CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216190Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	December 12, 2024
From	Natalie Getzoff, MD Laura Jawidzik, MD
Subject	Summary Memo
NDA/BLA # and Supplement #	216190
Applicant	Fidelity BioPharma Co
Date of Submission	June 12, 2024
PDUFA Goal Date	December 12, 2024
Proprietary Name / Non-Proprietary Name	Ontralfy (tizanidine)
Dosage Form(s) / Strengths	Oral solution (2 mg/mL)
Applicant Proposed Indication(s)/Population(s)	*Management of spasticity*
Applicant Proposed Dosing Regimen(s)	*Recommended starting dose: 2 mg; dose can be repeated at 6- to 8-hour intervals, up to a maximum of 3 doses in 24 hours; total daily dose should not exceed 36 mg*
Action or Recommended Action:	Approval

1. Background

The Applicant has resubmitted a new drug application (NDA) for Ontralfy (tizanidine oral solution) following a complete response (CR) action issued on March 29, 2024. The Applicant is seeking approval through the 505(b)(2) regulatory pathway and is relying on the findings of safety and effectiveness for the listed drug, Zanaflex tablets (NDA 020397) and Zanaflex capsules (NDA 021447). In addition, the Applicant provided data from two relative bioavailability studies to establish a pharmacokinetic (PK) bridge between Ontralfy and Zanaflex 4 mg tablets and Zanaflex 4 mg capsules. These studies were presented in the original submission.

Tizanidine is currently indicated for the management of spasticity, and the Applicant proposes the same indication for Ontralfy. The proposed dosing regimen is the same as tizanidine tablets and capsules: 2 mg; dose can be repeated at 6- to 8- hour intervals, up to a maximum of 3 doses in 24 hours; dosage can be increased by 2 mg to 4 mg per dose, with 1 to 4 days between increases; and the total daily dose should not exceed 36 mg.

The product quality deficiencies that led to the original CR action included numerous manufacturing deficiencies (deficiencies in the drug substance supplier's drug master file, the potential presence of a new drug substance related impurity, and inadequate information for the manufacturing process) and lack of information regarding the possible formation of (b) (4). In addition, there was inadequate information to support the proposed specification ((b) (4)%) for the unqualified degradant. No clinical pharmacology or clinical deficiencies were identified in the original NDA submission.

No new efficacy data were included in this resubmission. The Applicant provided a safety update that included a summary of a FAERS search from September 26, 2023, to May 20, 2024.

2. Product Quality

The technical lead on the Office of Product Quality (OPQ) review of the resubmission was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ reviews of the original submission (February 29, 2024, and March 29, 2024) and resubmission (November 7, 2024) for details of the product quality assessment.

The OPQ review of the original submission identified a number of deficiencies that were outstanding at the time of the final OPQ review dated February 29, 2024 (with addendum on March 29, 2024). The OPQ deficiencies identified in the original review cycle were related to the drug substance supplier's drug master file (DMF), the potential presence of (b) (4) (b) (4) inadequate information for the drug product manufacturing process, and inadequate information to support the proposed acceptance

criterion for [redacted] a degradation product of [redacted].

Drug Substance:
OPQ determined in their review of the original NDA submission that that the Applicant did not provide sufficient information regarding possible formation of [redacted] In the resubmission, the Applicant provided an updated risk assessment which initially did not include adequate control strategy for the [redacted] In response to an IR during the review of the resubmission, the Applicant provided an adequate control strategy for the [redacted]

Drug Product:
The Division of Pharmacology/Toxicology-Neuroscience, in conjunction with OPQ, determined in the review of the original submission, that the proposed specification of NMT [redacted]% for [redacted] would result in a maximum daily intake [redacted] mg) of [redacted] that exceeds the qualification threshold. In the resubmission, the Applicant provided an adequate justification for the proposed limit of NMT [redacted]% for [redacted]

Manufacturing:
Numerous deficiencies related to the manufacturing process were conveyed to the Applicant during the review of the original submission, but no response was received. These deficiencies were included in the complete response letter (CRL). In the resubmission, the Applicant provided an adequate response to all of the manufacturing deficiencies identified in the CRL.

OPQ recommendation: Approval.

3. Nonclinical Pharmacology/Toxicology

The Division of Division of Pharmacology/Toxicology-Neuroscience (DPT-N) review of the original submission (March 29, 2024) and the resubmission (November 18, 2024) was performed by Dr. Christopher Toscano, with Team Leader Dr. David Carbone, and Supervisory concurrence by Dr. Lois Freed.

The Applicant is relying on the nonclinical information in the tizanidine label (NDA 020397) and the FDA's finding of safety and effectiveness for oral tizandine tablets with no new studies needed to support the NDA. As noted above, the Applicant did not provide adequate justification for [redacted] a degradant of [redacted] In the resubmission, DPT-N concluded that the justification for the proposed daily intake of [redacted] is based on the established allowable levels of [redacted] in [redacted] [redacted]%) and [redacted] [redacted]%), as per USP monograph specifications and is acceptable.

DPT-N recommendation: Approval.

4. Clinical Pharmacology

No new clinical pharmacology data were included in the resubmission. The Office of Clinical Pharmacology (OCP) review of the original submission (March 13, 2024) was performed by clinical pharmacology reviewer Dr. Dawei Li, with Team Leader Dr. Bilal AbuAsal. OCP concluded that the pharmacokinetic studies conducted by the Applicant provide an adequate scientific bridge for this application to rely on the labeling information of the listed drug. See that review for details.

5. Clinical/Statistical-Efficacy

The effectiveness of Ontralfy is based on the demonstration of bioequivalence to the listed drug (LD). No new efficacy data were included in the resubmission.

6. Safety

The safety of Ontralfy is based on the demonstration of bioequivalence to the LD. Dr. Michael Dimyan, the clinical reviewer for this application, reviewed the safety data in the original submission and identified no new safety signals observed with Ontralfy. See the clinical review dated March 22, 2024, for details.

In the resubmission, the Applicant provided a safety update that included a summary of a FAERS search from September 26, 2023, to May 20, 2024. No safety signals were identified.

Clinical recommendation: Approval.

7. Advisory Committee Meeting

None required, as this drug is not a new molecular entity.

8. Postmarketing Recommendations

The submission did not include any pediatric data. An agreed initial pediatric study plan (iPSP) was included with the original NDA submission on May 31, 2023. In the agreed iPSP, the Applicant proposed to conduct a nonclinical juvenile toxicity study, a pharmacokinetic study in pediatric patients with spasticity, 2 to less than 18 years of age, and a long-term open-label safety study of pediatric patients with spasticity ages 2 to less than 18 years were described. The juvenile toxicology study was deemed to be no longer necessary, based on the information in the recently revised product labeling for the listed drug (Zanaflex, NDA 020397, November 22, 2024).

The following will be postmarketing requirements, which have been agreed upon with the Applicant:

PMR-1: An open-label pharmacokinetic (PK) and safety study of tizanidine in pediatric patients 2-17 years of age with spasticity. Patients will be enrolled from the following age groups: 2-5 years, 6-11 years, and 12-17 years, and each group will be adequately represented.

Draft Protocol Submission:	04/2025
Final Protocol Submission:	07/2025
Study/Trial Completion:	12/2027
Final Report Submission:	06/2028

PMR-2: An open-label observational safety study in pediatric patients 2-17 years of age with spasticity to evaluate for potential short-term and long-term effects of tizanidine in the pediatric population on physical and neurocognitive development. Patients will be enrolled from the following age groups: 2-5 years, 6-11 years, and 12-17 years, and each group will be adequately represented.

Draft Protocol Submission:	01/2028
Final Protocol Submission:	04/2028
Study/Trial Completion:	07/2030
Final Report Submission:	12/2030

9. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

The Division of Medication Error and Prevention Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP) provided consultations on the product labeling.

10. Conclusions

Approval of Ontralfy is recommended based on the finding that Ontralfy (tizanidine oral solution, 2 mg/mL) meets the bioequivalence criteria to the 4 mg dose of Zanaflex tablets, which the Agency has previously determined to be safe and effective for the treatment of spasticity. There are no outstanding product quality or nonclinical issues.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NATALIE B GETZOFF
12/12/2024 11:01:04 AM

LAURA A JAWIDZIK
12/12/2024 12:01:21 PM

Summary Review

Date	March 29, 2024
From	Laura Jawidzik, MD Deputy Director, Division of Neurology 1
Subject	Summary Memo
NDA/BLA # and Supplement#	NDA 216190
Applicant	Fidelity Biopharma
Date of Submission	May 31, 2023
PDUFA Goal Date	March 31, 2024
Proprietary Name	Ontralfy
Established or Proper Name	Tizanidine
Dosage Form(s)	Oral solution (2 mg/mL)
Applicant Proposed Indication(s)/Population(s)	Management of spasticity
Applicant Proposed Dosing Regimen(s)	Recommended starting dose: 2 mg; dose can be repeated at 6- to 8-hour intervals, up to a maximum of 3 doses in 24 hours; total daily dose should not exceed 36 mg
Recommendation on Regulatory Action	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Michael Dimyan
Pharmacology Toxicology Review	Christopher Toscano; David Carbone
OPQ Review	Integrated review
Clinical Pharmacology Review	Dawei Li; Bilal AbuAsal
OSE/DMEPA2	Rina Patel/Stephanie DeGraw

1. Background

The Applicant has submitted a 505(b)(2) new drug application (NDA) for Ontralfy (tizanidine oral solution). The proposed indication is for the management of spasticity. The proposed dosing regimen is the same as tizandine capsules/tablets: 2 mg; dose can be repeated at 6- to 8-hour intervals, up to a maximum of 3 doses in 24 hours; dosage can be increased by 2 mg to 4 mg per dose, with 1 to 4 days between increases; total daily dose should not exceed 36 mg.

Tizanidine is approved as a tablet and a capsule for the management of spasticity. There are numerous generic versions available of both the capsule and the tablet. Zanflex tablets and capsules are bioequivalent in the fasted state; however, Zanaflex capsules are not bioequivalent to the Zanaflex tablets in the fed state.

The Applicant had a preIND meeting with the Division in August 2021. At that time the Applicant was advised that a 505(b)(2) pathway appeared acceptable and reliance on Zanaflex tablets appeared acceptable. The Agency notified the Applicant that the new dosage form would be subject to the Pediatric Research Equity Act (PREA).

The Applicant conducted two relative bioavailability studies in healthy volunteers: Study TIZA-21-086 and Study TIZA-22-046. The Applicant claimed reliance on Zanaflex 4 mg tablets (NDA 020397) and Zanaflex 4 mg capsules as the listed drugs to support the safety and efficacy of their product.

2. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. The OPQ integrated review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

The final recommendation from the Office of Pharmaceutical Quality (OPQ) review team is to issue a complete response. From a quality perspective, the review team found several deficiencies with the application. The review team determined that the Applicant has not provided adequate information for the proposed drug product to ensure the identity, purity, and strength of the proposed drug product.

Drug Product:

The drug product is a clear, colorless to pale yellow solution with a strawberry flavor. The product strength is 2 mg/5 mL provided in a (b) (4) bottle. There is no dispensing device supplied with the bottle. Per the drug product reviewers, the Applicant has conducted adequate formulation studies to select and optimize the (b) (4) pH, (b) (4) content, (b) (4) and flavor. In addition, the Applicant also assessed the of the formulation. The extractable and leachable study was adequately conducted. The Applicant provided adequate data to support the proposed shelf-life of 24 months when stored at room temperature.

No outstanding drug product deficiencies were noted by the drug product reviewers.

Drug Substance:

Deficiencies: The drug substance reviewers determined that the Applicant did not discuss the possible formation of (b) (4) in the application nor the did Applicant provide data to demonstrate the absence of (b) (4)

The Agency sent an IR to the Applicant on November 29, 2023, requesting additional information regarding (b) (4) The Applicant's response was provided on February 8, 2024. The Applicant stated in the response that there is no potential for the formation of (b) (4) per the Applicant's overall review of the synthetic scheme and manufacturing process for the drug substance. However, the Applicant's conclusion was not made based on a proper application of the (b) (4) guidance as per the OPQ review team. The Applicant's response was deemed inadequate.

Manufacturing Process:

Deficiences: Numerous manufacturing deficiencies were conveyed to the Applicant via an information request dated January 12, 2024. A response was requested by January 18, 2024, but no response was received as of February 29, 2024. In the absence of an adequate response, the OPQ team has deemed the application inadequate.

In summary, OPQ recommends a complete response for NDA 216910. Outstanding issues are related to deficiencies in the drug substance supplier's drug master file, the potential presence of a new drug substance related impurity, and inadequate information for the manufacturing process.

3. Nonclinical Pharmacology/Toxicology

The Applicant is relying on the nonclinical information in the tizanidine label (NDA 020397) and the FDA's finding of safety and effectiveness for oral tizandine tablets with no new studies needed to support the NDA. If the product were to be approved, no additions to the nonclinical section of labeling are recommended. However, during the review cycle, it was determined that Ontralfy contains an unqualifed degradant, (b) (4) (b) (4) The Applicant did not provide adequate safety data to support the proposed specification (b) (4) %) for this degradant.

To support the proposed specification, the sponsor referenced the OECD SIDS initial assessment report on (b) (4) Based on the information provided in the OECD report, the Applicant calculated a permissible daily exposure of (b) (4) mg/day for (b) (4) (b) (4) Although the Applicant asserted that the proposed daily exposure to (b) (4) is qualified by the information in the OECD report, individual line listings for the data used to support the conclusion were not provided for review. Therefore, per the nonclinical team, the Applicant has not provided adequate safety data to support the proposed specification. It is recommended that the Applicant either reduce the specification for

(b) (4) to below the qualification threshold or provide additional nonclinical data to justify that the proposed daily intake of (b) (4) mg (b) (4) is qualified.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Dawei Li with Dr. Bilal AbuAsal as the team leader. OCP has concluded that the pharmacokinetic studies conducted by the Applicant provide an adequate scientific bridge for this application to rely on the labeling information of the listed drug.

The Applicant conducted two pharmacokinetic (PK) studies in healthy volunteers: 1) Study TIZA-21-086, a pivotal relative bioavailability study between Ontralfy and the listed drug Zanaflex tablet under fasting and fed conditions; 2) Study TIZA-22-046: a comparative PK study between Ontralfy and Zanaflex capsule under fed conditions. The OCP review team concluded that Study TIZA-22-046 was not necessary to support this application. Study TIZA-21-086 was adequate to support the scientific bridge between Ontralfy and the Zanaflex tablet as well as the food effect assessment of Ontralfy.

The results from study TIZA-21-086 showed that the 90% confidence intervals of the geometric least square means (LSMs) for Cmax and AUC0-inf were within the standard bioequivalence acceptance range (80 to 125%) under both fasting and fed conditions, indicating that Ontralfy and Zanaflex tablets are bioequivalent, and the food effect characteristics of Ontralfy and Zanaflex tablet are comparable.

5. Clinical Microbiology

The integrated OPQ reviews notes that the microbiology assessment was adequate.

6. Clinical/Statistical- Efficacy

The clinical effectiveness of Ontralfy was established through the demonstration of bioequivalence to the listed drug Zanaflex tablets (NDA 020397).

7. Safety

The safety of Ontralfy was established through the demonstration of bioequivalence to the listed drug. Dr. Michael Dimyan reviewed new safety data in the application. The safety review focused on the two bioequivalence studies submitted with the application: TIZA-21-086 and TIZA-22-046. Study 086 was a single dose comparative bioavailability study of tizandine oral solution and Zanaflex tablets under fasting and fed conditions. Study 046 was a single-dose bioavailabity study comparing tizanidine oral solution to Zanaflex capsules under fed conditions.

There were no deaths or serious adverse events in either study. There was one discontinuation due to the adverse event of vomiting. The most common treatment emergent adverse events

were consistent with the known AEs associated with the use of tizanidine. Dr. Dimyan noted that there were 6 events of QT prolongation in 5 subjects. Because of the frequency of this event, Dr. Dimyan reviewed the Interdisciplinary Review Team for QT Studies (IRT) consultation on the thorough QT study (tQT) performed under NDA 021447 for tizanidine oral capsules. The TQT was reviewed as a post-marketing requirement (PMR). Dr. Dimyan also consulted the QT-IRT for the application. The QT-IRT did not consider the 6 episodes of QTc prolongation to be of clinical concern. Please see Dr. Dimyan's clinical review and the IRT consultative review dated December 13, 2023 for further details.

Dr. Dimyan did not identify any new safety concerns with the use of tizanidine oral solution.

8. Advisory Committee Meeting

N/A

9. Pediatrics

The listed drug Zanaflex is approved for adult patients. The new dosage form triggers requirements for pediatric studies under the Pediatric Research Equity Act. However, because the application will receive a complete response, postmarketing requirements related to pediatric studies will not be issued at this time.

10. Other Relevant Regulatory Issues

The Applicant submitted the proposed proprietary name, Ontralfy. DMEPA2 found the name Ontralfy to be conditionally acceptable.

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection was not needed for the clinical site, Scitus Pharma. A site inspection had been recently performed in August 2023.

11. Labeling

Labeling will be deferred because the application will receive a complete response.

12. Postmarketing Recommendations

Not applicable

13. Conclusions

Although the Applicant claimed reliance on Zanaflex tablets and Zanaflex capsules, the review team concluded that study TIZA-22-046 was not necessary to support the application, and reliance on Zanaflex capsules was not needed. Study TIZA-21-086 was determined to be

adequate to support the scientific bridge between Ontralfy and the listed drug Zanaflex tablets. Although clinical efficacy and safety were established through the scientific bridge to Zanaflex tablets, there are CMC and nonclinical issues that preclude approval. The application will receive a complete response with the comments below to be conveyed to the Applicant.

14. Recommended Comments to the Applicant

Drug Substance Comments:

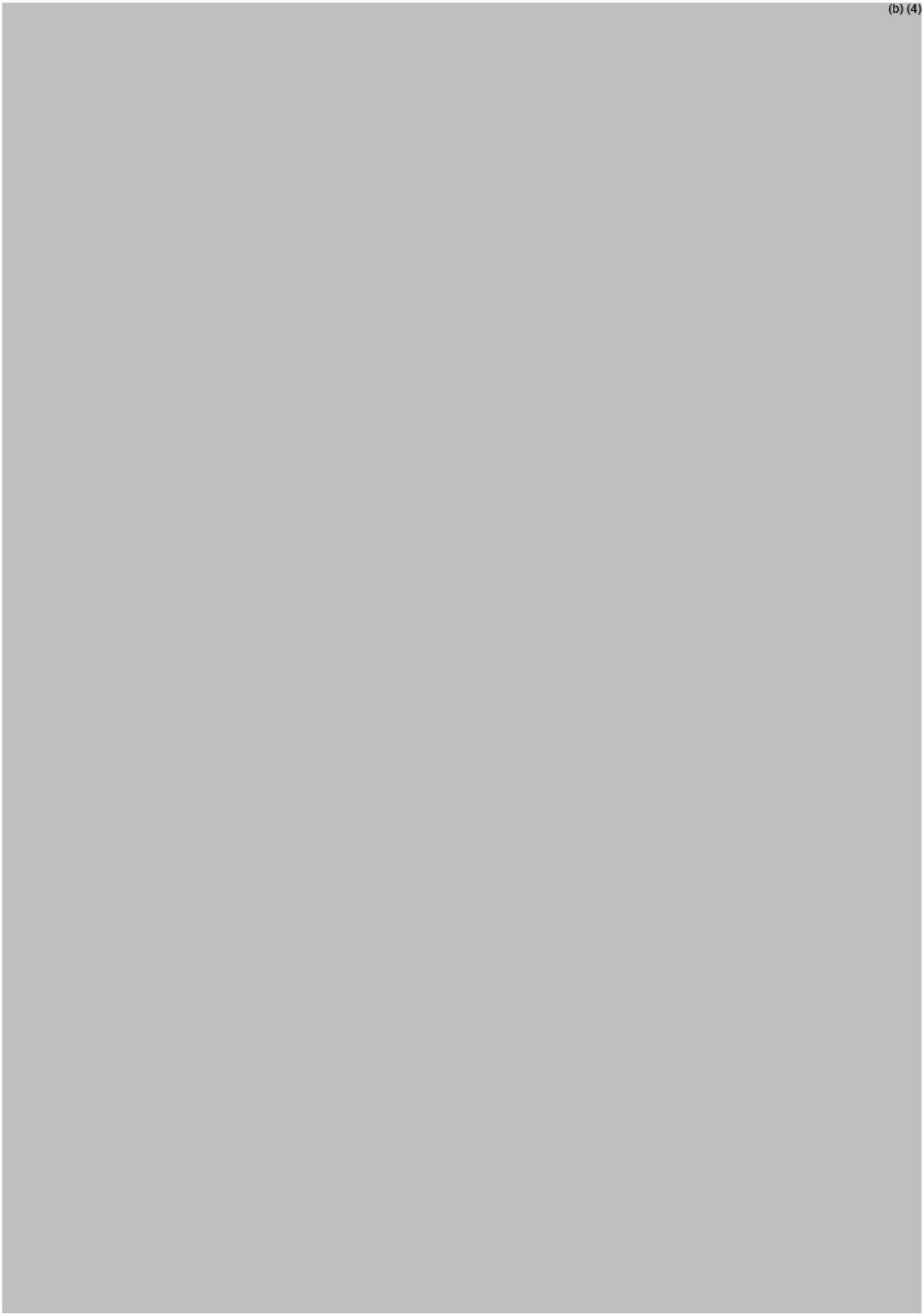
We acknowledge the response that you provided on 08-FEB-2024 for the Agency's (b) (4) IR dated 29-NOV-2023. While we have not performed an in-depth review, in the response, you stated that there is no potential for the formation of (b) (4) per Sun Pharma's overall review of the synthetic scheme and manufacturing process for the drug substance. However, your conclusion was not made based on a proper application of the (b) (4) guidance.[1]

You determined that the (b) (4) score is not applicable since the group in (b) (4) and is thus out of scope of (b) (4) Therefore, it requires the use of alternative methods for establishing an A . We recommend that you work with the DMF holder to establish an appropriate AI limit for control of (b) (4) that may be found in the API.

Process Comments:

(b) (4)

(b) (4)


(b) (4)

support the proposed (b) (4)

Nonclinical comments:

The information provided is not adequate to support the proposed specification of NMT (b) (4)% for (b) (4) which would result in a maximum daily intake (b) (4) mg) of (b) (4) that exceeds the qualification threshold, as recommended in guidance (ICH Q3B(R2), August 2006). The OECD SIDS Initial Assessment Report on (b) (4) upon which you rely, contains only a summary of the available information on (b) (4) To address this deficiency, you would need to lower the specification consistent with guidance or provide additional data to support the specification of NMT (b) (4)%.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK
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