDA recommendation, the Applicant revised the STERITALC® finished drug product quality control specifications to include Particle Size Distribution for batch release and during stability testing.

Biowaiver Request – *NOT NEEDED*

Reviewer's Assessment:

The Applicant's request to waive *in vivo* Bioavailability (BA) Studies for their proposed sterile talc powder for intrapleural use is not needed because the availability of intrapleurally administered talc at the site of action (the pleural space) can be established, based on 21 CFR 320.24(b)(6).

1. *In Vivo* BA Studies are not necessary because the proposed drug product (STERITALC®) contains 100% drug substance (asbestos-free talc powder with no excipients) which undergoes further processing to produce a sterile and non-pyrogenic material suitable for intra-pleural administration. The drug substance (talc) is insoluble and is not intended for systemic absorption. Traditional pharmacokinetic (PK) assessment studies to measure the rate and extent of systemic bioavailability are not feasible. Bioavailability is self-evident because for pleurodesis, the drug substance/product is (locally) administered at its intended site of action (the pleural space). The local exposures to talc following the intrapleural administration of powder and slurry forms are not anticipated to be significantly different.
2. *In Vivo* BA (PK) Studies to establish BE of STERITALC® to the Listed Drugs (LDs: Sterile™ Talc and Sclerosol®) are not needed because *In Vivo* BA studies were also not required for the approval of these LDs.

3. Clinical efficacy/safety trials to establish BE (i.e., therapeutic equivalence) between STERITALC® and Sterile™ Talc and/or Sclerosol® are not deemed necessary because the two Listed Drugs were also approved for (b) (4) malignant pleural effusion (indication #1 being sought by STERITALC®) based on medical literature evidence for sterile talc products. [Refer to the Medical Officer's review for the evaluation of the literature-based evidence of clinical efficacy and safety.]
4. Nevertheless, from a Product Quality perspective, STERITALC® (once approved) would have Finished Product QC Specifications that are comparable -- if not more stringent -- than those for the two Listed Drugs that were approved for the first of two indications being sought by the Applicant.
5. From a Biopharmaceutics perspective, successful bridging of STERITALC® to the sterile talc products evaluated for use in pleurodesis in the literature submitted (i.e., in terms of comparability of formulation/quality attributes) is a pre-requisite for the approval of the two indications sought (including (b) (4) pneumothorax). For this Reviewer's assessment of the bridgeability of the literature evidence of clinical efficacy and safety to the proposed drug product (STERITALC®), see the section above.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (3/23/2017)

Secondary Reviewer Name and Date: Okpo Eradiri, PhD (3/23/2017)

Table 1. Literature Studies for STERITALC®

Type of Study	Study Identifier	Objective(s) of the Study	Number of Subjects	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients	FINDINGS/ CONCLUSIONS
Efficacy	Ariyaratnam, 2011	A case of spontaneous pneumothorax 2 months after pneumonectomy	1 patient case report	Case report	Talc slurry, 8 g with 50 mL normal saline (STERITALC®), mean particle size 33.6 µm Single dose	Spontaneous pneumothorax	Patient remains free of recurrence 14 months after pneumonectomy
Safety	Bridevaux, 2010	To investigate the safety of large-particle talc for thoracoscopic pleurodesis to prevent recurrence of primary spontaneous pneumothorax	418	Prospective Uncontrolled	Talc poudrage, 2 g (Steritalc), median particle size 31.5 µm Single dose insufflation (poudrage) in pleural space	Patients with recurrent spontenous pneumothorax	No Acute Respitory Distress Syndrome (ARDS) or death following pleurodesis
Safety	Brown, 2007	To investigate the potential influence of the physical properties and chemical state of clinically administered talc on the frequency of acute respiratory distress syndrome in clinical outcomes	Not Applicable	-Particle Size Analysis -Surface area analysis -ζ potential analysis -Bulk composition -Crystalline impurities - Surface composition -Surface wettability	Talc powder samples: -Humco talc -Sclerosol -talc supplied by Dr. Rodriguez-Panadero -Steritalc	n/a	-

Efficacy	Cazas, 2011	To determine the efficacy of lung resection surgery using videothorascope and talc pleurodesis and to analyze complications	130 cases/ 121 available for follow-up	Retrospective descriptive study	3 g STERITALC® (insufflation), mean particle size 33.6 µm, asbestos-free	Patients with primary spontaneous pneumothorax	7% morbidity; No emphysema, pachypleuritis or ARD; 3% recurrence at 10.1 months follow-up
Efficacy, Safety	Moreno-Merino, 2012	To compare talc poudrage and pleural abrasion in the treatment of spontaneous pneumothorax	787	Retrospective, Controlled	Sterile, asbestos-free talc (Steritalc), asbestos-frre 2-3 g Single dose insufflation in pleural space	Patients with primary spontaneous pneumothorax	Compared to pleural ablation, talc poudrage showed shorter surgical times and length of hospital stay, and lower re-intervention rates and morbidity
Safety	Marmol Cazas, 2011	To determine the efficacy of lung resection surgery using a videothorascope and talc pleurodesis. To analyze the complications arising from the use of talc	121	Retrospective, Descriptive Uncontrolled	Sterile, asbestos-free talc (Steritalc), mean particle size 33.6 µm, 3 g Single dose instillation in pleural space	Patients with primary spontaneous pneumothorax	Same as Cazas (2011)?
Safety, Pharmacology	Froudarakis, 2006	To investigate whether systemic inflammatory response is due to talc poudrage or to thoracoscopy	35	Prospective Uncontrolled	Sterile asbestos-free talc (Steritalc), 2 g for pneumothorax, 4 g for MPE Single dose insufflation in pleural space	Patients with malignant pleural effusions and pneumothorax	Mild side effects. No severe complication such as infection or ARDS during hospital stay and folllow up
Pharmacology	Froudarakis, 2007	To investigate the type of lymphopenia in patients undergoing thoracoscopic talc poudrage	11	Prospective Uncontrolled	Sterile asbestos-free talc (Steritalc), less than 50% of partides less than 20 µm, 2 g for pneumothorax, 4 g for MPE Single dose insufflation	Patients with malignant pleural effusions and pneumothorax	-

Safety	Janssen, 2007	To establish whether use of large particle- size talc is safe in patients with malignant pleural effusion	558	Multicentre, Open-label, Prospective, Cohort Study	French graded large-particle talc (Steritalc, Novatech France); mean particle size 24.5 µm; 11% by volume <5 µm 4 g Single dose poudrage in pleural space	Patients with malignant pleural effusions	No patients developed acute respiratory distress syndrome after pleurodesis
Safety	Fysh, 2012	To compare MPE patients treated with indwelling pleural catheters vs. Pleurodesis in hospital bed days (from procedure to death or end of follow-up) and safety	160 referred /65 evaluated	Prospective, 12-month, multi-centred study Controlled	Graded talc (Novatech), or indwelling pleural catheter Single dose slurry or insufflation in pleural space	Patients with malignant pleural effusions	IPC-treated patients required significantly fewer days in hospital and fewer additional pleural procedures than those who received pleurodesis. Safety profiles and symptom control were comparable.
~~Pharmacology~~ Safety Efficacy	Maskell, 2004	To elucidate the difference of lung inflammation and hypoxemia following sclerosing procedure with tetracycline or talc	87 Consented (First Trial 31 Consented / 23 evaluated. Second Trial 56 consented /48 evaluated)	Prospective, Parallel, Randomized Controlled	Trial 1: Talc poudrage, 4 g (mixed-talc; (d_{50} <15 µm) or 20 mg/kg tetracycline Trial 2: Talc slurry consisting of 4 g (mixed-talc [Thornton & Ross, UK; (d_{50} <15 µm)] or graded talc [Novatech, France]; (d_{50} >25 µm; most particles <10 µm removed) in 500 mL normal saline. Both mixed-talc and graded-talc preparations were refined by Luzenac, Italy. single dose instillation in	Patients with malignant pleural effusions	Trial 1: Mixed-talc produced higher rates of lung and systemic inflammation than tetracycline. Trial 2: Mixed-talc worsened gas exchange and induced more systemic inflammation than graded-talc. Routine use of graded talc for pleurodesis would reduce the morbidity of this procedure. The pleurodesis was successful in 11 of the 14 (79%) survivors at Month 3 in the mixed-talc group, and in 12 of 14 (85%) of the survivors in

Pharmacology	Psathatkis, 2006	To investigate whether monitoring neutrophil and D-dimer levels into the pleural fluid, after talc instillation, could predict the outcome of pleurodesis	168	Prospective Uncontrolled	Asbestos-free sterile talc (Steritalc), mean (range) dose of 5.6 (4-6 g) Single dose insufflation in pleural space	Patients with malignant pleural effusions	-
Efficacy	Ishida, 2011	To evaluate a novel approach for talc pleurodesis by dedicated catheter through flexi-rigid thoracoscope under local anesthesia	9	Prospective Uncontrolled	Sterile talc (Steritalc), 4 g Single dose insufflation in pleural space	Patients with uncontrolled and symptomatic pleural effusion requiring pleurodesis	Partial to Complete response in all patients
Efficacy, Safety	Kolschmann, 2005	To determine the long-term efficacy and safety of pleurodesis by thoracoscopic talc poudrage in malignant pleural effusions	102	Retrospective, Uncontrolled	Sterile, asbestos-Free talc, (Steritalc) 8 g Single dose insufflation inpleural space	Patients with malignant pleural effusions	83% with successful pleurodesis; 16.7% mortality rate at 30 days; No episodes of talc-induced ARDS
Efficacy	Mohsen, 2011	To compare the efficacy, safety, and outcome of thorascopic talc poudrage (TTP)_ versus povidone-iodine pleurodesis (PIP) through a thoracostomy tube as a palliative treatment of pleural effusion due to metastatic breast carcinoma	42 (22 TTP; 20 PIP)	Prospective randomized controlled trial	TTP: Steritalc F2, 4 g, single dose insufflation PIP: 20 mL of 10% povidone-iodine and 30 mL of normal saline were injected into the pleural cavity	Patients with malignant pleural effusion, as a complication of breast carcinoma	PIP is a good alternative to TTP

Table 1A. Literature Studies for Sterile, Asbestos-Free, Graded Talc

Type of Study	Study Identifier	Objective(s) of the Study	Number of Subjects	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients	FINDINGS/ CONCLUSIONS
Efficacy, Safety	Ramos-Izquierdo, 2010	To analyze the immediate and long term results for treatment of primary spontaneous pneumothorax by videothoracoscopic talc pleurodesis	124	Retrospective, Uncontrolled	Sterile, asbestos-free graded talc (d_{50} >10 µm), 2 g Single dose insufflation in pleural space	Patients with Primary Spontaneous Pneumothorax	No mortality or episode of acute respiratory failure, pneumonia or subcutaneous emphysema.
Efficacy	Györik, 2007	To evaluate long-term outcome of patients with primary spontaneous pneumothorax treated with talc pleurodesis	112 referred/ 63 evaluable	Prospective follow-up	French sterile asbestos-free talc (d_{50} >10 µm), (insufflation) – total dose not given Single dose insufflation	Patients with primary spontaneous pneumothorax	95% had successful pleurodesis, and 95% had long-term success. No episodes of acute respiratory failure following pleurodesis

Table 2. Literature Studies for Talc, Based on Prospective Randomized Controlled Trials

Type of Study	Study Identifier	Objective(s) of the Study	Number of Subjects	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients	FINDINGS/ CONCLUSIONS
Efficacy, Safety	Agarwal, 2011	To compare the efficacy and safety of iodopovidone with that of cosmetic talc, for chemical pleurodesis.	73 (38 pleural effusions, 35 pneumo-thoraces	Prospective Randomized Controlled	Cosmetic talc (Johnson and Johnson baby powder®, talc with added fragrance), sterilized by autoclaving before use, 20 – 60 µm particle size measured by SEM, free from asbestos and impurities Talc slurry, 5 g Single dose instillation in pleural space via tube thoracostomy	Patients with recurrent pleural effusions and/or spontaneous pneumothorax	None of the patients developed ARDS. Complete response in all talc-treated patients with pneumothorax and in 16 of 19 patients with pleural effusions.
Efficacy	Almind, 1989	To compare the efficacy of talc slurry to tetracycline and simple drainage	96 referred/ 73 evaluated	Prospective Randomized Controlled	Talc (Pharmacopeia Danica), 5 g suspended in 250 ml isotonic saline or Simple drainage or 550 mg tetracycline in 20 mL sterile water	Patients with their first spontaneous pneumothorax	Talc pleurodesis resulted in a significantly lower recurrence rate than simple drainage and tetracycline pleurodesis. No infections reported.

Efficacy, Safety	Diacon, 2000	To compare the short and long-term efficacy of thoracoscopic talc poudrage under local anesthesia with that of bleomycin instillation via a small-bore tube	36 referred/ 31 evaluated	Prospective, Randomized, Controlled	Asbestos-free talc (Luzenac, Italy) poudrage, 5 g or 60 IU of bleomycin Single dose instillation in pleural space	Patients with malignant pleural effusions	Thoracoscopic talc pleurodesis under local anesthesia is superior to bleomycin instillation, especially in the long term. Both methods are safe, provide symptomatic relief, and have similar subjective tolerances. No major side effects or serious complications.
Efficacy, Safety	Dresler, 2005	To demonstrate the efficacy, safety, and appropriate mode of instillation of talc for sclerosis in treatment of malignant pleural	501 referred /482 evaluated (242- Thora-scopic talc insuflation	Prospective, Randomized Controlled	4 – 5 g administered via Talc slurry (in 100 mL saline solution) or Talc insufflations Single dose instillation in pleural space	Patients with malignant pleural effusions	No difference between talc slurry and poudrage in terms of preventing recurrence of MPE at 30 days.
Efficacy	Fentiman, 1983	Aiming to improve the results of palliative treatment of pleural effusions in patients with breast cancer	46 entered/ 37 evaluable	Prospective randomized controlled	Simple Talc British (Pharmacopeia grade) (Evans Medical) Talc insufflation (dose not given) or Tetracycline, 500 mg in 50 mL normal saline	Patients with pleural effusions due to breast cancer	Control of the effusion was achieved in 56% of those treated with mustine and 90% of the talc group.
Efficacy	Fentiman, 1986	Aiming to improve the results of palliative treatment of pleural effusions in patients with breast cancer	41 entered/ 33 evaluable	Prospective randomized controlled	"Simple Talc" insufflation (dose not given) or Tetracycline, 500 mg in 50 mL normal saline	Patients with pleural effusions due to breast cancer	Intracavitary talc is superior in providing effective palliation of metastatic pleural effusions secondary to breast cancer.

Efficacy, Safety	Haddad, 2004	To evaluate the efficacy, safety and cost of bedside pleurodesis for malignant pleural effusions using talc slurry or bleomycin, and to determine prognosticators for procedure failure	71	Prospective, Randomized Controlled	Sterile asbestos- free talc (Index Farmaceutica, Sao Paulo, Brazil) 4 g in 100 ml of normal saline solution. The mean size of the talc particles measured by the manufacturer was 27.5 µm. or 60 units bleomycin Single dose instillation in pleural space	Patients with malignant pleural effusions	No difference in success rates between talc slurry (TS) or bleomycin (BL; No major complications
Efficacy	Kuzdzal, 2003	To assess the efficiency of talc powder and doxycycline in pleurodesis in patients with malignant pleural effusion in comparable conditions	33	Prospective, Randomized Controlled	Talc powder, 10 g or 500 mg doxycycline Single dose instillation in pleural space	Patients with malignant pleural effusions	Talc powder is superior to doxycycline in achieving pleurodesis in patients with malignant pleural effusion, in both short- and long-term observations.

Efficacy, Safety	Mourad, 2004	To evaluate the success rate of management of advanced lung cancer patients with malignant pleural effusion comparing talc powder with tetracycline for pleurodesis	60 divded in to three groups of 20 each	Prospective, Randomized, controlled	Group I: 20-25 mg/kg tetracycline is diluted in 50ml normal saline Group II: 5-10gm of purified talc powder was mixed with 100ml normal saline and 10ml of 2% lidocaine Group III: 5-10gm of purified talc powder Single dose instillation in pleural space	Patients with lung cancer associated with malignant pleural effusion	Thoracoscopic talc insufflation was an effective, easy and low cost method for producing pleurodesis in patients with recurrent malignant pleural effusion and proved to be better than talc slurry and tetracycline.
Efficacy	Noppen, 1997	To compare the efficacy of talc administered as slurry via tube thoracostomy with that of bleomycin	26	Randomized, prospective, comparative study	Talc, 5 g in 50 mL saline, single dose Bleomycin, 1mg/kg in 50 mL saline Single dose via tube thoracostomy	Patients with proven malignant pleural effusions	(Abstract) Talc slurry and bleomycin areequally effective in achieving chemical pleurodesis via thoracostomy in patients with malignant pleural effusions, and the safety profile of both agents is similar.

Efficacy	Ong, 2000	To compare the efficacy of two commonly used agents, talc and bleomycin, for the pleurodesis of malignant pleural effusions	50	Randomized controlled	Pharmaceutical grade, USP certified, asbestos-free and sterilized talc (Merck, Germany), 5 g diluted with normal saline to 50 mL OR 10 mL of 1 % lignocaine and either 1 unit per kg bodyweight bleomycin mixed in 150 mL of normal saline Single dose sclerosing agent was injected into the thoracostomy tube	Patients with malignant pleural effusion	Talc slurry is as effective as bleomycin in preventing early recurrence of malignant pleural effusions.
Efficacy, Safety	Terra, 2009	To determine whether full postpleurodesis lung expansion is a determinant of a successful outcome after talc pleurodesis	60	Prospective, Randomized, Controlled	VATS Talc poudrage group (noncalibrated talc [Magnesita Refratarios, Brazil) with mixed particles of mean diameter 25 µm, and d_{10} <10 µm], 5 g or For Talc Slurry:- 5 g of talc in a 60-mL saline solution, to which 5 mL of a 2% lidocaine solution was added Single dose instillation in pleural space	Patients with recurrent malignant pleural effusions	Immediate total lung expansion more frequent in the VATS group. No differences between VATS group and TS in terms of recurrences, quality of life, complications, survival, etc.

Efficacy, Safety	Tschopp, 2002	To investigate whether talcage by medical thoracoscopy for primary spontaneous pneumothorax is more cost-effective than drainage	108	Prospective, Randomized, Controlled	Sterile asbestos-free talc, 2 g Insufflated into pleural space	Patients with primary spontaneous pneumothorax	Thoracoscopic talc pleurodesis under local anaesthesia is superior to conservative treatment by chest tube drainage in cases of primary spontaneous pneumothorax that fail simple aspiration, provided there is efficient control of pain by opioids.
Efficacy, Safety	Zimmer, 1997	To determine which agent, bleomycin or talc slurry, is superior in terms of effectiveness, safety and cost to treat MPE	35 referred /29 evaluated (33 treatments)	Prospective, Randomized Controlled	Pharmaceutical-grade USP-certified, asbestos-free sterile talc (Spectrum Chemical Manufacturing Corporation; CA) Talc slurry, 5 g or 60 Units Bleomycin, diluted to a total of 50 mL with normal saline solution Single dose instillation in pleural space	Patients with malignant pleural effusions	Given the similar efficacy and significant cost advantage, talc is the agent of choice when utilizing pleurodesis for control of symptomatic malignant pleural effusions. No significant adverse events including ARDS.
~~Pharmacology~~ Efficacy Safety	Maskell, 2004	(See Table 1)					
Efficacy	Mohsen, 2011	(See Table 1)					

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 3/23/2017 10:04:30AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 3/23/2017 10:42:35AM
GUID: 50bdfe8d00003559ede66be3fd299f65

MICROBIOLOGY

Product Background

NDA: 205555

Drug Product Name
Proprietary: Steritalc
Non-proprietary: Talc
Strength: 2 g, 3 g, and 4 g

Route of Administration: Intrapleural

Applicant Name: Novatech S.A.

Manufacturing Site:
Bess pro gmbh
Gustav-Krone-Strasse 7
14167 Berlin
Germany

Method of Sterilization: The drug product in the final container is (b) (4)

Supporting/Related Documents:
An LOA (dated March 2015) was provided in the original submission to access DMF (b) (4) (b) (4) used for depyrogenation of the subject stoppers (b) (4). The relevant information regarding the depyrogenation of the subject stoppers was reviewed in (b) (4).doc for a worst case stopper (M. Cruz-Fisher, dated 05/18/2016) and was deemed adequate.

Microbiology review 20-587r4.doc (D. Hussong, dated 12/22/1997) is referenced for endotoxins testing prior to release of commercial batches.

Microbiology review NDA 21-388-BI.doc (V. Pawar, dated 09/23/2002) is referenced for testing of *Deinococcus* for the drug substance.

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
04/14/2016	04/15/2016	N/A	04/25/2016
10/31/2016*	10/31/2016	N/A	10/20/2016
12/09/2016*	12/09/2016	N/A	12/09/2017
01/09/2017*	01/09/2017	N/A	01/09/2017

01/30/2017*	01/30/2017	N/A	01/30/2017
03/08/2017*	03/18/2017	N/A	03/18/2017
03/22/2017*	03/22/2017	N/A	03/22/2017
04/10/2017*	04/10/2017	N/A	04/10/2017
04/19/2017*	04/19/2017	N/A	04/19/2017

*IR Response

P.1 Description of the Composition of the Drug Product

- **Drug product description –**

STERITALC® (b) (4) and (b) (4) are supplied as powder for talc suspension (slurry) whereas STERITALC® (b) (4) is supplied as powder for usage with NOVATECH® TALCAIRTM – Powder Blower.

- **Drug product composition –**

(Section P.1, Description and Composition of the Drug Product.pdf, page 1 of 2)

	Component	Function	Grade	Amount per Vial
2 (b) (4) g Strength – STERITALC® (b) (4)	Talc	Active Ingredient	USP	2 g
3 (b) (4) g Strength – STERITALC® (b) (4)	Talc	Active Ingredient	USP	3 (b) (4) g
4 (b) (4) g Strength – STERITALC® (b) (4)	Talc	Active Ingredient	USP	4 g

- **Description of container closure system –**

(Section P.7, Container Closure System.pdf, page 2 of 8)

(b) (4)

The content of the (b) (4) and (b) (4) configurations is diluted with NaCl to produce a talc slurry which is administered via a drain or suitable syringe, whereas the (b) (4) configuration is developed for use with a powder blower; thus, the secondary packaging of (b) (4) contains additionally the application system. However, in the 10/20/2016 submission, the applicant indicated that for the

Yarery Smith

Digitally signed by Yarery Smith
Date: 4/24/2017 02:10:10PM
GUID: 508da70d00029036ac4e081b955894d3

Jesse Wells

Digitally signed by Jesse Wells
Date: 4/24/2017 02:11:17PM
GUID: 508da70b00028ea901ac6652677f7d00

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	(b) (4)	Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	No excipients used	Acceptable	
Physical stability (solid state) lyophilized small molecule products	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Not applciable	Acceptable	
Content uniformity (suspension)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	No excipients used	Acceptable	
Particle size distribution (suspension/ powder)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Specifications in DP and DS.	Acceptable	
Appearance (b) (4)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	Tested for appearance.	Acceptable	
Chemical stability	• Formulation • Container closure • Raw materials	L	Talc is an inert compound. No excipients used.	Acceptable	

	• Process parameters • Scale/equipments • Site				
Heavy metals	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	
Absence Asbestos	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	H	Specifications in DP and DS.	Acceptable	

30 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page