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APPLICATION NUMBER:

209260Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	January 26, 2018
From	Ta-Chen Wu, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 209260
Type	505(b)(2)
Applicant	Fresenius Kabi USA, LLC
Date of Submission	March 28, 2017
PDUFA Goal Date	January 28, 2018
Proprietary Name / Established (USAN) names	Atropine Sulfate Injection, USP
Dosage forms / Strengths	Atropine Sulfate Injection, USP/ 0.4 mg/mL in a 20 mL multi-dose glass vial (8 mg/20 mL)
Proposed Indication(s)	Temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue, an antivagal agent, an antidote for organophosphorus or muscarinic mushroom poisoning, and to treat (b) (4)
Recommended	Approval

This CDTL review is based on the primary reviews and memos from:

Discipline	Primary Reviewer/Team	Final Review Date(s)
Quality-CMC	Mohan Sapru (Application Technical Lead)	12/31/2017, 01/26/2018
Drug Substance	Ramsharan Mittal, Donna Christner	09/26/2017
Drug Product	Thomas Wong, Wendy Wilson-Lee	12/11/2017
Quality-Microbiology	Valerie Huse, Stephen Langille	09/01/2017, 01/26/2018
Manufacturing Process	Ziyang Su, Peter Guerrieri	12/07/2017
Manufacturing Facilities	Rose Xu, Derek Smith	12/01/2017
Biopharmaceutics	Gerlie Gieser, Ta-Chen Wu	12/12/2017, 01/25/2018
Clinical	Melanie Blank, Martin Rose	01/02/2018
Biometrics	Jialu Zhang, Hsien Ming J Hung	12/07/2017
Non-Clinical (Pharmacology/Toxicology)	William Link, Albert Defelice	12/14/2017
Clinical Pharmacology	Xiaolei Pan, Sudharshan Hariharan	No final review in DARRTS
Division of Pediatric and Maternal Health	Kristie Baisden, Tamara Johnson, Lynne Yao	09/28/2017
Medication Error Prevention and Analysis	Sarah Thomas, Chi-Ming Tu	11/08/2017, 12/11/2017, 12/27/2017
Prescription Drug Promotion	Zarna Patel, James Dvorsky	01/04/2018
Regulatory Project Manager	Sabry Soukehal	05/26/2017, 06/06/2017, 12/23/2017, 01/02/2018

1. Introduction and Background

On March 28, 2017, the Applicant (Fresenius Kabi USA, LLC) submitted an NDA 209260 under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Atropine Sulfate Injection, USP, 0.4 mg/mL in a 20 mL multi-dose glass vial. The proposed drug product is indicated for temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue, an antivagal agent, an antidote for organophosphorus or muscarinic mushroom poisoning, and to treat (b) (4). Atropine, a muscarinic antagonist, was approved by the FDA for prescription use in 1960. The proposed Atropine Sulfate Injection, USP, 0.4 mg/mL, a sterile nonpyrogenic isotonic solution in multi-dose vial for repeat use, is intended for intravenous, intramuscular, subcutaneous or endotracheal administration. Note that the Applicant proposed dosing recommendations for adults but did not provide an update for pediatric patients.

This 505(b)(2) NDA for the proposed product relies, in part, on published literature and FDA's findings of efficacy and safety for the Listed Drug, Atropine Sulfate Ansyr™ Plastic Syringe, 0.1 mg/mL, in a single-use syringe [NDA 21146 held by Hospira, approved in 2001]. On January 24, 2018, in the Response to the FDA Information Request dated January 23, 2018, the Applicant submitted a statement of reliance on two additional listed drugs (Bacteriostatic Sodium Chloride 0.9% in Plastic Container [NDA 018800] and Bacteriostatic Water for Injection in Plastic Container [NDA 018802]), which also contain 9 mg/mL benzyl alcohol, to support the safety of the benzyl alcohol content of Atropine Sulfate Injection (0.4 mg/mL) in adults.

To support the application and approval, the Applicant submitted a request for biowaiver of *in vivo* bioavailability/bioequivalence study for the proposed product in accordance with 21 CFR § 320.22(a), citing that bioequivalence between two products is self-evident. The Applicant provided comparison in terms of indications, active and inactive ingredients, and route of administration, and asserted that the proposed drug product and the Listed Drug are the same. The Applicant noted also the drug shortage of the Listed Drug, Atropine Sulfate Ansyr™ Plastic Syringe, and its samples being unavailable for analysis and comparison during development studies. Since no new clinical studies were conducted, clinical evaluation of the application relies on information in the public domain, including labels for other approved atropine sulfate injections, DESI findings of safety and efficacy for atropine sulfate, and published literature.

It is noted that the proposed drug strength is 0.4 mg/mL which differs from the Listed Drug, Ansyr™ 0.1 mg/mL. In addition to strength and presentation/packaging configuration, this multi-dose vial formulation of the proposed multi-dose injectable solution contains sulfuric acid as the pH adjuster and a preservative benzyl alcohol (0.9%) which is not present in the single-use syringe for Ansyr™. On June 06, 2017, FDA notified the Applicant that the biowaiver request per 21 CFR § 320.22(b)(1) is not feasible because the formulation of the proposed to-be-marketed parenteral drug product is not qualitatively and quantitatively the same as that of the Listed Drug. The Applicant was requested to provide additional supporting information/data for the bridge to the Listed Drug under the provision of 21 CFR § 320.24(b)(6).

2. Quality/Chemistry, Manufacturing and Controls (CMC)

Office of Product Quality (OPQ) recommends approval for NDA 209260 (Atropine Sulfate Injection, USP) from the chemistry, manufacturing, and controls (CMC)/quality perspective.

Drug Substance:

The drug substance Atropine Sulfate, USP is chemically designated l α H, 5 α H-Tropan-3-α-ol (±)-tropate (ester), sulfate (2:1) (salt) monohydrate, {(C17H23N03)2·H2S04·H20}, and is very soluble in water. The drug substance appears as colorless crystals or while crystalline powder, and is odorless. The CMC aspects of the drug substance, including structural characterization, impurity profile, manufacturing, analytical method validations, container closure system and stability, have been cross-referenced to Type II DMF # (b) (4), which has been reviewed in the context of this NDA submission and found to be adequate by Dr. Ramsharan Mittal. Furthermore, the proposed specifications meet the current USP requirements and are found to be adequate to control the identity, strength, quality, physical and chemical purity, and potency of the drug substance. The drug substance has a proposed retest period of (b) (4) months which is supported by stability data.

Drug Product:

The Applicant developed Atropine Sulfate Injection, USP 0.4 mg/mL (sterile, nonpyrogenic isotonic solution of atropine sulfate in water) in a 20 mL multi-dose glass vial. The proposed composition of atropine sulfate injection, 0.4 mg/mL, is:

Strength	0.4 mg/mL			
Packaging Configuration	(b) (4) mL fill in a 20 mL vial			
Vial	20 mL, (b) (4) glass vial			
Stopper	20 mm, (b) (4) stopper			
Seal	20 mm, Flip-cap Aluminum crimp seal			
Component	**Content (per mL)**	**Content (per vial)**	**Function**	**Quality of Ingredient**
Atropine sulfate monohydrate[1]	0.4 mg	8 mg	Active Ingredient	USP
Sodium Chloride	9 mg	180 mg	Tonicity adjuster	USP
Benzyl Alcohol	9 mg	180 mg	Preservative	NF
Sulfuric Acid[2]	QS	QS	pH adjuster	NF
Water for Injection	QS to mL	QS to 20 mL	(b) (4)	USP

[1] Equivalent to 0.33 mg/mL Atropine free base

[2] (b) (4)

In addition to strength and presentation/packaging configuration, the formulation of the proposed multi-dose injectable solution differs from the Listed Drug with respect to the addition of benzyl alcohol (9 mg/mL) as preservative and sulfuric acid as the pH adjuster. From a CMC perspective, these differences will not affect the therapeutic equivalence or stability of the product. Dr. Thomas Wong also concluded that all excipients used in the proposed product meet the USP requirements and no incompatibilities are revealed. Further, the acceptance criteria for assay, pH and bacterial endotoxins test were found to either conform to or are tighter than the USP monograph limits. All the analytical methods have been adequately validated.

It is noted that the extractable volume has been revised to NLT (b) (4) mL and NMT (b) (4) mL

(slightly [(b) (4)] the USP <1151> recommended limit of 20.6 mL for 20 ML vial) due to [(b) (4)]. Based on patient safety-relevant risk assessment, OPQ found the proposed upper limit of NMT [(b) (4)] mL for the extractable volume acceptable.

Atropine Sulfate Injection, USP is filled into [(b) (4)] 20 mL glass vials, closed with 20 mm [(b) (4)] rubber stoppers and capped with aluminum crimped flip-off seals. OPQ concluded the acceptability of the Applicant's proposed specification, results of extraction study on stoppers, the very low risk of glass delamination, and no concern leachable substances into the drug product for the duration of the shelf-life of the product.

Manufacturing:

Dr. Ziyang Su concluded that the in-process controls [(b) (4)] are adequate and the risk of [(b) (4)] during manufacturing the product is low. The overall proposed control strategy (including environmental controls, and in-process controls and specifications) are adequate to ensure product quality.

Microbiology:

The microbiological aspects have been cross-referenced to Type V DMF [(b) (4)] which has been previously reviewed and found adequate. In addition, the drug product release specification includes sterility and bacterial endotoxins testing. Dr. Valerie Huse concluded that (1) the antimicrobial effectiveness was adequately demonstrated for the proposed multiple-dose drug product, (2) the drug product's microbiological quality throughout the shelf-life period was supported by the stability data, and (3) based on the life-saving indication, the proposed endotoxins specification of [(b) (4)] EU/mg (based on an amendment dated 1/9/2018) is acceptable.

Expiration Date and Storage Conditions:

The Applicant's stability data support a shelf-life of 24 months when stored at controlled room temperature (20°C – 25°C; 68°F – 77°F). Based on the in-use stability data provided, the drug product can be stored at 20°C to 25°C for the 24-hour use period after the initial puncture. The container label and labeling recommendation for Section 2.1 (Full Prescribing Information) will reflect the findings.

Facilities review/inspection:

The Office of Process and Facilities recommended approval for all the currently listed manufacturing facilities concerning this NDA.

3. Biopharmaceutics

To support the approval of this 505(b)(2) NDA relying on FDA's findings of efficacy and safety for the Listed Drug, Ansyr™ (atropine sulfate) Injection (0.1 mg/mL) in a single-use syringe, the Applicant requested for biowaiver of *in vivo* bioavailability/bioequivalence (BA/BE) study for the proposed product per 21 CFR § 320.22(b)(1). Note that the Applicant reported that Ansyr™ cannot be procured for comparative in vitro analytical testing because it is currently in the FDA Drug Shortage List. The Biopharmaceutics Reviewer, Dr. Gerlie Gieser, focused on the evaluation of the Applicant's biowaiver request and supporting justification for providing the bridge to the Listed Drug.

In an Information Request dated 6/6/2017, Biopharmaceutics review team notified the

Applicant that their biowaiver request per 21 CFR § 320.22(b)(1) is not feasible because the formulation of the proposed to-be-marketed parenteral drug product is not qualitatively and quantitatively the same as that of the Listed Drug, as noted under the ***Drug Product*** section, including strength, presentation/packaging configuration, and the presence of benzyl alcohol as preservative, (9 mg/mL) in the proposed product. However, based on applicant's follow-up email Responses (7/6/2017 and the 11/29/2017) and information available in the Ansyr™ labeling, it is evident that the test and the reference products are sterile, non-pyrogenic and clear/colorless solutions. In addition, both products were shown to have similar physico-chemical properties [specifically, the comparable pH and osmolality to the Listed Drug (pH 3.0 to 6.5, and 308 mOsmol/L [calculated]), physico-chemical stability during 12 months of long-term storage and under similar storage condition]. Note that the addition of benzyl alcohol as preservative to the proposed product is not anticipated to alter the systemic bioavailability of atropine sulfate introduced directly into systemic circulation. However, it is not clear how the presence of benzyl alcohol in the proposed multi-dose atropine sulfate injectable drug product could potentially impact the reported rapid absorption rate of atropine (Tmax within 30 min) and its disposition following intramuscular or subcutaneous administration. I agree with Dr. Gieser's view that the Applicant's proposal to adopt the language from the Listed Drug labeling stating preference for IV (over IM, SC, or endotracheal) administration of atropine sulfate injection appears to be justified. Therefore, in accordance with 21 CFR § 320.24(b)(6), the Biopharmaceutics review team determined that the Applicant has provided a scientific justification to establish the bridge between its proposed product and Ansyr™, permitting reliance on FDA's findings for that Listed Drug.

With respect to the proposed strength, note that the higher 0.4 mg/mL strength falls between two strengths of already approved products, i.e., 0.1 mg/ml (e.g., Ansyr™) and 2 mg/0.7 ml (e.g., Abbvie's discontinued product; ANDA 71295) and is deemed unlikely to pose safety and efficacy concerns because of the higher strength. The efficacy and safety of a 0.4 mg/mL strength of atropine sulfate solution are expected to be similar to 0.1 mg/mL strength approved for Ansyr™ (i.e., when considering that the same drug amount (on a mg basis) is introduced into the injection site), with advantage in reduced injectable volume via the intramuscular or subcutaneous routes.

To support the safety of the benzyl alcohol content in the proposed drug product, the Applicant is relying on FDA's safety findings for two additional listed drugs: Bacteriostatic Water for Injection in Plastic Container (NDA 018802) and Bacteriostatic Sodium Chloride 0.9% Injection in Plastic Container (NDA 018800), both of which also contain 9 mg/mL benzyl alcohol. Dr. Gieser noted that the typical maximum cumulative amount (135 mg) of benzyl alcohol received from using the proposed drug product as indicated in the labeling is anticipated to be comparable or lower to that received (up to 270 mg) when up to 30 mL of Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride 0.9% Injection is administered intravenously, intramuscularly, or subcutaneously. Note however that the approved package inserts of these two listed drugs include warnings and precautionary statements regarding use in neonates and pregnant females, due to the benzyl alcohol content. Thus, I agree with Dr. Gieser's view that the presence of 9 mg/mL of benzyl alcohol in the Applicant's 0.4 mg/mL Atropine Sulfate for Injection is expected to be safe for use by adults. However, warning in labeling for use in pediatric patients, pregnant women, and lactating mothers is warranted.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted as part of this application. The Nonclinical reviewer (Dr. William Link) noted similarity of formulations and the acceptability of all excipients used that meet the USP requirements, but had concern for the addition of the benzyl alcohol to the drug product and the resultant risk in the pediatric population. Dr. Link concluded that the concerns are adequately described in the Package Insert under Section 5 Warnings and Precautions. Consequently, the proposed drug product is approvable with no recommended labeling changes.

5. Clinical Pharmacology

Dr. Xiaolei Pan communicated in an e-mail (dated 12/28/2017) that Office of Clinical Pharmacology (OCP) did not perform a review for this NDA because there was not pertinent clinical pharmacology information provided in this submission.

6. Clinical – Efficacy

There is no clinical trial conducted for the evaluation of efficacy and safety of the proposed drug product since the Applicant is relying on FDA's previous findings for the Listed Drug, Atropine Sulfate Ansyr™ Plastic Syringe, 0.1 mg/mL.

Clinical Reviewer, Dr. Melanie Blank, performed a thorough review on information in the public domain, including labels for approved atropine sulfate injections, DESI findings of safety and efficacy for atropine sulfate, and published literature (see ***APPENDIX*** for References) and provided rationale to support for the proposed labeling changes to Sections 1 and 2 of the proposed labeling with respect to indication and dosing for both adult and pediatric patients.

Section 1 (INDICATIONS AND USAGE):

Current American Heart Association (AHA) guidelines (2010) recommend atropine for symptomatic bradycardia, rather than (b) (4) as proposed by the Applicant. Dr. Blank recommends the change to "*Atropine is indicated for temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue or an antivagal agent before or during surgery, an antidote for organophosphorus or muscarinic mushroom poisoning and to treat symptomatic bradycardia*."

Section 2 (DOSAGE AND ADMINISTRATION):

The Applicant proposed dosing recommendations for the adults but did not provide an update for the pediatric patients. The current labeling states that (b) (4) As per Dr. Blank, successful use of atropine in adults and children since the 1950's has been documented, and there is published literature addressing atropine dosing in both adult and pediatric populations. In addition, clinical guidelines on atropine use have been provided by American Heart Association, the Environmental Protection Agency, the World Health Organization and other authoritative for current medical practice. Dr. Blank proposed more thorough tabular recommendations for adult and pediatric dosing, as summarized below.

Recommended Adult Dosage:

Use	Dose (adults)	Repeat	Maximum total dose
Antisialagogue or other antivagal	0.5 mg to 1 mg (1.25 mL to 2.5 mL)	As needed every 30-60 minutes preoperatively then every 4-6 hours as needed.	3 mg**
Organophosphorus carbamate or muscarinic mushroom poisoning	2 mg to 3 mg (5 mL to 7.5 mL)	Repeat in 3-5 minutes if no change in clinical symptoms. See paragraph below table for further instructions.	See paragraph below table for further instructions.
Symptomatic bradycardia*	0.5 mg (1.25 mL)	As needed every 3 to 5 minutes;	3 mg**

* Do not rely on atropine in type II second-degree or third-degree AV block because these bradyarrhythmias are not likely to be responsive to reversal of cholinergic effects by atropine.

** Limit dose to 0.03-0.04 mg/kg in patients with coronary artery disease (see section 5.2).

Clinical Reviewer noted that "dose may be doubled with each administration until atropinization and cardiovascular and respiratory status improvement. Once adequate atropinization is achieved, maintain the patient on an atropine continuous infusion at about 10%-20% of the loading dose per hour and titrate to effect. Regular clinical observations are necessary to ensure that atropinization is achieved without serious toxicity such as delirium, hyperthermia, and ileus. Anticholinesterase or nerve gas poisonings may require large doses of atropine and the addition of pralidoxime." It is recommended also that carbamate poisoning be added to the list of poisonings for which atropine should be indicated for both adult and pediatric patients.

Recommended Pediatric Dosage:

Use	Dose (pediatrics)	Repeat	Maximum single dose	Maximum total dose
Antisialagogue or other antivagal and in specific emergency intubations when there is higher risk of bradycardia	0.02 mg/kg IV/IO	As needed every 30-60 minutes preoperatively then every 4-6 hours as needed.	0.4 mg for a child and 1 mg for an adolescent	1 mg for a child and 2 mg for an adolescent

Organophosphate, carbamate or muscarinic mushroom poisoning	0.05 mg/kg IV	See paragraph below table for further instructions.		See paragraph below table for further instructions.
Symptomatic bradycardia due to increased vagal tone or primary AV conduction block (not secondary to hypoxia)	0.02 mg/kg IV/IO 0.04-0.06 mg/kg via endotracheal tube**	As needed every 5 minutes.	0.5 mg for a child and 1 mg for an adolescent	1 mg for a child and 2 mg for an adolescent

IV=intravenous; IO=intraosseous; *Available evidence does not support the routine use of atropine in emergency intubation of critically ill infants and children except in in specific emergency intubations when there is higher risk of bradycardia. ** flush with 1-5 mL of normal saline depending on size and follow with 5 ventilations.

Clinical Reviewer noted that "Victims of organophosphate poisoning can tolerate large doses of Atropine. May double dose and repeat every 5-10 minutes until atropinization or cardiovascular and respiratory status improvement."

7. Clinical - Safety

This application primarily relies on the FDA's previous findings of safety for the Listed Drug, Atropine Sulfate Ansyr™ Plastic Syringe. No new clinical study has been conducted. Refer also to the above Section 6 for the clinical review on published literature.

The proposed drug product has a higher drug concentration compared to the Listed Drug (0.4 mg/mL vs. 0.1 mg/mL), is packaged in a 20-mL multiple-dose vial, and is formulated to contain benzyl alcohol as preservative (9 mg/mL). A safety concern was raised during review cycle regarding the presence of 9 mg/mL benzyl alcohol for pediatric use because of the unknown minimum amount of benzyl alcohol at which serious adverse reactions may occur. Note also that atropine crosses the placenta leading to fetal exposure, there are no studies or data evaluating atropine use during human pregnancy, lactation or its effect on fertility, and serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and infants who received drugs benzyl alcohol-containing drugs.

Note that the support for the safety of the benzyl alcohol content (9 mg/mL) of Atropine Sulfate Injection (0.4 mg/mL) in adults come from two additional listed drugs: Bacteriostatic Sodium Chloride 0.9% in Plastic Container [NDA 018800] and Bacteriostatic Water for Injection in Plastic Container [NDA 018802]. Please refer to pertinent information described under Biopharmaceutics section.

Division of Pediatric and Maternal Health (DMPH) was consulted to provide input on format and content for labeling update. Warning was recommended regarding the use of the proposed benzyl alcohol-containing atropine drug product in Sections 5, 6, 8 and 17 for neonates, infants, pregnancy, lactation, and reproductive potential.

8. Statistical

The Biometrics review (dated 12/07/2007), by Dr. Jialu Zhang, stated that this submission is literature based and contains no clinical data. Therefore, statistical review was not performed.

9. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the proposed drug product. No Advisory Committee Meeting was held.

10. Pediatrics

This application does not trigger Pediatric Research Equity Act (PREA) because this product does not contain a new active ingredient, a new indication, a new dosage form (note: multi-dose vial is not considered a new dosage form), a new dosing regimen or a new route of administration. No pediatric exclusivity has ever been granted for this active moiety Atropine. For pediatric dosing recommendation, refer to Section 6 for Dr. Blank's review.

11. Other Relevant Regulatory Issues

This NDA was first submitted to Office of Generic Drug (OGD) and subsequently through the 505(b)(2) pathway, as the drug product did not meet the conditions of use of the RLD.

On May 22, 2017, the Applicant communicated with the FDA that it does not intend to submit a proprietary name for Atropine Sulfate Injection, USP, under NDA 209260 [in DARRTS on 12/27/2017].

In the January 24, 2018 Response to the FDA Information Request (dated 1/23/2018), the Applicant submitted a statement of reliance on two additional listed drugs (Bacteriostatic Sodium Chloride 0.9% in Plastic Container [NDA 018800] and Bacteriostatic Water for Injection in Plastic Container [NDA 018802]) to support the safety of the benzyl alcohol content of Atropine Sulfate Injection (0.4 mg/mL) in adults.

There is no need for post-marketing recommendation for REMS, PMC, or any safety-based PMR.

12. Labeling

The DPMH noted that the Applicant submitted revised labeling and the requested supporting information on June 30, 2017, per the FDA's information request (dated 6/7/2017), which was adequate.

The labeling for the proposed Atropine Sulfate Injection, USP was agreed upon between FDA and the Applicant on 1/25/2018. Please see the final labeling included in the Division action letter.

Proprietary Name: On May 22, 2017, the Applicant communicated with the FDA that they do not intend to submit a proprietary name for Atropine Sulfate Injection, USP, under NDA 209260 [correspondences in DARRTS on 12/27/2017].

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval with labeling changes is recommended for NDA 209260 for Atropine Sulfate Injection, USP.

Risk-Benefit Assessment: This application relies on the FDA's previous findings of safety and efficacy for the listed drug, Atropine Sulfate Ansyr™ Plastic Syringe, 0.1 mg/mL. The labeling of the proposed Atropine Sulfate Injection, USP, 0.4 mg/mL, adequately inform providers or care takers on risk and benefits associated with the use of atropine injection for adult and pediatric patients. Please refer to pertinent information described under Clinical-Efficacy, Clinical-Safety, and Biopharmaceutics sections.

Recommendation for Postmarketing Risk Evaluation and Management Strategies: None

Recommendation for other Postmarketing Requirements (PMR) and Commitments: None

Recommended Comments to Applicant: None in the regulatory action letter.

Appendix

References (Clinical - Efficacy):

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/s/

TA-CHEN WU
01/26/2018
We have received the 505(b)(2) clearance.

NORMAN L STOCKBRIDGE
01/26/2018
I concur.