Deborah Droza
Chem IQ FZCO
Unit No HD-03, 25th Floor
Sheikh Rashid Tower
Dubai World Trade Centre
Dubai, United Arab Emirates

December 20, 2022

Re: Docket No. FDA-2022-P-1667

Dear Ms. Droza:

This letter responds to your citizen petition dated July 22, 2022 (Petition).[1] In the Petition, you request that the Food and Drug Administration (FDA or Agency) take certain actions with respect to Indocin (indomethacin) suppositories, 50 milligrams (mg), approved under new drug application (NDA) 017814 and indomethacin suppositories, 50 mg, approved under abbreviated new drug application (ANDA) 073314.[2] Specifically, you request FDA take the following actions:

1. Ensure that the currently marketed reference standard (RS) for indomethacin suppositories, 50, mg, approved under ANDA 073314 complies with the International Council for Harmonisation (ICH)[3] guidelines and established impurity acceptance criteria; and

2. Refrain from approving any ANDAs which justified higher impurities levels citing results of current marketed RS indomethacin suppositories (ANDA 073314) rather than complying with ICH guidelines, FDA regulations and established acceptance criteria with respect to impurities.[4,5]

We have carefully considered the information in the Petition. For the reasons described below, your Petition is denied.

[1] The Petition submitted by ChemIQ FZCO (Petitioner) was received and processed under 21 CFR 10.30 by FDA on July 25, 2022.
[2] Petition at 1.
[3] Formerly the International Conference on Harmonisation.
[4] Petition at 2.
[5] The Agency notes that the Petitioner did not specify which "ICH guidelines" were being referred to in the Petition. FDA interprets this term to mean guidance for industry *Q3A Impurities in New Drug Substances* (Rev. 2) (June 2008) (ICH Q3A Guidance) and guidance for industry *Q3B(R2) Impurities in New Drug Products* (Rev. 3) (Aug. 2006) (ICH Q3B(R2) Guidance). These guidance documents were issued by FDA and developed with the Expert Working Group (Quality) of International Conference on Harmonisation of Technical requirements for Registration of Pharmaceuticals for Human Use (ICH). They are FDA guidance documents and as such, they are not binding on the Agency or the public. These guidance documents can be found on FDA's website by searching the FDA guidance documents web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

I. BACKGROUND

A. Indocin (indomethacin suppositories)

On August 13, 1984, Egalet Corporation (Egalet) obtained approval for NDA 017814 for Indocin (indomethacin) suppositories, 50 mg, a nonsteroidal anti-inflammatory drug indicated for:

- Moderate to severe rheumatoid arthritis including acute flares of chronic disease
- Moderate to severe ankylosing spondylitis
- Moderate to severe osteoarthritis
- Acute painful shoulder (bursitis and/or tendinitis)
- Acute gouty arthritis.[6]

On August 31, 1992, Cosette Pharmaceuticals, Inc. (Cosette), obtained approval for a generic version of indomethacin suppositories, 50 mg, that referenced NDA 017814 as a listed drug in ANDA 073314. Egalet's NDA 017814 was later withdrawn from sale.[7] Currently, the Orange Book lists ANDA 073314 as the RS. Currently, there are no other approved ANDAs for indomethacin suppositories, 50 mg.

B. Applicable Statutory and Regulatory Framework

1. ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to, among other things, add section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs.[8] To obtain approval, an ANDA applicant is not required to provide independent evidence to establish the safety and effectiveness of the proposed drug product, as is required for an NDA. Instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.[9] To rely on this finding, an ANDA applicant must provide sufficient information to show that its drug product is bioequivalent to the RLD.[10] An ANDA applicant generally must also demonstrate, among other things, that its drug product has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain

---

[6] Indocin prescribing information (Apr. 2021), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/017814s044lbl.pdf.

[7] On August 6, 2003, (68 FR 46645) FDA published a notice in the *Federal Register* announcing that the Agency has determined that NDA 017814 was not discontinued or withdrawn from sale for safety or effectiveness reasons.

[8] For purposes of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

[9] A *reference listed drug* or RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3(b) (21 CFR 314.3(b))). RLDs are identified in FDA's list of *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the Orange Book, available at https://www.accessdata.fda.gov/scripts/cder/ob/.

[10] *See* section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); § 314.94(a)(7) (21 CFR 314.94(a)(7)) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); and 21 CFR 314.127(a)(6)(i) (stating that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

permissible differences) labeling as the RLD.[11] FDA must approve an ANDA unless it finds that, among other things, the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity.[12] The scientific premise underlying the Hatch-Waxman Amendments is that bioequivalent drug products with the same active ingredient(s), route of administration, dosage form, and strength are therapeutically equivalent and may be substituted for each other.[13]

2. *Qualification of Impurities in Drug Products*

Under FDA regulations, applicants, including ANDA applicants, are required to include in an application for a proposed drug product the specifications that are necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product.[14] In general, FDA recommends that the level of impurities in a drug product should be controlled. FDA has issued relevant guidances for industry on impurities in drug products and adopted many of the ICH guidelines on impurities in drug products (i.e., degradation products or degradants).[15] The ICH guidelines[16] and FDA guidances are collectively referred to as "Impurities Guidances" in this document. These Impurities Guidances provide a paradigm for control of impurities, and set specific recommended thresholds for reporting, identification, and qualification.[17] The Impurities Guidances identify recommended qualification threshold (QT) values based on maximum daily dose of the drug. They describe a risk-based model for establishing qualification thresholds, stating, for example, that "higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs, based on scientific rationale and level of concern, including drug class effects and clinical experience"[18] and "lower thresholds can be appropriate if the impurity is unusually toxic."[19] If the specified threshold limits exceed the recommended levels, the impurities should be qualified for safety, and the acceptance criteria[20] should be "set no higher than the level that can be justified by safety data" and should be consistent with "the

---

[11] Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; *see also* § 314.94(a).
[12] Section 505(j)(4) of the FD&C Act; *see also* § 314.127(a).
[13] *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. § 314.3(b).
[14] *See* 21 CFR 314.50(d)(1)(ii) and 314.94(a)(9)(i).
[15] ICH Q3A Guidance; ICH Q3B(R2) Guidance; guidance for industry *ANDAs: Impurities in Drug Products* (Nov. 2010) (ANDAs Impurities Guidance). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. Additionally, CDER issued MAPP 5017.2 Rev. 1 *Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance* (May 1, 2020), which provides guiding principles and approaches for establishing drug product impurity acceptance criteria for certain NDAs and ANDAs.
[16] *See supra* note 5.
[17] *Qualification* is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. ICH Q3A Guidance at 6; ICH Q3B(R2) Guidance at 6; ANDAs Impurities Guidance at 4.
[18] ICH Q3A Guidance at 7.
[19] ICH Q3A Guidance Attachment 1: Thresholds.
[20] *Acceptance criteria* are numerical limits, ranges, or other suitable measures indicating an acceptable level of an impurity in a drug product or active pharmaceutical ingredient. ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (Dec. 2000), Glossary. The ICH Q3 series of guidances have been adopted by FDA as Agency guidances for industry.

level achievable by the manufacturing process and the analytical capability."[21] If the impurity is at or below the recommended qualification threshold, the guidances indicate that the impurity needs no further safety qualification.[22] The recommendations summarized above are made by FDA in guidance documents, as such they represent the Agency's current thinking and are not binding on the Agency or the public.[23]

II. DISCUSSION

In your Petition, you make two requests: (1) that the Agency ensure that impurity levels in the currently marketed indomethacin suppositories, 50 mg, approved under ANDA 073314 "complies with the ICH guidelines and established impurity acceptance criteria" and (2) that FDA not approve any ANDAs that justify higher impurities levels based on reference to ANDA 073314.[24]

To support your requests, you state that "[c]urrently marketed samples" of indomethacin suppositories, 50 mg, "have been shown to contain high levels of organic impurities compared to ICH acceptance criteria and to a previously-published U.S. Pharmacopeia (USP) monograph."[25] Your petition states there are "risks presented by a high amount of organic impurities in Indomethacin Suppositories. "[26] It also states that "Indomethacin is known to interact with glycerol" and degrade.[27]

We have reviewed the Petition and deny these requests for the following reasons.

First, we address your claim that indomethacin suppositories, 50 mg, currently marketed under ANDA 073314 show "high levels of organic impurities" compared to "ICH acceptance criteria." You state that you have used an "in-house, validated method" to conduct testing of five (5) samples of currently marketed indomethacin suppositories, 50 mg, and found levels of unspecified organic impurities exceeding the amounts listed in ICH guidelines and a no-longer-current USP monograph for indomethacin.[28] However, no further details of the "in-house" method used nor description of the validation and sample preparation methods are provided. The only information provided to the Agency is the result of your analysis. In the absence of such detailed information, including the sample preparation method, quantification method, and validation data, we are unable to assess your results. Consequently, we are unpersuaded by the information you submit about the level of organic impurities in ANDA 073314 in support of the actions requested in your Petition.

Second, we turn to the claim that ANDA 073314 showed levels of impurities higher than those previously permitted under the USP monograph.[29] As you state in the Petition, the current USP

[21] ICH Q3B(R2) Guidance at 6. *See also* ICH Q3A Guidance at 6 and ANDAs Impurities Guidance at 4 and 5.
[22] Impurities Guidances.
[23] ICH Q3A Guidance at 1; ICH Q3B(R2) Guidance at 1; and ANDAs Impurities Guidance at 1.
[24] Petition at 2.
[25] *Id*.
[26] Petition at 1.
[27] Petition at 3.
[28] Petition at 4-5.
[29] Petition at 5.

monograph for Indomethacin Suppositories does not include an acceptance criteria for organic impurities.[30] Accordingly, this outdated standard is not relevant to granting or denying the actions you request for indomethacin suppositories, 50 mg.

Third, with respect to the ICH guidelines, your Petition misconstrues them. FDA guidance documents provide recommendations to applicants on the content and qualification of impurities in new drug products, including recommendations for reporting, identification, and qualification thresholds (QT). FDA guidance and ICH guidelines describe how an ANDA may establish impurity acceptance criteria below the recommended qualification threshold or provide an appropriate scientific rationale and safety data to support limits for impurities that exceed the recommended threshold.

For instance, if a specified impurity with a proposed acceptance criterion is greater than the recommended QT in the Impurities Guidances, that specified impurity may nevertheless be qualified in some in cases. For example, if the observed level and the proposed acceptance criterion do not exceed the level that has been adequately evaluated in toxicology studies or are adequately justified by the scientific literature, then the proposed acceptance criterion may be adequate to support approval of the ANDA.[31] The acceptability of impurity levels exceeding the QT is based on the information provided in an ANDA and determined in the context of a specific ANDA's evaluation. Every ANDA must meet the same statutory and regulatory requirements for approval, and FDA applies the same review standards to each ANDA for qualifying degradation products in the drug product, which may be informed by recommendations in guidance documents and other regulatory documents.[32] Therefore, the inference made in your Petition that an ANDA does not "compl[y] with the ICH guidelines, FDA regulations and established acceptance criteria with respect to impurities"[33] if it justifies a higher impurities level is misplaced. Additionally, even though ANDA 073314 was approved in 1992 prior to FDA adopting the ICH guidelines, its impurity profile meets the acceptance criteria described in the Impurities Guidances.

Lastly, your Petition mentions "risks presented by a high amount of organic impurities in Indomethacin Suppositories."[34] However, nowhere in the Petition are these risks further described or explained save a short passage on the known interaction between Indomethacin and glycerol. FDA ensures that individual organic impurities are identified and qualified and evaluates the safety of individual organic impurities and their amounts when they exceed qualification thresholds as outlined in the Impurities Guidances. Although your Petition lacks the necessary quantitative information and the specific organic impurities that is the focus of your concern, both of which the Agency requires to assess the validity of your claim, as described previously, FDA evaluates the safety of impurities in accordance with the Impurities Guidances. As such, we believe the concerns raised in your Petition are adequately addressed by our approach to assessing the impurity profile of indomethacin suppositories, 50 mg.

---

[30] Petition at 4-5. *See* USP (Indomethacin Suppositories. In: USP–NF. Rockville, MD: United States Pharmacopeia. Accessed December 7, 2022. https://doi.org/10.31003/USPNF_M40423_03_01*)*. The official USP monograph was revised in 2019 by USP and removed the organic impurities test.

[31] *See, e.g.*, ANDAs Impurities Guidance at 4.

[32] *See supra* note 14.

[33] Petition at 2.

[34] Petition at 1.

In conclusion, your Petition has not presented any verifiable evidence that ANDA 073314 does not "compl[y] with ICH guidelines and established impurity acceptance criteria," upon which to base a change to FDA's previous determination that the ANDA met the statutory and regulatory standards for approval. Likewise, the Petition does not present the impurities posing safety concerns with using the product. Further, unlike the characterization in the Petition and as described above, the Impurities Guidances provide multiple recommendations relating to impurity acceptance criteria. Those recommendations encompass scenarios when the impurities in an ANDA are below the recommended qualification threshold or when the ANDA sponsor provides an appropriate scientific rationale and safety data to support limits for impurities that exceed the recommended threshold. Furthermore, even if the organic impurities exceed the ICH guidelines in a hypothetical ANDA for indomethacin suppositories, 50 mg, (i.e., exceed the QT recommended in the ICH Q3B(R2) Guidance), such impurity levels may be acceptable for an ANDA for indomethacin suppositories, 50 mg, if information were to be submitted in the ANDA that supports the safety of the proposed impurities limit, such as explained further above. The acceptability of impurity levels exceeding the QT is based on the information provided in an ANDA and determined on a case-by-case basis, in the context of a specific ANDA's evaluation.

In sum, we do not agree with your requests that action is needed (1) to ensure that ANDA 073314 complies with ICH guidelines and established impurity acceptance criteria or (2) FDA not approve any ANDAs that justify impurities levels that exceed a recommended QT level based on reference to ANDA 073314.[35]

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2022.12.20 14:51:12 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[35] Petition at 2.