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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205555
Supporting document/s:	10
Applicant's letter date:	April 14, 2016
CDER stamp date:	April 14, 2016
Product:	STERITALC Talc Powder ((b) (4) (b) (4) and (b) (4)
Indication:	1. Malignant pleural effusion
	2. Pneumothorax
Applicant:	Novatech S.A.
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	La Ciotat CEDEX, France 13705
	(US Agent: Boston Medical products Inc.
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Review Division:	Division of Hematology Oncology Toxicology
	(Division of Oncology Products 1)
Reviewer:	C.J. George Chang, DVM, MS, PhD, DABT
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1 Executive Summary

1.1 Introduction

Talc is a sclerosing agent, and instilling talc into pleural cavity leads to an inflammatory reaction promoting adherence of visceral and parietal pleura.

On April 15, 2016, Novatech S.A. (the Applicant) resubmitted through Boston Medical Products Inc. (the Applicant's US agent) a 505(b)(2) new drug application (NDA) for STERITALC Talc Powder. The Applicant proposed the two following indications:

- Malignant pleural effusion – To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion (2-5 g; a cumulative dosage of 10 g should not be exceeded);
- Pneumothorax (b) (4)-2 g; a cumulative dosage of 10 g should not be exceeded).

The listed drugs that the Applicant is relying on are:

- "SCLEROSOL" (metered/intrapleural aerosol; approved in 1997 in the US under NDA 020587);
- "Sterile Talc Powder" (powder/intrapleural; approved in 2003 in the US under NDA 021388).

Both listed drugs that the Applicant specified were approved with the indication to prevent or decrease recurrence of malignant pleural effusion in symptomatic patients following maximal drainage of the pleural effusion.

1.2 Brief Discussion of Relevant Nonclinical Findings

The Applicant did not submit any nonclinical study data or reports in support of this 505(b)(2) NDA. Instead, the Applicant relied on nonclinical data from the labels of the approved listed drugs mentioned above. During the review of this application there were two main issues to be addressed by the Pharmacology/Toxicology team.

First, talc is a mined product that is produced from material obtained from a quarry. As such, it contains various levels of elemental impurities as part of the particles of talc, (b) (4) . As a result, the applicant should provide an adequate elemental impurity risk assessment as recommended in ICH Q3D in order to determine levels and variability of specific elemental impurities. This is important to determine if additional controls are warranted for specific impurities or any labeling recommendations may be helpful in communicating particular risks to providers. Upon review of an adequate elemental impurity risk assessment, levels of lead, (b) (4) in STERITALC Talc Powder drug product were found to result in exposures exceeding the permitted daily exposures (PDEs) specified in the ICH Q3D guideline.

The Pharmacology/Toxicology team, the CMC team and the Applicant agreed to an acceptable specification for lead in the drug product of (b) (4) ppm, which would result in a maximum exposure of (b) (4) µg of lead, and testing for lead at (b) (4) as an additional control measure. While this exceeds the PDE of (b) (4) µg/day for parenteral lead, the intrapleural administration route and the single or maximum of two administrations for a maximum total of 10 g of talc and the seriousness of the indication justify this level. In addition, the exposure to a potential (b) (4) µg of lead assumes all of the lead in the talc particles will enter the systemic exposure rapidly. While this accounts for the worst case scenario, it is more likely that the elemental impurities would leach out of the talc over time, leading to a lower potential maximum exposure. Given that there is no safe level of lead, especially in children, changes made to the package insert for STERITALC are warranted to communicate the potential risk of lead exposure and to limit the exposure in pregnant or lactating women and in children with pneumothorax.

Levels of (b) (4) also exceeded their respective PDEs specified in ICH Q3D for parenteral drugs. Given the intrapleural administration route and the single or maximum of two administrations for a maximum total of 10 g of talc and the seriousness of the indication, levels of (b) (4) are justified and do not warrant additional labeling changes. The Applicant proposed to test for the levels of these four elemental impurities (b) (4) The Applicant's elemental impurity risk assessment and agreed upon controls and labeling adequately support the approval of this NDA from pharmacology/toxicology perspective.

The second issue that was addressed by the Pharmacology/Toxicology team during the review of this application was the potential risk for carcinogenesis by STERITALC. A literature search with the "Web of Science™" search engine with "Talc and Toxicity" was conducted to cover related scientific publications from 2003 to 2016. One hundred twenty-one (121) publications were briefly reviewed, and the only one nonclinical publication relevant to talc carcinogenicity suggests that talc was not carcinogenic for female genital system in a pilot long-term study in rats.[1]

Various reports indicated that talc distribution in multiple organs occurred in rats, rabbits and humans after intrapleural instillation, suggesting the presence of migrated talc beyond pleural cavity. Kennedy et al., reported that talc was found outside of the pleural space in mediastinal lymph nodes (in 18% of rabbits), kidney (in 17% of rabbits), and spleen (in 40% of rabbits) after instillation of sterile asbestos-free talc slurry (70 mg/kg) into the pleural space of normal New Zealand white rabbits.[2] Werebe et al., reported that a non-dose dependent systemic deposition of talc particles occurred within 24 hours in organs including heart, brain, spleen, kidney, liver, coronary artery, meninges, urinary

[1] Keskm N, YA Teksen, EG Ongun, Y Ozay, H Saygilli, 2009, Does long-term talc exposure have a carcinogenic effect the female genital system of rats? An experimental pilot study, Arch Gynecol Obst, 280(6):925-931.
[2] Kennedy L, RA Harley, SA Sahn, C Strange, 1995, Talc slurry pleurodesis – pleural fluid and histologic analysis, Chest, 107:1707-1712.

tract, pulmonary artery, myocardium etc., after catheter administration of talc (10 or 20 mg/rat) through left minimal thoracotomy in normal Wistar rats.[3] De Campos et al., reported that talc crystals were found in a deceased patient in ipsilateral and contralateral lung, brain, liver, kidney, heart, spleen, and skeletal muscle, after bilateral talc pleurodesis.[4] Though talc was reported to migrate to the extrapleural organs as indicated in these published reports, the impact to patients is unclear.

The labels for the listed drugs relied upon for this application include a description of studies assessing the carcinogenic potential of talc in rodents by non-standard designs. STERITALC is to be administered as a single dose, or a maximum of two doses. According to the ICH S1A guideline, "The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals," rodent carcinogenicity studies are not generally warranted for pharmaceuticals administered for less than 6 months on a continual basis. There does not appear to be a scientific cause for concern that warrants additional rodent carcinogenicity studies given the product characteristics, administration route and frequency of administration of STERITALC.

1.3 Recommendations

1.3.1 Approvability:

The Pharmacology/Toxicology team did not identify any issues that would preclude approval of this NDA.

1.3.2 Additional Non Clinical Recommendations

The following information requests (IRs) related to elemental impurities were sent to the Applicant.

I. **On September 28, 2016**, the FDA issued an information request for a risk assessment document and the related necessary controls on elemental impurities.

"Regarding the drug product specification, provide the following:
c. Provide risk assessment and indicate any necessary controls on elemental impurities as per ICH Q3 (D)."

II. **On October 26, 2016**, the FDA issued an information request for data on the absence of Class (b) (4) elemental impurities other than lead. It stated that:

[3] Werebe EC, PR Pazetti, JRM de Campos, PP Fernandez, VL Capelozzi, FB Jatene, FS Vargas, 1999, Systemic distribution of talc after intrapleural administration in rats, Chest, 115:190-193.
[4] De Campos JRM, FS Vargas, EdC Werebe, P Cardoso, LR Teixeira, FB Jatene, RW Light, 2001, Thoracoscopy talc poudrage – A 15-year experience, Chest 2001, 119:801-806.

"On page 5 of the report entitled "risk assessment and control of elemental impurities", you indicated that talc includes a natural lead content. However, you did not provide any data or justification why there are no other Class (b) elemental impurities, i.e., (b) (4) present in talc. Please provide data or justification accordingly."

III. **On November 15, 2016**, the FDA issued an information request for a need to correct errors in the risk assessment document.

"Drug Product

On Page 12 of the updated report entitled "risk assessment and control of elemental impurities", you have corrected the errors we pointed out to you during PAI. We have noticed additional errors: Pb limit and content in tables 12, 13, and 14. Please scan through your document and correct any other errors in the document. Please respond to Drug Product comments by COB November 18, 2016."

IV. **On November 23, 2016**, the FDA issued an information request.

"Your justification for the proposed specification for lead of (b) (4) ppm, or (b) (4) µg/g, is not adequate. The risk assessment provided does not actually address the level of potential risk from lead in patients receiving Steritalc at the maximum administered dose. Provide a risk assessment of the relevant concerns for lead at the proposed specification at the maximum proposed dose of Steritalc in the intended patient population, which should include the following:
1. Describe the amounts of lead that have been detected in the drug substance and drug product of Steritalc as they relate to the proposed specification.
2. Specify the maximum amount of lead that the intended patients will be exposed to at your proposed specification for lead at (b) (4) µg/g in Steritalc.
3. Provide your risk assessment and detailed justification for exceeding the permitted daily exposure (PDE) of (b) (4) µg/g for lead specified in ICH Q3D guideline. This should include a risk assessment for typical real-world use of Steritalc at the recommended daily dose as well as the worst case scenario addressing the potential for bilateral administration of multiple doses at the same time, repeated administrations in the same patient, and use in pediatric patients.
4. Provide an adequate justification for not conducting additional controls for lead content in Steritalc."

V. **On December 16, 2016**, the FDA issued another information request and requested that the Applicant modify the lead specification for products.

"Based on the risk assessment you submitted on 12/9/2016, the drug product specification for lead of (b) (4) ppm, or (b) (4) µg/g, is not justified. It is our understanding that USP will be revising individual product specific monographs to comply with the PDEs for elemental impurities in ICH Q3D, so it is not adequate to rely on the

USP monograph for talc which sets the limit for lead at (b) (4) µg/g at this time. A limit of (b) (4) µg/g of lead in the drug product appears to be supported based on your calculation of an adjusted PDE for led in talc with a maximum potential dose of 10 g in adult patients. According to the data you presented on lead testing in your drug product, the highest level detected was (b) (4) µg/g. Revise your drug product specification to include a limit of NMT (b) (4) ppm for lead."

VI. On **January 19, 2017** through a telephone conference with the Applicant, the FDA issued a third information request and requested that the Applicant analyze the products according to ICH Q3D recommendation.

"The risk assessment for elemental impurities submitted to your NDA on 12/9/2016 is inadequate. The levels of elemental impurities in the drug product were not assessed according to recommendations in ICH Q3D. (b) (4)

(b) (4)

(b) (4) *The summary of the risk assessment should identify the elemental impurities and the controls and acceptance criteria, as needed.*

Provide an adequate elemental impurity risk assessment for Steritalc according to recommendations in ICH Q3D, which should include testing of an adequate number of lots and a discussion about the need for additional controls or acceptance criteria. As needed, provide a justification for any levels or acceptance criteria that exceed the PDEs recommended in ICH Q3D, which should include a safety assessment."

The Applicant's final (submitted February 28, 2017) version of the risk assessment for elemental impurities including lead, (b) (4) and proposed control strategies are acceptable to support the approval for this NDA. There are no outstanding Pharmacology/Toxicology deficiencies or issues with elemental impurities in STERITALC.

1.3.3 Labeling

The recommended maximal lead exposure specified by the Applicant for STERITALC [redacted] and the maximum dose of STERITALC is 10 g. Therefore, a section titled "Lead Content" was added in the "Warning and Precautions" section (Section 5.3) of the package insert. This was intended to alert providers that STERITALC contains lead, which may be administered at a dose that may be associated with adverse reactions. Since there is no safe level of lead, the language in this section was added to provide information about how much lead is in STERITALC and what toxicities are associated with lead exposure.

Children are more sensitive than adults to the toxic effects of lead, particularly on the developing CNS. In addition to the Warning and Precautions section, STERITALC was contraindicated in Pregnancy. As a result of the risk vs. benefit consideration, the use of STERITALC Talc Powder products in children with malignant pleural effusion is acceptable as it is a life-threatening condition. Alternatively, STERITALC Talc Powder is not indicated in children with pneumothorax due to the concern of Pb content in the drug product and the presence of other therapeutic options for these patients which do not contain Pb as an impurity. [redacted] this indication was limited to adults with pneumothorax.

The recommendation not to breastfeed while taking STERITALC and for 5 months following the last dose was included in section 8.2. The period of 5 months accounts for approximately 5 half-lives of lead.

No other labeling modifications are needed regarding the elementary impurities other than lead.

2.3 Drug Formulation

The components and composition of the 2 [redacted] g (STERITALC [redacted], 3 [redacted] g (STERITALC [redacted], and 4 [redacted] g (STERITALC [redacted] strength of STERITALC Talc Powder drug products are listed in the table below.

Table 1 Strengths of STERITAC® Talc Powder Products

Comp		
2 [redacted] g	[redacted]	
Talc		
3 [redacted] g	[redacted]	[redacted]
Talc		
4 [redacted] g	[redacted]	
Talc		

(Excerpted from the Applicant's application)

The proposed recommended dosage and administration of STERITALC Talc Powder do not match exactly with that of the listed drugs. The recommended dosages for "Sclerosol" and "Sterile Talc Powder" are 4-8 g and 5 g, respectively.

2.5 Comments on Impurities/Degradants of Concern

In the original NDA submission, the content of Pb, (b) (4) specified in the ICH Q3D guideline. See tables below.

For Pb impurity, the Applicant provided a risk assessment (Ver. 3 and earlier versions) including the analytical results for lead from (b) batches each of drug substance and drug product. The risk assessment included a justification for the lead content above the ICH Q3D PDE, a proposed Pb specification for the drug product, and a proposed control strategy for Pb to test (b) (4).

Table 2 Analytical Results of Mineral Impurities in STERITALC Talc Powder Products

(b) (4)

(Excerpted from the Applicant's Lead Risk Assessment (ver. 4))

A. Lead (Pb)

Lead as Health Concern[5]

According to ICH Q3D guideline, Class (b) (4) elements are human toxicants that have limited or no use in the manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (mined excipients). Testing of Class (b) (4) elements should be applied when risk assessment identifies it as the appropriate control to ensure that the PDE will be met. Pb is a Class (b) (4) element to include in the risk assessment for drug products. The health effects in humans from lead are summarized below from the ATSDR 2007 publication[5].

The main target for Pb toxicity is the nervous system, both in adults and children. Pb exposure may cause weakness in fingers, wrists, or ankles; increases in blood pressure; anemia; damage to brain and kidneys in adults or children and ultimately cause death; miscarriage in pregnant women; damage to organs responsible for sperm production; and probably a human carcinogen. Children are more sensitive to the health effects of Pb than adults. Pb affects children in different ways depending on the amount of Pb a child swallows or exposed through other routes. Symptoms of Pb toxicity in children include anemia, kidney damage, colic (severe "stomach ache"), muscle weakness, brain damage which can kill the child, affecting mental and physical growth, mental development and lower intelligence later. Symptoms of Pb toxicity in fetuses can lead born prematurely and have lower weights at birth.

Risk Assessment of Lead

Based on ICH Q3D, adverse neurobehavioral effects are considered to be the most sensitive and most relevant endpoint in humans after oral exposure. Data from epidemiological studies show that blood lead levels <5 µg/dL may be associated with neurobehavioral deficits in children[6] .

According to the US EPA model (Integrated Exposure Uptake Biokinetic (IEUBK) (100% absorption, no other sources of lead)[7], oral intake of 5 µg/day translates into a blood level of 1-2 µg/dL for children age 0-7 years (0-82 months)[8]. Since the oral effects are based on blood levels, the parenteral PDE is equal to the oral PDE.

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[5] ATSDR. Toxicological profile for lead. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2007.
[6] NTP. Monograph on health effects of low-level lead. National Toxicology Program, U.S. Department of Health and Human Services. 2012.
[7] US EPA. Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead. 1994, updated 2009. (http://www.epa.gov/superfund//health/contaminants/lead/products.htm; Accessed March 25, 2014)
[8] US EPA. User's Guide for the Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) Windows. 2007.

As children are the most sensitive population for Pb, the PDE for Pb (specified in ICH Q3D guideline is 5 µg/day for drugs administered parenterally) was used by the Applicant to provide a justification for an acceptable level of lead administered through STERITALC for adults. In addition, the PDE was based on chronic daily exposure, whereas STERITALC will be administered once or a maximum of two times. An acceptable level of lead for adults with a single administration was provided according to the following procedures:

(b) (4)

Figure 1 Subdivision of the Usual Uncertainty Factor of 100 Used in Setting Guidance Values for the Exposure of the General Population

AD_{UF} = Unc
AK_{UF} = Unc
HD_{UF} = Unc
HK_{UF} = Unc

(Excerpted from Harmonization Project No. 2, WHO, 2005, Figure 2, p.17)

Safe Maximal Daily Parenteral Exposure (SMDPE) to Pb in STERITALC for an adult (once or twice application with a maximal dose of 10 g STERITALC Talc Powder)

(b) (4)

(b) (4) **= 39.5 µg/day**

The Applicant's Risk Assessment for Lead Exposure in STERITALC Talc Powder

[9] World Health Organization (WHO), 2005, Harmonization Project Document No. 2: Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment, (Figure 2 p.17).

The Pb specification in the STERITALC Talc Powder ((b) (4) (b) (4) and (b) (4) was originally proposed at (b) (4) µg/g by the Applicant claiming (b) (4) This was not an acceptable approach since no risk assessment was provided to justify that level and it was not in compliance with the PDE in ICH Q3D.

Later the Applicant's proposed a revised lead specification of (b) (4) µg/g and submitted a supporting risk assessment for lead, which justified the safety of approximately 40 µg/day, or 4 µg/g for a 10 g dose. Therefore, a specification of (b) (4) µg/g for lead was acceptable from the Pharmacology/Toxicology team based on the provided safety assessment and was reasonable based on the actual levels of lead measured in STERITALC drug substance lots.

The Applicant's Risk Assessment for Pb Exposure Excludes the Use of STERITALC Talc Powder in Children, Pregnant or Lactating Women

The Applicant's risk assessment included the statement that STERITALC is not for use in children or pregnant or lactating women due to the particular sensitivity to lead toxicity in those populations. Therefore, STERITALC Talc Powder is not recommended for use in children with pneumothorax or pregnant or lactating women.

Exposure Limits for Pb in STERITALC Talc Powder

The Applicant claims that the STERITALC Talc Powder is asbestos-free (see review from CMC team for detail), and the Pb impurity comes directly from their single natural talc source. The revised Pb specification set by the Applicant is (b) (4) for STERITALC Talc Powder. As the maximal dose that the Applicant proposed is 10 g for single dose of STERITALC Talc Powder, the adult daily exposure to Pb is estimated at 40 µg/day approximating the adult Pb SMDPE derived from the Pb PDE estimated from children and published in the ICH Q3D guideline. Therefore, the December 2, 2016 revision (ver. 4) of the Applicant's Pb risk assessment is acceptable for Pb impurity from the pharmacology/toxicology perspective.

Results of the (b) (4) batches each of STERITALC Talc Powder drug substance and products tested showed that the Pb contents were below the revised/finalized (b) (4) specification.

2.7 Regulatory Background

STERITALC (Sterile Talc) was granted the following 2 orphan drug designations:

1. Orphan Drug No. 97-1067 (granted on 12/8/97): Malignant pleural effusion
2. Orphan Drug No. 97-1092 (granted on 12/8/97): Pneumothorax

The NDA that the Applicant submitted in March 2013 received a "refused for filing" action from the FDA due to the presence of significant deficiencies noted by the review team. The deficiencies noted included deficiencies in the general content and format of the application including the proposed label; chemistry, manufacturing and controls (CMC); clinical pharmacology; and clinical safety and efficacy sections.

8 Carcinogenicity

ICH S1A guideline specifies that carcinogenicity studies should be performed for any pharmaceuticals whose expected clinical use is continuous for at least 6 months and when there is concern about their carcinogenic potential.[13]

As STERITALC Talc Powder is proposed to be used as a single administration, or a maximum of two administrations, conducting carcinogenicity studies is not warranted to establish the safety profile of STERITALC Talc Powder for the proposed use.

As a 505(b)(2) NDA, the Applicant is relying on FDA's previous findings of safety and efficacy for the listed drugs as reflected in the product labeling. The label for the listed drugs includes a description of studies assessing the carcinogenic potential of talc, although not standard design. There does not appear to be a scientific cause for concern that warrant additional rodent carcinogenicity studies given the product characteristics, administration route and frequency of administration.

[13] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1995, Guideline on the need for carcinogenicity studies of pharmaceuticals S1A (Step 4 version), International Conference on Harmonisation.

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/s/

CHING-JEY G CHANG
04/24/2017

TODD R PALMBY
04/24/2017

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 205555 **Applicant: Boston Medical Products** **Stamp Date: 4/15/16**

Drug Name: STERITALC Talc Powder **NDA Type: 505(b)(2)**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		This is a 505(b)(2) relying on FDA's previous finding of safety and efficacy of a listed drug. The need for additional nonclinical studies, including those to support the proposed new indication (b) (4) of pneumothorax, will be determined during review of the NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A: This is a 505(b)(2) relying on previous findings from the innovator. No studies were required or requested.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A: This is a 505(b)(2) relying on previous findings from the innovator. No studies were required or requested.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The label appears to be generally consistent with the listed drug label for nonclinical sections.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		None identified to date. New impurity issues will be addressed during the review.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

CHING-JEY G CHANG
06/12/2016

TODD R PALMBY
06/20/2016