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VIA ELECTRONIC SUBMISSION AT REGULATIONS.GOV TO
Docket No. FDA-2013-S-0610

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Citizen Petition Requesting FDA to Revoke Approval of ANDA No. 211654 and Order Recall

The undersigned, on behalf of petitioner Vanda Pharmaceuticals Inc. (Vanda), submits this petition under 21 U.S.C. §§ 355(j)(2)(A)(iv) and 355(j)(4)(F) in accord with 21 C.F.R. §§ 10.25(a) and 10.30. Vanda requests that the Commissioner of Food and Drugs revoke approval of Abbreviated New Drug Application (ANDA) No. 211654, submitted by MSN Pharmaceuticals Inc. (MSN), for 20 mg tasimelteon capsules, and order a recall of any product that has been distributed under ANDA No. 211654 (if any) because it fails to satisfy the bioequivalence requirement.

Bioequivalence is the touchstone of any ANDA. If an applicant fails to demonstrate bioequivalence through an appropriately designed study, there is no way to know whether the product it is selling into the United States market is safe and as effective as the reference listed drug. A basic tenet of safe and appropriate drug development generally—and in bioequivalence studies specifically—is that studies should be conducted in a population representative of the population the drug is intended to treat. Indeed, for three decades, FDA has advocated that females be included in bioequivalence studies. And FDA has more recently renewed emphasis on the importance of ensuring racial and ethnic representation in clinical trials. The reason is commonsense: the way to demonstrate bioequivalence in the population intended to take a drug—and thereby establish the drug's safety and efficacy in that population—is to use a representative population for the study.

MSN, however, flouted these basic principles and FDA guidance. MSN did *not* submit a study that demonstrates bioequivalence in the intended population: **MSN only tested its drug in 44 Indian[1] males**.

[1] MSN identifies that the trial was sited in Hyderabad, India, and that the trial population was exclusively Asian males. *See* Exhibit 1, Redacted Biopharmaceutics Review and Report from Division of Bioequivalence Review for ANDA No. 211654 at 1, 18, 23 (MSN Bioequivalence Review). Based on these representations, it appears that all trial participants were Indian.

To demonstrate bioequivalence, MSN did not test the drug in any women nor in a population representative of the racial and ethnic makeup of the United States.

And FDA let it. FDA reviewers disregarded FDA's own general and specific guidance and rubber-stamped MSN's woefully inadequate study design. Indeed, an FDA reviewer specifically considered whether the demographic profile of MSN's study satisfied FDA's guidance, and the reviewer said "Yes."

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

Exhibit 1, Redacted Biopharmaceutics Review and Report from Division of Bioequivalence Review for ANDA No. 211654 at 12 (MSN Bioequivalence Review). But MSN's demographic profile did *not* satisfy FDA's general bioequivalence-testing guidance *nor* product-specific guidance for tasimelteon:

Subjects: Healthy males and nonpregnant females, general population

Exhibit 2, FDA, *Draft Guidance on Tasimelteon* (Sept. 2015), perma.cc/U8KS-HWSM (2015 Guidance).

MSN has cut serious corners in its ANDA application. And this corner-cutting raises serious safety concerns. *See* Roth Decl. ¶ 67. FDA's guidance reflects what the relevant science has demonstrated: Ignoring gender or racial/ethnic differences when trying to demonstrate bioequivalence can result in lower effectiveness or an increased risk of adverse reactions for the unstudied populations, an especially concerning outcome for a drug intended to be distributed in the United States general population and to treat a disorder often suffered by women. *See infra* Section I.B.2.d.

MSN's error in excluding any representation of females or any racial/ethnic profiles other than Indian men is compounded by other issues that call into question the reliability of MSN's submitted data—including MSN's decision to use, contrary to widely accepted practice, an open-label instead of a blinded study, and FDA's observation of objectionable conditions at the analytical site. Even more concerning are serious discrepancies in MSN's bioequivalence data—including (1) dissolution data for the same lot number of the reference listed drug that diverges substantially from the dissolution data submitted by another ANDA applicant, and (2) Cmax and AUC values for MSN's supposed reference listed drug that are multiples greater than both the Cmax and AUC values FDA found for Vanda's Hetlioz® during NDA review and the values submitted by Apotex, which tested the same lot of Hetlioz® in evaluating bioequivalence of its own generic product (ANDA No. 211607). *See infra* Section I.B.3.c.

FDA's approval of MSN's ANDA without sufficient information to establish bioequivalence to Hetlioz® presents a serious risk to patient safety. Bioequivalence is a necessary prerequisite to ANDA approval because generic applicants do not conduct the full range of clinical trials that must accompany NDAs. While one of Congress's goals for the Hatch-Waxman Act was to increase price competition by enabling an abbreviated path to approval for generic drugs, that benefit to generic manufacturers came with significant obligations designed to protect patients—the generic manufacturer must develop a drug that can be proven bioequivalent to the reference listed drug. Absent the information necessary to establish

bioequivalence in the entire patient population, the safety and effectiveness of MSN's drug cannot be assumed—and may result in less effectiveness and greater and more severe adverse events than in patients taking Hetlioz®. *See* Roth Decl. ¶ 67. Vanda submits this citizen petition, with the accompanying declaration of Thomas Roth, Ph.D., and Exhibits 1-79 now in the interest of protecting a patient population it has devoted years to helping with Hetlioz®.

Vanda requests prompt agency action withdrawing MSN's ANDA approval and recalling any product distributed under ANDA No. 211654 (if any) due to the severe and immediate risks to public safety.

A. Actions Requested

Vanda asks the agency to exercise its power under 21 C.F.R. § 314.150(b)(10) and/or its inherent authority to revoke agency approval of ANDA No. 211654 on the grounds that MSN's ANDA failed to satisfy FDCA's bioequivalence requirement. Vanda also requests that FDA accordingly recall, or if necessary, seize any tasimelteon product distributed under ANDA No. 211654 (if any) because it will lack FDA approval and continue to harm the patient population.

B. Statement of Grounds

The FDCA, FDA regulations, and FDA guidance compel revocation of FDA's approval of ANDA No. 211654. ANDA applicants must submit information sufficient to show that their drug is bioequivalent to the reference listed drug through an adequately designed study. FDA's own guidance makes clear that to establish bioequivalence in a drug, the subjects in the bioequivalence study must reflect the population that will receive the drug—which necessitates including female and male subjects and subjects from racial and ethnic backgrounds that reflect the general U.S. population. *See* Roth Decl. ¶¶ 35-40. MSN's study, which included *zero* females, and *zero* individuals who were not Asian, could not establish bioequivalence to Hetlioz® for use in females and males in the United States to treat Non-24. *See id.* ¶¶ 47-59.

MSN's study also suffered from additional shortcomings that further call into question the reliability and veracity of its data and attendant conclusions. MSN designed its study as an open-label study, instead of a blinded study, thereby introducing bias into its study and analysis. *See* Roth Decl. ¶¶ 62-63. FDA observed "significant objectionable conditions" at the analytical site, which it determined impacted the reliability of other studies at the same site. *See id.* ¶¶ 62-63. And the data itself contains serious discrepancies—including a dissolution profile for the reference listed drug that conflicts with that calculated by Apotex for the *same lot number*, and AUC and Cmax data for the reference listed drug that are significantly higher than the results that FDA found for Hetlioz® during NDA review. There is no explanation provided for all these discrepancies.

FDA's approval of MSN's generic product despite the blatant insufficiency of information establishing bioequivalence of its product to Hetlioz® violates statutory and regulatory requirements and threatens to immediately harm patients suffering from Non-24 and the public interest at large. The agency must exercise its inherent or statutory authority to revoke MSN's ANDA for failure to comply with the FDCA and FDA regulations, and any tasimelteon product distributed under ANDA No. 211654 (if any) must be recalled under 21 C.F.R. §§ 7.45(a)(3), 7.40(c), or, if necessary, seized under 21 C.F.R. § 7.40(c).

1. Hetlioz® (tasimelteon)

Vanda holds approved New Drug Application No. 205677 for Hetlioz® (tasimelteon) capsules, 20 mg, approved by FDA on January 31, 2014, for the treatment of Non-24. *See* Exhibit 3, Letter from Ellis F. Unger, Dir., Office of Drug Evaluation I, Center for Drug and Evaluation Rsch., to Paolo Baroldi, Chief Medical Officer, Vanda Pharm., NDA Approval at 1 (Jan. 31, 2014) (Hetlioz® Non-24 Approval Letter). Non-24 is a serious chronic disorder in which the body cannot synchronize its internal circadian rhythmicity—the process that regulates the sleep-wake cycle—with the 24 hour day. *See* Exhibit 4, Sabra M. Abbott, *Non-24-Hour Sleep-Wake Rhythm Disorder*, 37 Neurol. Clin. 545, 545-546 (2019) (Abbott 2019); Exhibit 5, Nat'l Org. for Rare Disorders, Non-24-Hour Sleep-Wake Disorder (2017), perma.cc/8SS8-M6EX (NORD). Most people have a natural circadian rhythm that oscillates with an intrinsic period that is longer than 24 hours, but their bodies can reset that rhythm in response to daily environmental cues, like morning light (a process known as entrainment), and thereby maintain relatively consistent sleep/wake times. *See* Exhibit 5, NORD, *supra*. Individuals with Non-24, however, lack this ability.

In the classic expression of this disorder, the longer-than-24-hour circadian cycle progressively delays the sleep-wake cycle by minutes or hours each day, such that individuals with Non-24 will sleep and wake at a later time each day than the day before. Exhibit 5, NORD, *supra*. The individual's cycles of body temperature and hormone rhythms also follow a non-24-hour rhythm. *Id.* Eventually, the individual comes "all the way around the clock" and is temporarily aligned with the 24-hour day, until the cycle starts once again. *Id.* During the intervals in which the individual's body is misaligned from the day-night cycle, individuals with Non-24 experience insomnia and excessive daytime sleepiness. Exhibit 4, Abbott 2019, *supra*, at 546; Exhibit 5, NORD, *supra*. The symptoms of chronic sleep deprivation also accumulate, resulting in fatigue, depression, difficulty concentrating, and memory problems. Exhibit 5, NORD, *supra*, at 2; *see also* Exhibit 6, FDA, from Janet Woodcock, Dir., Center for Drug Evaluation Rsch., FDA, to Elizabeth Bardehenn, Sammy Almashat, and Sidney M. Wolfe, Public Citizens, Re: Docket No. FDA-2015-P-2142 at 2-3 (Jan. 27, 2020), perma.cc/M4K9-VQ24.

Hetlioz® was the first FDA-approved treatment for Non-24. In support of its NDA, Vanda submitted results from numerous clinical trials, including two studies (the SET and RESET studies) in subjects with Non-24. Exhibit 7, Center for Drug Evaluation and Research, *Application No: 205677Orig1s000 Medical Review(s)*, U.S. FOOD AND DRUG ADMIN. 18-29 (Nov. 29, 2013). The SET study involved 84 subjects, of whom 58% were male and 42% were female. Exhibit 8, Steven W Lockley et al., *Tasimelteon for Non-24-Hour Sleep-Wake Disorder in Totally Blind People (SET and RESET): Two Multicentre, Randomized, Double-Masked, Placebo-Controlled Phase 3 Trials*, 386 THE LANCET 1754, 1758 (Aug. 5, 2015) (Lockley 2015). The racial background of the subjects included American Indian or Alaska Native, Asian, Black, White, and Other. *Id.* The RESET study involved 20 subjects, 60% male and 40% female. *Id.* The racial background was predominantly white, with two participants identifying as Black or "Other." *Id.*

Vanda also conducted pharmacokinetic studies with tasimelteon to determine the absolute bioavailability of tasimelteon and to discover whether there are any age-based and sex differences in bioavailability. *See* Roth Decl. ¶¶ 14-19. In Vanda's Bioavailability Study, Vanda assessed the absolute bioavailability of tasimelteon in seven male and seven female healthy subjects, of which 57.1% were White subjects and

42.9% were Black subjects. *Id.* ¶ 14. Vanda's Bioavailability Study discovered the absolute bioavailability of tasimelteon and that tasimelteon likely undergoes first-pass metabolism. *Id.* ¶ 15. In Study 003, Vanda's predecessor, Bristol-Myers Squibb (BMS), assessed the bioavailability of tasimelteon in twenty females and twenty males, with an even distribution of elderly and young patients. *Id.* ¶ 16. Of the subjects enrolled in Study 003, 62.5% identified as White, 25% identified as Black, 7.5% identified as Hispanic/Latino, and 5% identified as Asian/Pacific Islander. *Id.* Study 003 discovered that young females experience 20 to 30% greater exposure to tasimelteon than young males. *Id.* ¶ 17. The studies conducted by Vanda were reflective of the patient population for Non-24. *Id.* ¶¶ 51, 57.

2. FDA's approval of ANDA 211654 is unlawful under the FDCA's bioequivalence requirement and agency regulations.

a. The bioequivalence requirement

The Federal Food, Drug, and Cosmetic Act (FDCA) requires that generic applicants submit "information to show that the new drug is bioequivalent to the listed drug," and FDA may not approve an ANDA if the "information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application." 21 U.S.C. §§ 355(j)(2)(A)(iv), (4)(F); *see also Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) ("[A] showing of bioequivalence is required for FDA approval.").

A drug is bioequivalent to a listed drug if

> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single does or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

21 U.S.C. § 355(j)(8)(B); *see also* 21 C.F.R. § 320.23(b)(1) ("Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.").

By regulation, FDA has concluded that, to demonstrate bioequivalence, there must be a showing of "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose *under similar conditions in an appropriately designed study*."

21 C.F.R. § 314.3 (emphasis added). Measured by FDA's own guidance, MSN's bioequivalence study design had substantial flaws that undermine any finding of bioequivalence. *See* Roth Decl. ¶ 46.

b. FDA guidance has long directed that "appropriately designed" bioequivalence studies should reflect the demographics of the intended treatment population.

For at least three decades, FDA has recognized that "[t]he patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed." Exhibit 9, U.S. FOOD & DRUG ADMIN., GUIDANCE: GUIDELINE FOR THE STUDY AND EVALUATION OF GENDER DIFFERENCES IN THE CLINICAL EVALUATION OF DRUGS; NOTICE, 58 Fed. Reg. 39,406, 39,410 (July 22, 1993), perma.cc/GQD9-ZCE8 (1993 Guidance); *see also id.* at 39,409 (given potential qualitative and quantitative differences in how drugs behave in demographic subsets of the population, "sponsors are expected to include a full range of patients in their studies"). In particular, FDA has recognized the importance of including representative proportions of subjects of each sex and race.

i. Representation of both sexes

As early as 1993, FDA recognized that "[t]here is no regulatory or scientific basis for routine exclusion of women from bioequivalence trials." Exhibit 9, 1993 Guidance, 58 Fed. Reg. at 39,406. Consistent with that recognition, FDA's guidance on bioequivalence studies over the past several decades has unwaveringly admonished—including guidance in effect at the time MSN completed and had its bioequivalence studies reviewed—that bioequivalence studies for drugs "should be representative of the general population, taking into account age, sex, and race" and that "[i]f a drug product is intended for use in both sexes, the applicant should include similar proportions of males and females in the study." Exhibit 10, U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE: BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS FOR DRUGS SUBMITTED UNDER AN ANDA 4-5 (Dec. 2013), perma.cc/H785-ATEA; *see also* Exhibit 11, U.S. FOOD & DRUG ADMIN., GUIDANCE: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS – GENERAL CONSIDERATIONS, 2003 WL 24014257, at *7 (Mar. 1, 2003) ("This guidance recommends that in vivo BE studies be conducted in individuals representative of the general population, taking into account age, sex, and race. We recommend that if the drug product is intended for use in both sexes, the sponsor attempt to include similar proportions of males and females in the study.").

As Diana Vivian, PhD, the Acting Associate Director of the Division of Bioequivalence II put it, "we've always recommended applicants to include similar proportions of males and females in the [bioequivalence] study." Exhibit 12, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA*, U.S. FOOD AND DRUG ADMIN. 1:00:50-1:01:13 (Feb. 24, 2022), available at www.youtube.com/watch?v=jGffUS-8JVA (FDA Bioequivalence Webinar). Indeed, even now, FDA guidance continues to direct that, "unless otherwise recommended in a [product-specific guidance], … [i]f a drug product is intended for use in both sexes, the applicant should include similar proportions of males and females in the study or provide a justification supporting the use of a single-sex population." Exhibit

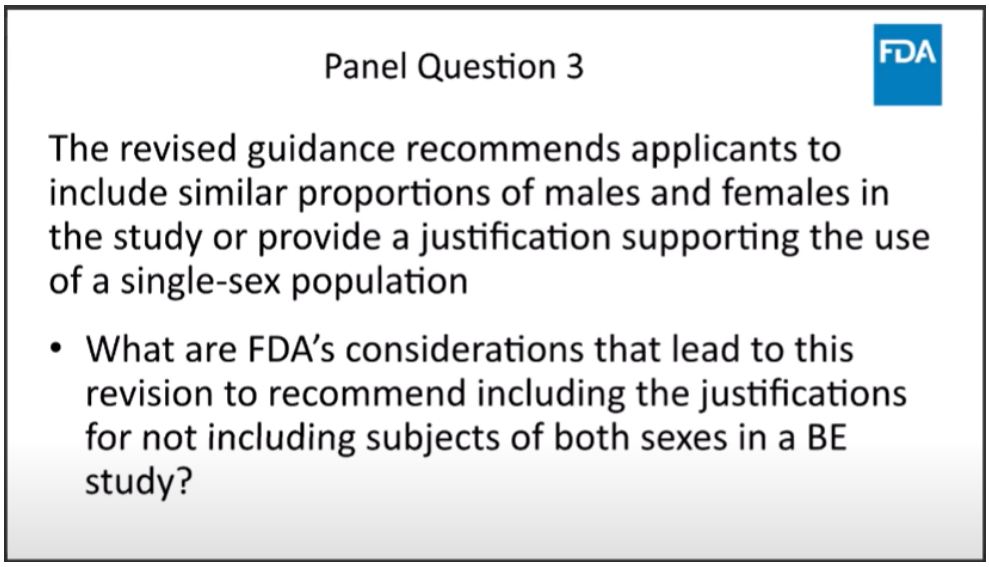
13, U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE: BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS FOR DRUGS SUBMITTED UNDER AN ANDA 4-5, perma.cc/HHA4-6PRX.[2]

FDA's guidelines are consistent with other organization recommendations and the general scientific consensus that bioequivalence studies should include male and female subjects.[3] *See generally* Roth Decl. ¶¶ 35-37. For example, FDA helped develop similar guidelines for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, which recommends that "[i]f a drug product is intended for use in both sexes, it is recommended the study include male and female subjects." Exhibit 15, U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE: BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS FOR DRUGS SUBMITTED UNDER AN ANDA 3 (2023), perma.cc/6MUM-TEUA. And the World Health Organization likewise recommends that "[i]f the pharmaceutical product is intended for use in both sexes, the sponsor should include both males and females in the [bioequivalence] study." Exhibit 16, *WHO Technical Support Series: WHO Expert Committee on Specifications for Pharmaceutical Preparations* 198, WHO (2017), perma.cc/HFH8-PJWU.

These guidelines are based on and justified by sex-related differences in pharmacokinetics and pharmacodynamics. *See* Roth Decl ¶¶ 25-27. FDA acknowledged and described these scientific differences in a webinar in February 2022 offered by personnel in the Office of Generic Drugs (OGD). *See* Exhibit 12, FDA Bioequivalence Webinar, *supra*. Specifically, OGD personnel discussed the following panel question:

[2] It was not until years after MSN conducted and submitted its all-male bioequivalence study that FDA revised its guidance to give ANDA applicants the opportunity to justify excluding female subjects. *See* Exhibit 12, FDA Bioequivalence Webinar at 1:00:50-1:01:13 (Diana Vivian, PhD, explaining that FDA was "not making a major change here; we've always recommended applicants to include similar proportions of males and females in the study. *Really the change is just the opportunity to provide a justification to support the use of a single-sex population, if that's chosen*." (emphasis added)).

[3] *See, e.g.*, Exhibit 14, Manuel Ibarra et al., *Sex Effect on Average Bioequivalence*, 39 Clin. Therapeutics 23, 31 (2017), perma.cc/Y75A-YGKY (Ibarra 2017) ("[I]t is necessary for BE studies to include similar proportions of men and women (50-50) unless the product (eg, oral contraceptives) is intended for use in only 1 of the sexes or the study entails a specific risk to 1 sex.").



Id. at 57:40-1:01:40. Liang Zhao, PhD, explained that physiological differences, including pH, fluid volume in GI, gut transit time, metabolism may be different across sex groups and affect bioequivalence conclusion. *Id.* at 59:08-59:38.

Other literature also confirms the biological differences. *See* Roth Decl. ¶¶ 25-27. For example, references reflect that are differences in gastrointestinal physiology between males and females that can affect a drug's oral bioavailability and absorption windows. Exhibit 14, Ibarra 2017, *supra*, at 25; *see also* Exhibit 17, Offie P. Soldin et al., *Sex Differences in Drug Disposition*, 2011 J. BIOMED BIOTECHNOL. 1, 2 (2011) (Soldin 2011) (noting differences in gut transit time between men and women and sex differences in bile acid composition and concentrations of cholic and chenodeoxycholic acid, and study results showing that Cmax and AUC were greater in women in the vast majority of the time).

Studies have also shown that the phenotypic expression of many P450 enzymes differ in men versus women, suggesting sex differences in absorption and bioavailability. Exhibit 17, Soldin 2011, *supra*, at 2, 5-6. Additionally, chronobiology differences in sex hormones often result in higher intrasubject variability for female subjects. Exhibit 14, Ibarra 2017, *supra*, at 26-27; *see also* Exhibit 17, Soldin 2011, *supra*, at 5-9; Exhibit 18, G. Koren et al., *Gender Differences in Drug Bioequivalence: Time to Rethink Practices*, 93 CLINICAL PHARMACOLOGY & THERAPEUTICS 260 (2013) (Koren 2013) ("[I]n most cases, variability among women is much larger, precluding generalizability from men to women."). Accordingly, "[bioequivalence] cannot be deemed similar in men and women for any medication, and, if a generic is to be used also by women, it has to be tested with sufficient power in women." Exhibit 18, Koren 2013, *supra*, at 2; *see also* Exhibit 14, Ibarra 2017, *supra*, at 24 ("[E]xtrapolation of [bioequivalence] results from the male population to the female population is not always valid."); Exhibit 17, Soldin 2011, *supra*, at 1 (noting guidance "to ensure that both sexes are represented in all phases of clinical trials" because "pharmacokinetics, pharmacodynamics, and responses during clinical trials differ between men and women").

ii. Racial and ethnic representation

Ethnicity and race are also recognized characteristics that may affect pharmacokinetics. *See, e.g.*, Exhibit 19, J.A. Johnson, *Influence of Race or Ethnicity on Pharmacokinetics of Drugs*, 86 J. PHARM. SCI. 1328, 1332 (Dec. 1997) (explaining that racial differences can be found in "(1) bioavailability for drugs which undergo gut or hepatic first-pass metabolism, (2) protein binding, (3) volume of distribution, (4) hepatic metabolism, and (5) renal tubular secretion"); Exhibit 9, 1993 Guidance, 58 Fed. Reg. at 39,406 ("A number of demographic characteristics may affect pharmacokinetics: … ethnic groups [may] differ in the prevalence of metabolic abnormalities such as slow acetylation and G6PD deficiency … ."); *see also* Roth Decl. ¶¶ 28-29. In fact, drugs like tasimelteon that undergo first-pass metabolism are more likely to exhibit race-based differences. *See id.* ¶ 56.

Other racial characteristics can affect pharmacokinetics. For example, research has shown that certain transporters and CYP enzymes are "markedly lower in Asian/Indian and African American populations compared to a North American/Caucasian one." Exhibit 20, Deniz Ozdin et al., *Influence of Different Populations on Pharmacokinetic Bioequivalence Results: Can We Extrapolate Bioequivalence Results from One Population to Another?*, 23 J. OF PHARMACY AND PHARM. SCI. 357, 359 (2020) (Ozdin 2020); *see also* Exhibit 21, MV Relling et al., *Racial and Gender Differences in N-acetyltransferase, xanthine oxidase, and CYP1A2 activities*, 52 CLIN. PHARMACOL. THER. 643, 654 (1992) ("Race was also a significant predictor of the CYP1A2 ratio, with white subjects having higher activity … ."). And a review of bioequivalence study data for certain drug products revealed that the food effect for the vast majority of studied reference products was significantly different between North and American and Indian populations—suggesting that "two formulations that are assessed as bioequivalent in one population may not necessarily be bioequivalent in another one." Exhibit 20, Ozdin 2020, *supra*, at 383. This review ultimately concluded "that extrapolating bioequivalence study results from one population/region to another may not always be appropriate." *Id.* at 384.

Because of these differences, some countries forbid the use of subjects who are ethnically different from the country's population if there are differences in dissolution rates between the reference and test products or "if ethnic differences in gastrointestinal physiology including the level of gastric acidity are thought to affect the evaluation of bioequivalence due to formulation characteristics." Exhibit 22, *English Translation of Attachment 1 of PSEHB/PED Administrative Notice: Guideline for Bioequivalence Studies of Generic Products: Q & A*, NAT'L INST. OF HEALTH SCI. (Mar. 19, 2020), perma.cc/2QHN-YMCN.

FDA itself has touted that "[e]nrollment in clinical trials should reflect the diversity of the population that is ultimately going to use the treatment." Exhibit 23, *FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials*, U.S. FOOD AND DRUG ADMIN. (Apr. 13, 2022), perma.cc/E67P-3JKB (FDA News Release 2022). Vanda has implemented that suggestion, but MSN has not. *See* Roth Decl. ¶¶ 58-59.

c. MSN's wholesale exclusion of females and non-Asian males from its study renders its information insufficient to establish bioequivalence.

MSN flagrantly flouted FDA's guidance and well-accepted principles of bioequivalence study design. MSN's subject population bore no resemblance to the target drug population. *See generally* Roth Decl. ¶¶ 47-59. MSN's study included *only* males, no females; and the only males included were males in India. *See* Exhibit 1, MSN Bioequivalence Review at 14 (44 male subjects, 0 female subjects), 23 (44 Asian male subjects), 18 (identifying a single clinical site in Hyderabad, India). Hetlioz® and MSN's generic drug product, however, are indicated for treating Non-24 in both sexes in the United States. *See* Exhibit 24, *Highlights of Prescribing Information, HETLIOZ® (tasimelteon)* at 1, U.S. FOOD AND DRUG ADMIN., https://perma.cc/D9FG-DN6W (Dec. 2020) (Hetlioz® Label) ("HETLIOZ capsules are indicted for the treatment of … Non-24-Hour Sleep-Wake Disorder (Non-24) in adults … [and] Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older."); Exhibit 25, *Highlights of Prescribing Information, Tasimelteon- Tasimelteon Capsule: Amneal Pharmaceuticals NY LLC*, DAILYMED (last visited May 14, 2023)[4] ("Tasimelteon capsules are indicated for the treatment of: … Non-24-hour Sleep-Wake Disorder (Non-24) in adults"). Non-24 is a disorder that occurs in both the male and female populations. *See* Roth Decl. ¶ 48. Although the exact incidence of Non-24 in males versus females is unknown, "[a]mong support groups the number of male and female patients are roughly equal." Exhibit 5, NORD, *supra*. Thus, as a general matter, FDA guidance instructs that a bioequivalence study should be conducted in both males and females and in non-Asian males representative of the U.S. population.

Thus, MSN's study should have included females and males, as well as individuals from a range of races and ethnicities, reflective of the overall U.S. population.

This is specifically true in the context of tasimelteon, for two reasons.

First, FDA's tasimelteon-specific guidance directed that any bioequivalence study involving tasimelteon should include male and female subjects in the general population.

[4] Based on the National Institute of Health's DailyMed website (*see* Exhibit 25), Vanda understands that MSN's tasimelteon product is being or will be distributed by Amneal Pharmaceuticals NY LLC.

Recommended Studies:	One in vivo study
1.	Type of study: Fasting Design: Single-dose, two-way crossover in vivo Strength: 20 mg Subjects: Healthy males and nonpregnant females, general population Additional comments: Females subjects should not be pregnant or lactating, and, if applicable, should practice abstinence or contraception during the study

Exhibit 2, 2015 Guidance, *supra*. Accordingly, under FDA's guidance, MSN's study should have included females and males, as well as individuals from a range of races and ethnicities, reflective of the overall U.S. population. *See* Roth Decl. ¶¶ 41-42. Because MSN's study did not, FDA unlawfully concluded that "the demographics profile of subjects completing the bioequivalence study [is] in agreement with the current drug product recommendation." Exhibit 1, MSN Bioequivalence Review, *supra*, at 23; *see also* Roth Decl. ¶¶ 47-59.

Second, as noted above, Vanda's clinical studies included roughly the same number of male and female subjects. Exhibit 8, Lockley 2015, *supra*, at 1758; *see also* Roth Decl. ¶¶ 14, 16. And, as reflected in FDA's review of Hetlioz®, differences between males and females in Vanda's clinical study results indicate potential pharmacokinetic differences between males and females: "the mean overall AUC of tasimelteon [in females] was approximately 32% higher and Cmax was about 60% higher when compared to males." Exhibit 26, Center for Drug Evaluation and Research, *Application No: 205677Orig1s000 Clinical Pharmacology and Biopharmaceutic(s)* 7, U.S. FOOD AND DRUG ADMIN. (Dec. 4, 2013), https://perma.cc/6P5S-SDC9 (Hetlioz® Clinical Pharmacology and Biopharmaceutics Review(s)) *see also* Roth Decl. ¶¶ 25-29. Vanda's FDA-approved Hetlioz® label accordingly observes that "[t]he mean overall exposure of tasimelteon was approximately 20-30% greater in female than in male subjects." Exhibit 24, Hetlioz® Label at 10, perma.cc/EA4X-YEU8. Indeed, the only population that MSN studied (i.e., Asian males aged 18 to 40) comprises an age range similar to that for which Vanda measured a disparity in bioavailability between the sexes (*i.e.*, young male and female subjects aged 18 to 45). *See* Roth Decl. ¶ 23. This is yet a further reason to believe that, had MSN included female subjects in its bioequivalence study for its tasimelteon product, it may have observed an overall AUC and Cmax in females that is incommensurate with Hetlioz® per FDA standards. *See id.* ¶¶ 47-51.

Because of the specific observations of tasimelteon, even had FDA not wrongfully concluded that MSN complied with the product specific guidance when it had not, there still would have been no justification for MSN's failure to study bioequivalence in male and female subjects and in a population reflective of the racial and ethnic makeup of the United States.

MSN's failure to comply with the guidelines and to use instead only a very narrow and specific demographic for its study population skewed its results in favor of finding bioequivalence and rendered the information it submitted insufficient to establish the bioequivalence of MSN's product to Hetlioz® in the general population as required by the FDCA and regulations. *See supra* at I.B.2.a; *cf.* Exhibit 14, Ibarra

2017, *supra*, at 25 (explaining that the sex of subjects can be one of the sources for subject-by-formulation interactions that has the highest impact on bioequivalence conclusions).

d. FDA's approval of ANDA 211654 harms Non-24 patients and the public interest.

FDA's approval of MSN's ANDA based on a faulty bioequivalence study has serious consequences for patient safety. Generic applicants are not required to conduct the full panoply of clinical trials that must be done to establish safety and effectiveness during the development of a reference listed drug. Instead, they may piggyback off of FDA's previous finding that the reference listed drug is safe and effective—but they can only do this if they show that their drug is bioequivalent. 21 U.S.C. § 355(j)(2)(A)(iv); *see also* Exhibit 27, Ltr. from Janet Woodcock, M.D., Director, Ctr. for Drug Eval. & Research, FDA, to Philip J. Honerkamp, Vice Pres., Strategic Operations, Jazz Pharmaceuticals, Inc., Re: Docket No. FDA-2012-P-0499 at 3 (Nov. 13, 2012), perma.cc/4RWP-ER5F (noting that the "basic assumption" underlying the Hatch-Waxman Act's provisions permitting ANDA applicants to rely on FDA's previous finding that the reference listed drug is safe and effective is that drug products that meet the bioequivalence requirement and other criteria "are therapeutically equivalent and may be substituted for each other"). Absent a showing of bioequivalence, there is no basis for assuming the safety and effectiveness of the generic drug product. *See* Roth Decl. ¶ 67.

"The consequence of ignoring gender differences in BE studies may result on the one hand in less effectiveness and on the other hand in an increased risk of adverse drug reactions." Exhibit 18, Koren 2013, *supra*, at 2; *see also* Exhibit 17, Soldin 2011, *supra*, at 10 ("[S]ex differences in drug disposition and response … may affect drug safety and effectiveness."). Indeed, this has been borne out through history. As FDA has recognized, females and racial minorities have historically been excluded from bioequivalence and other clinical drug studies. *See* Exhibit 9, 1993 Guidance, 58 Fed. Reg. at 39,407-39,408; Exhibit 30, FDA, *Draft Guidance for Industry*, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials,* at 1 (2022), perma.cc/258E-ABDA. An analysis of the data in the FDA Adverse Events Reporting System (AERS) revealed that women experience more adverse events than men, and in general, the adverse events are more serious. Exhibit 17, Soldin 2011, *supra*, at 2; *see also* Exhibit 18, Koren 2013, *supra*, at 25 ("[I]t is well documented that women experience more adverse events than men, and in general these adverse events are of a more serious nature."). And eight of the ten drugs withdrawn from the market between January 1, 1997 through December 2000 were withdrawn to due to risks of adverse effects in women. Exhibit 17, Soldin 2011, *supra*, at 2; Exhibit 18, Koren 2013, *supra*, at 2. Similarly, racial differences "can make a treatment more or less toxic for one racial or ethnic group than another" and/or "less effective for certain groups." Exhibit 23, FDA News Release 2022, *supra*; *see also* Roth Decl. ¶ 28.

Thus, FDA's approval of MSN's ANDA without information establishing bioequivalence of MSN's product and Hetlioz® for the general U.S. population creates the risk of such adverse events and ineffectiveness in individuals who take MSN's product.

3. Concerns about MSN's data call into question the accuracy and sufficiency of MSN's bioequivalence information.

Beyond the serious deficiencies in the bioequivalence study design itself, there is also reason to question the veracity and reliability of the data submitted from that study. And absent confidence in the information submitted, that information is insufficient to establish bioequivalence of MSN's product to Hetlioz®.

a. MSN's failure to blind its study contravenes accepted norms and introduces bias into its study.

First, MSN introduced bias into its study by conducting its study as an open-label, as opposed to a double-blind study. *See* Exhibit 1, MSN Bioequivalence Review, *supra*, at 22. Conducting an open-label clinical trial is contrary to general recommendations and guidelines for clinical trials, which call for studies to be double-blind—that is, where neither the subject nor the investigator knows which treatment is administered to which subject. *See* Exhibit 29, FDA, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, E10 CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS at 4 (2001) (FDA 2001 Guidance); Exhibit 30, Upendra C. Galgatte, et al., *Study on Requirements of Bioequivalence for Registration of Pharmaceutical Products in USA, Europe and Canada*, 22 SAUDI PHARMACEUTICAL J. 391, 397 (2013); Exhibit 31, EUROPEAN MEDS. AGENCY, ICH GUIDLINE E8 (R1) ON GENERAL CONSIDERATIONS FOR CLINICAL STUDIES 18 (2022). Blinding studies is critical to "minimiz[ing] the potential biases resulting from differences in management, treatment, or assessment of patients, or interpretations of results." Exhibit 29, FDA 2001 Guidance, *supra*, at 4; *see also* Roth Decl. ¶ 44; Exhibit 32, Thomas F. Monaghan et al., *Blinding in Clinical Trials: Seeing the Big Picture*, MEDICINA (2021); Exhibit 33, Mandy Wan et al., *Blinding in Pharmacological Trials: The Devil is in the Details*, 98 ARCHIVES DISEASE CHILDHOOD 656, 656 (2013). MSN's failure to blind its study introduces bias from both the investigators and the enrolled subjects, calling into question the validity of MSN's bioequivalence study. Roth Decl. ¶ 62-63.

b. "Significant objectionable conditions" at the analytical site undermine the reliability of MSN's data.

The conditions at the analytical site—as documented by FDA—further undermine the reliability of MSN's dissolution and bioequivalence data.

Under the Federal Food, Drug, and Cosmetic Act, the FDA may not approve an ANDA if the "methods used in, or the facilities and controls used for" manufacturing, processing, packing, and testing of the drug are "inadequate to assure and preserve [the drug's] identity, strength, quality, and purity." 21 U.S.C. § 355(j)(4)(A); *see also* Exhibit 34, U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM 7346.832 ch. 46 at 8 (2022), perma.cc/LR5U-SFGD. In particular, following the rampant submission of fraudulent bioequivalence data by generic companies in the wake of the passage of the Hatch-Waxman Act, FDA established new systems and requirements to ensure the integrity of applications. *See* Exhibit 35, Garth Boehm et al., *Development of the Generic Drug Industry in the US After the Hatch-Waxman Act of 1984*, 3 ACTA PHARMACEUTICA SINICA B 297, 299-300 (2013) (noting that only 6 of 39 generic drug companies investigated by Subcommittee on Oversight and Investigations appeared free of criminal or regulatory

taint). Thus, FDA inspectors must ensure that the data submitted with the ANDA is accurate and complete, including verifying the integrity of the bioequivalence study. Exhibit 34, Compliance Program 7346.832 ch. 46, *supra*, at 36; *see also* Exhibit 36, U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM 7348.004 ch. 48 at 7 (2018), perma.cc/US92-LHUW (objectives of the *in vivo* BA/BE Bioresearch Monitoring Program include "ensur[ing] the quality, integrity and validity of clinical, analytical, and statistical data from BA/BE studies" and "ensur[ing] compliance with applicable FDA regulations and . . . identify[ing] significant deviations").

During FDA's inspection of MSN's analytical site, "[s]ignificant objectionable conditions were observed . . . that impacted the reliability of a portion of the audited studies," resulting in the inspector issuing a Form FDA 483. Exhibit 1, MSN Bioequivalence Review, *supra*, at 15-17. The issuance of that form indicated that the inspector had observed conditions "that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts," and that would indicate that any drug in the facility "is being prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health." Exhibit 37, *FDA Form 483 Frequently Asked Questions*, U.S. FOOD & DRUG ADMIN., perma.cc/JG6W-R4M5 (last visited May 12, 2023); *see also* Roth Decl. ¶ 45. Upon review, OSIS reviewers confirmed that THB and EHB concentrations were not accurately measured and impacted the reliability of data. Exhibit 1, MSN Bioequivalence Review, *supra*, at 16. Nevertheless, OSIS concluded that "the inspectional findings were isolated in nature" and were "not likely to have an impact on the outcomes of the current ANDA." *Id.* at 17.

But together with the study design flaws discussed above, the objectionable conditions observed in MSN's test facility raise serious concerns about the reliability of MSN's bioequivalence data. *See* Roth Decl. ¶ 65. And especially when considered in light of the significant discrepancies in MSN's data discussed below, there is a strong basis for concluding that the objectionable conditions observed at MSN's test facility did impact the reliability of MSN's bioequivalence data.

c. Discrepancies in MSN's dissolution and bioequivalence data compound concerns about the veracity of MSN's data.

Finally, the data submitted by MSN contains such obvious discrepancies as to raise grave concerns about that data and, thus, whether it is sufficient to establish bioequivalence.

First, MSN's dissolution profile for the reference listed drug is inconsistent with the dissolution profile for the alleged *same lot* of the reference listed drug tested by Apotex. According to their reviews, both MSN and Apotex tested the same lot of the reference listed drug—Lot no. 3140788 (Exhibit 38, Redacted Biopharmaceutics Review and Report from Division of Bioequivalence Review for ANDA No. 211607 at 23, 24 (Apotex Bioequivalence Review); Exhibit 1, MSN Bioequivalence Review, *supra*, at 43)—so one would expect to see the same dissolution results.

But MSN's dissolution profile of "Hetlioz®" Lot 3140788 differs wildly from Apotex's. While Apotex's data shows Hetlioz® reaching 100% release in 15 minutes,[5] MSN's data *never* shows Hetlioz® reaching 100% release, even after 30 minutes. *Compare* Exhibit 38, Apotex Bioequivalence Review, *supra*, at 24, *with* Exhibit 1, MSN Bioequivalence Review, *supra*, at 43-45.

Second, as we have explained, MSN only tested Indian males. And, as FDA noted during its review of the Hetlioz® NDA, female subjects taking Hetlioz® had higher Cmax and AUC than male subjects. *See* Roth Decl. ¶ 17. By comparing the NDA-reported population data to the alleged reference listed drug, we observe that MSN's results for the reference listed drug it tested are *significantly* higher than Vanda observed in Hetlioz®. For males, the MSN Hetlioz® values are 2.6x and 2.0x higher than the Vanda Hetlioz® values for Cmax and AUC∞. And these values in males are even higher than Vanda's Hetlioz® showed in *females*, which FDA found had a 20-30% greater exposure. MSN's findings also diverge substantially from the Cmax and AUC∞ found for the same lot of reference listed drug that was tested by another generic manufacturer (Apotex) with an approved ANDA for tasimelteon (No. 211607).

	MSN's Hetlioz (N=44)[6]	Apotex's Hetlioz (N=24)[7]	Vanda's Hetlioz® (5 PK studies, N=115)[8]		
Sex	Only Male	Both	Both	Male Est.	Female Est.
Cmax (ng/ml)	461.18	249.81	234.9	180.69[9]	289.11[10]
AUC∞(ng*hr/ml)	699.08	346.02	411.4	354.66[11]	468.14[12]

[5] Apotex's chart labels its dissolution "collection time" in "hours." *See* Exhibit 38, Apotex Bioequivalence Review, *supra*, at 23. We believe this to be a typographical error as it would be highly unusual to conduct dissolution testing other than in minutes, and the "proposed specification" is designated in an increment of "20 minutes." *Id.*

[6] *See* Exhibit 1, MSN Bioequivalence Review, *supra*, at 3.

[7] *See* Exhibit 38, Apotex Bioequivalence Review, *supra*, at 2.

[8] *See* Exhibit 26, Hetlioz® Clinical Pharmacology and Biopharmaceutics Review(s) at 7, 17-18, perma.cc/42G9-QNVM. We calculated these amounts by taking the Cmax of 234.9 and AUC of 411.4, assuming a 50/50 split among males and females, and accounting for the 60% higher Cmax and 32% higher AUC reflected in females as described on pages 5 and 11.

[9] Male Cmax = (234.9*2) / 2.6 = 180.69.

[10] Female Cmax = (234.9*2) – 180.69 = 289.11.

[11] Male AUC = (411.4*2) / 2.32 = 354.66.

[12] Female AUC = (411.4*2) – 354.66 = 468.14.

These multiple unexplained discrepancies in MSN's data should have precluded approval of MSN's ANDA absent explanation for them. A generic cannot, by definition, satisfy the obligation to show that "the rate and extent of absorption of the drug" are not "significant[ly] differen[t] from the rate and extent of absorption *of the listed drug*" (21 U.S.C. § 355(j)(8)(B) (emphasis added)) when the ANDA applicant's results are so widely divergent from the FDA's own analysis of the rate and extent of absorption of the listed drug and another ANDA applicant's results for the very same lot of the listed drug. MSN's data contains several hallmarks of lack of credibility, which means its application was "insufficient to show that the drug is bioequivalent," and its ANDA approval should be withdrawn. *Id.* § 355(j)(4)(F).

4. FDA has statutory and inherent authority to correct its mistake by revoking MSN's ANDA approval and recalling any product.

21 U.S.C. § 355(e) specifies that the agency may "withdraw approval of an application with respect to any drug under this section if [it] finds … (3) on the basis of new information before [FDA] with respect to such drug, evaluated together with the evidence available to [FDA] when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof … [or] (5) that the application contains any untrue statement of a material fact." Because FDA erred in approving MSN's label given the shortcomings in MSN's bioequivalence study design and the discrepancies in its data, FDA may now correctly determine that MSN failed to provide sufficient information to establish bioequivalence and proceed to withdraw its approval.

Moreover, "the FDA is not limited to these statutorily provided circumstances for withdrawing ANDA approval, as it may also rescind an ANDA approval under its 'inherent authority' if done within a reasonable period of time." *Lannett Co., Inc. v. United States Food & Drug Admin.*, 300 F. Supp. 3d 34, 38 (D.D.C. 2017); *cf. Mazaleski v. Treusdell*, 562 F.2d 701, 720 (D.C. Cir. 1977) ("We have many times held that an agency has the inherent power to reconsider and change a decision if it does so within a reasonable period of time."). Thus, the agency has previously exercised this inherent authority to revoke ANDA approvals upon realizing that they were unlawful. *See, e.g.*, *Lannett Co.*, 300 F. Supp. 3d at 40 (exercising inherent authority to revoke ANDA approval upon discovering that the agency had wrongly certified that the generic manufacturer was in cGMP compliance); *Am. Therapeutics, Inc. v. Sullivan*, 755 F. Supp. 1, 1 (D.D.C. 1990) (similar); *Mylan Lab'ys, Inc. v. Thompson*, 389 F.3d 1272, 1281 (D.C. Cir. 2004) (exercising inherent authority to revoke ANDA approval after a district court concluded that the name brand drug manufacturer was still entitled to a period of patent exclusivity); *Apotex Inc. v. U.S. Food & Drug Admin.*, 508 F. Supp. 2d 78, 82 (D.D.C. 2007) (similar).

Upon the revocation of MSN's ANDA approval, FDA has the authority to order a recall of product distributed under ANDA No. 211654 (if any). Recalls "protect the public health from distributed products [that are] in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and other laws administered by FDA." Exhibit 39, U.S. FOOD & DRUG ADMIN., GUIDANCE: INITIATION OF VOLUNTARY RECALLS UNDER 21 CFR PART 7, SUBPART C 1 (2022), perma.cc/9AXL-CSJ7; *see also* Exhibit 40, *FDA's Role in Drug Recalls*, U.S. FOOD AND DRUG ADMIN. (July 3, 2018), perma.cc/9CU8-NHRW ("A drug recall [] is the most effective way to protect the public from a … potentially harmful product."). Recalls

are appropriate when "agency action is necessary to protect the public health and welfare." 21 C.F.R. § 7.45(a)(3).

A "recall may be undertaken … at the request of the Food and Drug Administration," and a recall request is appropriate for "urgent situations" and should be "directed to the firm that has primary responsibility for the manufacture and marketing of the product that is to be recalled." 21 C.F.R. § 7.40(b). Additionally, seizure is appropriate "where the agency has reason to believe that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing." *Id.* § 7.40(c).

Given that FDA's approval of MSN's ANDA despite its deficient bioequivalence study design and questionable data was clearly erroneous and will put patients in harm's way, the agency must exercise its inherent authority in this case to reverse its mistake by immediately revoking MSN's ANDA approval and recalling any product distributed under ANDA No. 211654 (if any). The ongoing violation and risk of harm make this an "urgent situation[]." 21 C.F.R. § 7.40(b). As discussed above, because MSN has not established the bioequivalence of its product and Hetlioz® in the general public, the safety and effectiveness of MSN's product cannot be assumed, and individuals taking MSN's product face a risk of serious adverse events. *See* Roth Decl. ¶ 67.

There is no justification for delay. Hetlioz® has been available since 2014, and patients suffering from Non-24 can continue their treatment by using Hetlioz® even if products cannot be distributed under ANDA No. 211654.

For these reasons, FDA must revoke its approval of MSN's ANDA.

C. Environmental Impact

This petition is subject to a categorical exclusion under 21 C.F.R. § 25.30(h).

D. Economic Impact

Information will be submitted if requested by the Commissioner following review of this petition.

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.

Sincerely,

Paul W. Hughes