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BY ELECTRONIC DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, Arnall Golden Gregory LLP (the "Petitioner") submits this Petition, in accordance with 21 C.F.R. §§ 10.25 and 10.30, to request the Commissioner of Food and Drugs ("Commissioner"), through the Food and Drug Administration ("FDA"), issue a regulation or guidance document to establish new science-based limits to control for 2-methyl-3-phenylaziridine in amphetamine salts active pharmaceutical ingredients (APIs), because we believe that up to 0.099 percent contamination is too high a level for this aziridine impurity. We believe there are potential safety risks, particularly for children who take amphetamine-containing Attention Deficit Hyperactivity Disorder ("ADHD") drugs, which are potentially contaminated with 2-methyl-3-phenylaziridine. We recommend that it be controlled to less than 0.01 percent as a new standard.

A. Action Requested

Petitioner respectfully requests that FDA establish new science-based limits to control for 2-methyl-3-phenylaziridine in amphetamine salts APIs, because we believe that up to 0.099 percent contamination is too high a level for this aziridine impurity, and recommend that it be controlled to less than 0.01 percent.

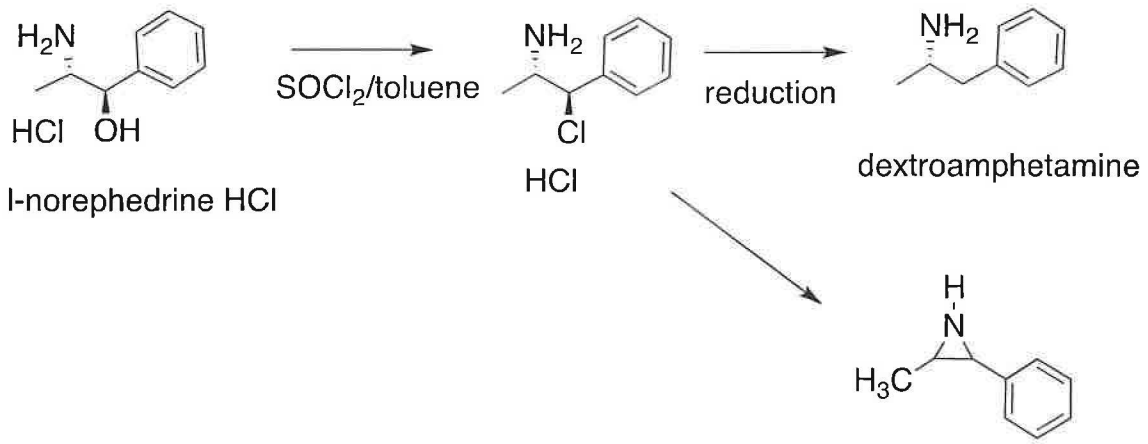
B. Statement of Grounds

There are immediate release and delayed release dextroamphetamine, racemic amphetamine, and amphetamine mixed salts products on the market today, either sold as branded or generic formulations such as Benzedrine, Dexedrine and Adderall® for the treatment of ADHD, narcolepsy and other indications. There are four APIs used in amphetamine mixed salts products: dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate, and amphetamine aspartate. Synthetic amphetamines are used for all of these commercial medicines.

The most popular route to manufacture amphetamine salts in the United States, as well as dextroamphetamine for conversion to lisdexamfetamine, relies on some variation of the Emde

process, which uses norephedrine as starting material.[1] A reaction by-product formed in the Emde process is the aziridine compound, 2-methyl-3-phenylaziridine. Based on not being listed in the USP specifications for dextroamphetamine sulfate,[2] 2-methyl-3-phenylaziridine is currently controlled to < 0.1% in the bulk API, which is then formulated into amphetamine-containing dosage forms, or further used to manufacture lisdexamfetamine dimesylate API.

Modified Emde Preparation of Dextroamphetamine



Amphetamine products manufactured by modified Emde routes account for virtually 100% of the amphetamines distributed to the public, used in hospitals, and sold to the military. Furthermore, children are the most affected population. By regulation, all amphetamine-containing dosage forms (and their active ingredients) sold in the United States must be made within the United States. Petitioner is aware of a new, proprietary process in late development for the manufacture of amphetamine salts APIs that does not form 2-methyl-3-phenylaziridine as a by-product. Petitioner is also aware that this technology is being used to develop a process for the manufacture of lisdexamfetamine dimesylate, the active ingredient in Vyvanse®, also a leading drug for the treatment of ADHD. Therefore, requiring stricter control of this potentially genotoxic impurity would not cause the withdrawal of these important medicines from a physician's toolbox.

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[1] Emde, H. "Uber Diastereomerie I. Konflguration des Ephedrins" *Helv. Chim. Acta.* 1929, 12, 365-376. Attachment A.

[2] The current USP monograph (USP 29-NF24, page 663 of the 2006 Edition of the US Pharmacopeia) for dextroamphetamine sulfate describes an HPLC method for impurities. USP specifications call for not more than 0.1% of any impurity and not more than 0.5% of total impurities. Because 2-methyl-3-phenylaziridine is not mentioned in the monograph, current drug substance manufacturers can control to less than 0.1% of this aziridine impurity and deliver product meeting USP specifications. The same holds true for the other amphetamine salts. Attachment B.

The above described impurity (2-methyl-3-phenylaziridine) is encountered in commercial versions of the Emde process for the manufacture of amphetamine salts. As long as a manufacturer can lower the concentration of 2-methyl-3-phenylaziridine to < 0.1%, the bulk API is approved for formulation to drug product, even though it may likely still contain up to 0.099% (or up to 990 ppm) of this trace aziridine impurity.[2]

We believe this trace impurity has the potential to be genotoxic. In 1976, an article exploring the metabolic reaction of aziridine derivatives with rat liver enzymes was published.[3] The authors ran pure trans 2-methyl-3-phenylaziridine and the cis-trans mixture of 2-methyl-3-phenylaziridine through their rat liver microsomes system and found there was reactivity to form the olefin (1-phenylpropene) and a nitroso compound which then further decomposed. They could not account for about 10% of the aziridine they charged to their test system. They concluded: "Generally, two fundamental processes are recognized as important biological reactions of aziridines. One of them is the hydrolysis of the three-member rings to form amino alcohols and the other is alkylation with protein or DNA...."[3]

In 1990, a study demonstrated pure 2-methyl-3-phenylaziridine only partially converted (4% conversion) to amphetamine when administered to laboratory rats.[4] The balance of the injected compound was unaccounted for and was presumed to be totally bound to the rat and not recoverable. In 2002, an *in vitro* study on 2-methyl-3-phenylaziridine showed irreversible binding, via an alkylation process, to a specific human liver enzyme (CYP2D6).[5] This type of irreversible liver enzyme binding reaction is the basis of the Ames test.[6] A positive Ames test indicates that the chemical is potentially mutagenic and, therefore, may act as a carcinogen. The authors concluded that these impurities have the potential to contribute to the pharmacological profile of amphetamine (and d-methamphetamine) prepared by the Emde process.[5]

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[3] Hata, Y.; Watanabe, W.; Matsubara, T.; Touchi, A. "Fragmentation Reaction of Ylide. 5. A New Metabolic Reaction of Aziridine Derivatives" *J. Amer. Chem Soc.* 1976, *98(19)*, 6033-6036. Attachment C.

[4] Mori, A.; Akita, H.; Oishi, T.; Ishiyama, I.; Carbon-Nitrogen Bond Cleavage in Aziridine Ring *In Vivo*, *Act. Crim. Japon.*, 1990, *56*, 251-257. Attachment D.

[5] Rege, B.; Carter, K. M.; Sarkar. M., A.; Kellogg, G. E.; Soine, W. H.; Irreversible Inhibition of CYP2D6 by (-)-Chloroephedrine, A Possible Impurity in Methamphetamine, *Drug Metabolism and Disposition,* 2002, *30*, 1337-1343. Attachment E.

[6] The Ames test is a widely employed method that uses bacteria to test whether a given chemical can cause mutations in the DNA of the test organism. More formally, it is a biological assay to assess the mutagenic potential of chemical compounds.[a] A positive test indicates that the chemical is mutagenic and therefore may act as a carcinogen. because cancer is often linked to mutation. The test serves as a quick and convenient assay to estimate the carcinogenic potential of a compound because standard carcinogen assays on mice and rats are time-consuming (taking two to three years to complete) and expensive. However, false-positives and false-negatives are known.[b]

(a) Mortelmans K. Zeiger E (November 2000). "The Ames Salmonella/microsome mutagenicity assay". *Mutation Research* 455 (1–2): 29–60. Attachment F.

(b) Charnley G (2002). Encyclopedia of Public Health. eNotes.com. Archived from the original on 4 February 2009. (per Wikepedia, the free encyclopeida "Ames Test", Accessed on March 28, 2022). Attachment G.

The DNA reactive/genotoxic limits, according to the current European Union and FDA guidelines are based on the potential long-term, daily exposure for healthy adults. The guidelines do not have any recommended daily exposure limits for children. It is our understanding that the FDA acceptable daily intake for an individual DNA reactive impurity, for a duration of greater than 10 years to lifetime is, 1.5 µg/day and shorter durations of treatment allow up to 20 µg/day for duration of treatment of 1 – 12 months.[7]

Adderall usual daily dosages range between 5 - 60 mg per day, given in divided doses. Many children continue taking ADHD medication into adulthood. An impurity at a level of a little below 0.1% would equate to approximately 5 - 60 µg/day (depending on dosage consumed), well above the FDA acceptable exposure for long term use, even at the lowest dose. Although current FDA guidelines specifically state "This guidance is not intended to be applied retrospectively (i.e., to products marketed prior to adoption of this guidance)",[7] FDA has more recently adopted and applied a stricter specification approach to the management of trace impurities that could potentially impact the health and welfare of the public. We believe, because children are the mostly likely population to receive this drug, and are administered this drug for years, addressing this safety issue is critical to the public's welfare.

The International Agency for Research on Cancer classifies aziridine compounds as possibly carcinogenic to humans (IARC Group 2B).[8] In making its overall evaluation, the IARC Working Group took into consideration that aziridine is a direct-acting alkylating agent, which is mutagenic in a wide range of test systems and forms DNA adducts that are promutagenic.

To the best of our knowledge, there are limited published studies seeking to evaluate long-term exposure to stimulant-based ADHD drugs and cancer. The studies we could find were designed to focus on the API, not process or degradation impurities, with methylphenidate (a non-amphetamine based ADHD medicine) seeming to receive the most attention. Because of the likely contamination with a potentially genotoxic aziridine impurity in the widely-used and chronically-dosed amphetamine containing children's medications, we believe the potential risks to this large and vulnerable population group necessitate a closer evaluation of any associated health and safety risks.

Given the potential genotoxicity of 2-methyl-3-phenylaziridine, which we believe is currently a trace impurity in all synthetic amphetamine-based ADHD drugs on the market today, we respectfully request that FDA establish new science-based limits to control for 2-methyl-3-phenylaziridine in amphetamine salts APIs, because we believe that up to 0.099 percent contamination is too high a level for this aziridine impurity. We recommend that it be controlled

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[7] US Food and Drug Administration, Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation Research (CBER) (March 2018) M7(R1) "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" Guidance for Industry; US Food and Drug Administration web site https://www.fda.gov/media/85885/download. Accessed on March 3, 2022. Attachment H.

[8] Some Aziridines, N-, S- and O-Mustards and Selenium (PDF). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Vol. 9. 1975. ISBN 978-92-832-1209-6. Archived from the original (PDF) on 2009-11-14. Retrieved 2019-11-24. Attachment I.

to less than 0.01 percent. The safety of our country's children is too important not to consider this potential risk to their future.

It is not the Petitioner's position that FDA should require zero exposure to 2-methyl-3-phenylaziridine in children prescribed amphetamine-based ADHD medicines. However, we believe the recommendation above should address the underlying concerns noted in this Petition, because the potential exposure risks to this chemical by-product warrant greater control of its limits in these important medicines.

C. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.30(h).

D. Economic Impact

As provided in 21 C.F.R. § 10.30(b), economic impact information will be provided if requested by FDA.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Respectfully Submitted,

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