22 July 2022
VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

CITIZEN PETITION

Request That FDA Take Certain Actions With Respect to Indomethacin Suppositories

Dear Sir or Madam:

On behalf of Chem IQ FZCO ("Company"), the undersigned submits this Citizen Petition pursuant to the Federal Food, Drug and Cosmetic Act (the "FD&C Act") and in accordance with 21 C.F.R. §§ 10.25, 10.30, 10.31 and 314.70 to request that the Commissioner of Food and Drugs take certain actions with respect to Indocin® (indomethacin) Suppositories, 50 mg, originally approved under New Drug Application ("NDA") 017814 and Indomethacin Suppositories, 50 mg, approved under Abbreviated NDA ("ANDA") 073314. NDA 017814 is identified in the Discontinued Drug Product List section of the Food and Drug Administration's ("FDA's") *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") as a Reference Listed Drug ("RLD"), and ANDA 073314 is listed in the Prescription Drug Product List section of the Orange Book as a Reference Standard ("RS").

As discussed below, considering the risks associated with impurities exceeding established limits, and given the therapeutic utility of Indomethacin Suppositories, FDA should ensure that ANDA sponsors and applicants comply with International Conference on Harmonization ("ICH") guidelines and established drug product impurity acceptance criteria.

A. ACTIONS REQUESTED

Petitioner respectfully requests that FDA take the following actions considering the risks presented by a high amount of organic impurities in Indomethacin Suppositories:

(1) Ensure that the currently marketed RS for Indomethacin Suppositories, 50 mg, approved under ANDA 073314 complies with ICH guidelines and established impurity acceptance criteria; and

(2) FDA should refrain from approving any ANDAs which justifies 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.

B. STATEMENTS OF GROUNDS

1. Factual Background – Indomethacin Suppositories

Indomethacin has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of Indomethacin, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Indomethacin is a potent inhibitor of prostaglandin synthesis in vitro. Indomethacin concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

FDA initially approved NDA 017814 for Indocin® Suppositories, 50 mg, on August 13, 1984. Until the drug product was discontinued, it was indicated for multiple indications, including:

- 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); and
- Acute gouty arthritis.

On August 31, 1992, FDA approved ANDA 073314 for a generic version of Indocin® Suppositories, 50 mg. That drug product was eventually withdrawn from the market and the NDA holder requested that FDA withdraw approval, which the Agency did. *See* FDA, Determination That Benztropine Mesylate Tablets and Nine Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 68 Fed. Reg. 46645, 46646 (Aug. 6, 2003). After Indocin® Suppositories, 50 mg, approved under NDA 017814 was withdrawn from the market, ANDA 073314 became the RS for subsequent ANDA applicants. The table below summarizes the details on the two approved Indomethacin Suppository, 50 mg, drug products listed in the Orange Book:

Active Ingredient	Proprietary name	Application Number	Strength	RLD	RS	Applicant Holder	Approval Date
Indomethacin	Indocin	N017814	50 mg	Yes	-	Egalet US Inc	Aug 13, 1984
Indomethacin	Indomethacin	A073314	50 mg	-	Yes	Cosette Pharmaceuticals Inc	Aug 31, 1992

Since the 1984 and 1992 approvals of NDA 017814 and ANDA 073314, respectively, there has been a significant evolution in the understanding of impurity identification, quantification, and the toxicities associated with drug product impurities.

2. Legal Background – Drug Product Impurities

The FD&C Act states that FDA shall approve an ANDA unless the Agency finds that "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." FD&C Act § 505(j)(4)(A). Similarly, FDA's implementing regulations state that ANDA applicants are required to submit as part of their application specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and drug product. *See generally* 21 C.F.R. §§ 314.50(d)(l)(i), 314.50(d)(l)(ii), and 314.94(a)(9)(i). In particular, ANDA applicants are required to provide information on impurities and residues in the drug substance and drug product as part of the chemistry, manufacturing, and controls section of an ANDA. FDA will refuse to approve an ANDA if "[t]he methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to ensure and preserve its identity, strength, quality, and purity." 21 C.F.R. § 314.127(a)(1).

While the FD&C Act and FDA's implementing regulations do not require that ANDA applicants use the same chemical synthesis or manufacturing process as those used by the brand-name RLD or the RS—and similarly, the statute does not require that the impurity profile of a generic drug to exactly match those of the drug products referenced in their applications, *see* FD&C Act § 505(j)(2)(A)(vi)—FDA recommends that impurities present in the ANDA product at higher levels than in (or not contained in) the drug products referenced in their applications be qualified in accordance with the framework set forth in current FDA guidance. Thus, for example, current FDA guidance states:

> In establishing degradation product acceptance criteria, the first critical consideration is whether a degradation product is specified in the United States Pharmacopeia (USP). If there is a monograph in the USP that includes a limit for a specified identified degradation product, we recommend that the acceptance criterion be set no higher than the official compendial limit.
>
> If the level of the degradation product is above the level specified in the USP, we recommend qualification. Then, if appropriate qualification has been achieved, an

applicant may wish to petition the USP for revision of the degradation product's acceptance criterion.

If the acceptance criterion for a specified degradation product does not exist in the USP and this degradation product can be qualified by comparison to the reference listed drug (RLD), the acceptance criterion should be similar to the level observed in the RLD. In other circumstances, the acceptance criterion may need to be set lower than the qualified level to ensure drug product quality. For example, if the level of the significant metabolite impurity is too high, other quality attributes, like potency, could be seriously affected. In this case, we would recommend that the degradation product acceptance criterion be set lower than the qualified level.

We recommend that ANDA sponsors develop robust formulations and manufacturing processes that are based on sound state-of-the-art scientific and engineering principles and knowledge.

Although routine manufacturing variations are expected, significant variation in batch-to-batch degradation product levels or an unusually high level of degradation products may indicate that the manufacturing process of the drug product is not adequately controlled or designed.

FDA, Guidance for Industry - ANDAs: Impurities in Drug Products, at 3-4 (Nov. 2010).

As a general principle, FDA has made clear that drug product impurities should be minimized. Indeed, FDA has explained that "[i]n general, impurities provide some risk and no benefit. Even in cases where data on the risk of an impurity is lacking, the lack of data itself conveys some risk of adverse effects. Further, if an impurity conveys essentially no benefit, the exposure to risk is high compared to the benefit (if any), resulting in a substantially negative risk/benefit ratio. Consequently, the general principal that FDA applies is that impurities should be minimized." FDA, Citizen Petition Response, Docket No. FDA-2012-P-0583, at 6 (Nov. 30, 2012).

3. Indomethacin Suppositories Organic Impurities Assessment

Currently 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 USP monograph. *See* USP, Indomethacin Suppositories (Exhibit A). For example, Indomethacin Suppositories, 50 mg, approved under ANDA 073314 contains

glycerol as an inactive ingredient. Indomethacin is known to interact with glycerol and consequently degrades it. The published literature suggests that some of the impurities in Indomethacin Suppositories, 50 mg, were a result of the interaction of indomethacin and 4-chlorobenzoic acid (a known impurity) with glycerin used in the suppository base. *See* HPLC Analysis of Indomethacin and Its Impurities in Capsule and Suppository Formulations, E. KWONG, G. K. PILLAI, and K. M. McERLANE, Journal of Pharmaceutical Sciences, Vol. 71, No. 7, July 1982 (Exhibit B).

Petitioner analyzed samples of currently-marketed Indomethacin Suppositories, 50 mg, approved under ANDA 073314 using an in-house, validated method. An in-house method was used due to the unavailability of a current USP monograph for organic impurities in Indomethacin Suppositories. The Petitioner's analysis of multiple drug product lots showed impurity levels higher than permitted under ICH guidelines and higher than those previously permitted under the relevant USP monograph for unknown impurities. The results of Petitioner's analysis are shown in the table below.

Name of the product	**Indomethacin Suppositories, 50 mg (ANDA 073314)**				
Batch No./Lot No.	**1014035**	**1013284**	**1012267**	**1014068**	**1014169**
Analysis Date	21/02/2022	25/03/2022	25/03/2022	25/03/2022	25/03/2022
Expiry/Retest date	Jul-23	Jul-23	Oct-22	Jul-23	Sep-23
Impurity name: Acceptance criteria	**Observed results**				
Indomethacin related compound A: Not more than 0.2%	0.08	0.08	0.11	0.08	0.08
Indomethacin related compound B : Not more than 0.2%	BQL (0.03)	BQL (0.04)	BQL (0.04)	0.06	BQL (0.02)
Any individual unspecified organic impurities: Not more than 0.2%	**0.32** (RRT 0.71), 0.16 (RRT 1.02)	**0.30** (RRT 0.71), **0.22** (RRT 1.04)	**0.44** (RRT 0.71), **0.30** (RRT 1.04)	**0.31** (RRT 0.71), **0.21** (RRT 1.04)	**0.29** (RRT 0.71), 0.19 (RRT 1.04)

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Total Organic impurities: Not more than 0.4%	**0.6%**	**0.7%**	**1.0%**	**0.7%**	**0.6%**

Note: BQL 0.05%

4. Conclusion

For the reasons described above, Petitioner respectfully requests that FDA grant the actions requested in this citizen petition. Considering the risks associated with impurities exceeding established limits, and given the therapeutic utility of Indomethacin Suppositories, FDA should ensure that Indomethacin Suppositories, 50 mg, ANDA sponsors and applicants comply with ICH guidelines and established drug product impurity acceptance criteria.

C. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), Petitioner will submit economic information upon the request by the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: 16 May 2022. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Chem IQ FZCO. I verify under penalty of perjury that the foregoing is true and correct as of the data of the submission of this petition.

Sincerely,

Deborah Droza
Authorised Signatory
Chem IQ FZCO

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