BEFORE THE UNITED STATES JUDICIAL PANEL ON MULTIDISTRICT LITIGATION

IN RE: CHANTIX (VARENICLINE) MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION (No. II)	MDL No. 3050

PFIZER INC.'S RESPONSE TO PLAINTIFF COUNTY OF MONMOUTH'S MOTION FOR TRANSFER OF ACTIONS PURSUANT TO 28 U.S.C. § 1407[1]

Pursuant to 28 U.S.C. § 1407 and Rule 6.2(a) of the Rules of Procedure of the Judicial Panel on Multidistrict Litigation ("the Panel"), Pfizer Inc. ("Pfizer") respectfully submits this Response to Plaintiff County of Monmouth's ("Movant's") Motion for Transfer of Actions for coordinated pretrial proceedings (the "Motion").

INTRODUCTION

Plaintiff's Motion should be denied at this time. Transfer pursuant to 28 U.S.C. § 1404 is well underway and working efficiently to date, consistent with the Panel's guidance that parties should first seek alternatives to centralization under Section 1407 before asking the Panel to intervene. With that guidance in mind, given the small number of actions and few plaintiffs' counsel involved, Pfizer has, from the outset of this litigation, coordinated with plaintiffs' counsel on possible venues for these actions. As part of that coordination, the parties agreed to stay all other then-filed actions and litigate Pfizer's Section 1404 transfer motion in a single case, which Pfizer sought to transfer from the plaintiffs' preferred district, the Southern

[1] Pfizer objects to Plaintiff County of Monmouth's proposed case name of "In re: Chantix (Varenicline) Marketing, Sales Practices, and Products Liability Litigation" because (1) it does not accurately describe the Related Actions, since, as Plaintiff concedes, "none asserts a claim for personal injury," Pl.'s Mot. at 1, and (2) it likely will lead to confusion since the Panel previously established in 2009 a multidistrict litigation with a similar case name ("In re: Chantix (Varenicline) Products Liability Litigation"), involving very different factual allegations and legal claims, which terminated in 2016. Should the Panel find centralization warranted under Section 1407, Pfizer requests that it assign a new case name that more accurately reflects the nature of the Related Actions and avoids confusion with the prior MDL, such as "In re: Chantix (Varenicline) Consumer Litigation."

District of Florida ("S.D. Fla."), to the Southern District of New York ("S.D.N.Y."), which Pfizer views as the appropriate venue because it is the district of the first-filed action and the one district that would have jurisdiction over all similar actions. The S.D. Fla. recently granted Pfizer's Section 1404 transfer motion. After Pfizer informed plaintiffs' counsel and the judge in the S.D.N.Y. that it would begin filing Section 1404 transfer motions in the remaining actions, Plaintiff in the then last-filed action—in which Pfizer also has a pending Section 1404 transfer motion to the S.D.N.Y.—filed this Motion. Under these circumstances, the Panel should not encourage litigants to ignore the Panel's long-standing direction to exhaust other options before seeking centralization under Section 1407 and should deny the Motion. Alternatively, if the Panel believes that centralization is warranted now, the Related Actions[2] should be transferred and coordinated for pretrial proceedings in the S.D.N.Y.

FACTUAL BACKGROUND

A. Pfizer's Precautionary, Voluntary Recall of Chantix, an Effective Smoking Cessation Aid.

Cigarette smoking is the single most preventable cause of death in the United States. One in three cancer deaths are due to cigarette smoking. Ex. 1, at 1. Chantix is a highly effective prescription medicine that has helped patients quit smoking, thereby significantly reducing their risk of cancer and other serious health conditions. Ex. 2. Chantix also has a strong safety record, supported by an extensive clinical program and more than 15 years of real-world use globally. Ex. 3. During that time, no medical, scientific, or regulatory body has suggested that Chantix could cause or increase the risk of cancer.

In 2018, FDA began investigating the potential presence of nitrosamines in medicines. Ex. 4, at 2. Nitrosamines are organic compounds common in water and foods, including cured

[2] The pending cases are listed in the accompanying Schedule of Actions (collectively, "the Related Actions").

and grilled meats, dairy products, and vegetables. Ex. 5. Because nitrosamines are ubiquitous in the environment, nearly every human is exposed to some level of nitrosamines in their daily lives. *Id.* Certain nitrosamines—several of which are present in cigarettes—are classified by the World Health Organization ("WHO") as probable or possible human carcinogens (i.e., substances that could cause cancer in humans). Ex. 4, at 5.

In evaluating nitrosamine levels in medicines, FDA and other regulators have established acceptable daily intake ("ADI") thresholds, which extrapolate the amount a person could ingest every single day for her entire life without increasing her theoretical cancer risk above 1 in 100,000. Ex. 4, at Appendix B. The ADI threshold assumes that a person will take the medicine every day for 70 years. *Id.* Because patients are typically prescribed Chantix for twelve to twenty-four weeks only, the 70-year daily intake assumption used to set FDA's ADI limit does not reflect how Chantix is actually prescribed and used: for weeks, not decades.

Nonetheless, on July 19 and August 16, 2021, after testing of Chantix revealed the presence of a novel nitrosamine (N-nitroso-varenicline), Pfizer voluntarily recalled consumer lots of the product and offered patients reimbursement for the cost of any unused Chantix. In September 2021, Pfizer further expanded the voluntary recall to include all Chantix lots. FDA press releases at the time informed patients that "there is no immediate risk to patients taking this medication. The health benefits of stopping smoking outweigh the theoretical potential cancer risk from the nitrosamine." Ex. 6. Moreover, as FDA acknowledged, "[t]here are no data available to directly evaluate the carcinogenic potential of N-nitroso-varenicline." Ex. 7. As a result, the Chantix recall was classified as Class II, which means that FDA determined that "the probability of serious adverse health consequences is remote." Ex. 8. Thus, the decision to

voluntarily recall Chantix was a precautionary measure, not based on evidence of any actual cancer risk associated with real-world use of the medication.

B. The Related Actions.

All of the Related Actions are consumer class actions resulting from the plaintiffs' alleged purchase and/or reimbursement of Chantix. Plaintiffs allege that the Chantix they purchased and/or reimbursed was "worthless" because it had been voluntarily recalled. *See Harris v. Pfizer Inc.*, No. 21CV6789 (DLC), 2022 WL 488410, at *1 (S.D.N.Y. Feb. 16, 2022). They assert similar claims of breach of express warranty, breach of implied warranty, violation of consumer protection statutes, fraud, negligent misrepresentation, and unjust enrichment, for which the plaintiffs seek economic damages and, in some cases, medical monitoring. There are no personal injury claims. *See* Pl.'s Mot. at 1.

Currently, there are eleven Related Actions: nine brought by individual purchasers and two brought by third-party payors. The Related Actions are pending in nine district courts, one each in the S.D.N.Y., Northern District of California, Southern District of Illinois, Northern District of Illinois, District of Minnesota, District of New Jersey, and Western District of Pennsylvania, and two each in the S.D. Fla. and the Eastern District of Pennsylvania.

Five of the eleven Related Actions were brought by the same plaintiffs' counsel, Honik LLC. The remaining six actions were each brought by different plaintiffs' counsel. Pfizer is the only defendant.

Seven of the Related Actions are stayed with no activity. The four active actions are all at the pleadings stage. In two of those actions, *Abreu* and *County of Monmouth,* Pfizer has moved to dismiss pursuant to Rule 12(b)(6), with briefing on the motion to dismiss in *Abreu* completed and briefing in *County of Monmouth* to be completed by October 17. *See Abreu v. Pfizer, Inc.*, No. 1:22-cv-01433 (S.D.N.Y.), ECF No. 16; *County of Monmouth v. Pfizer, Inc.*,

No. 3:22-cv-02050 (D.N.J.), ECF No. 8. In *County of Monmouth*, Pfizer also moved to transfer the case to the S.D.N.Y. pursuant to the first-filed rule and Section 1404. *See County of Monmouth v. Pfizer, Inc.*, No. 3:22-cv-02050 (D.N.J.), ECF No. 7. The other two actions were filed late last week. *See Lima v. Pfizer, Inc.*, No. 0:22-cv-02243 (D. Minn.), ECF No. 1; *Baptiste v. Pfizer, Inc.*, No. 2:22-cv-03647 (E.D. Pa.), ECF No. 1. Pfizer has contacted plaintiffs' counsel about staying the two recently filed actions except for purposes of briefing Section 1404 transfer, but plaintiffs' counsel have not indicated yet how they would like to proceed.

No discovery has taken place in any of the actions. Pfizer is in the process of filing Section 1404 transfer motions in the other Related Actions, including by seeking permission to lift the stays for the sole purpose of filing the transfer motions. One already has been filed to date, with the remaining expected to be filed over the next month. *See Houghton v. Pfizer Inc.*, No. 1:21-cv-23987 (S.D. Fla.), ECF No. 16.

C. Procedural History.

Movant's Motion omits any discussion of the extensive efforts taken by Pfizer and other plaintiffs' counsel over the last year to coordinate these actions.

Initially, two plaintiffs' firms—Bursor & Fisher, P.A. and Honik LLC—filed a handful of copycat consumer class action complaints in federal district courts in New York, California, Pennsylvania, and Florida. In August 2021, Bursor & Fisher, P.A. filed the first action on behalf of plaintiff Rosalyn Harris in the S.D.N.Y., where Pfizer maintains its corporate headquarters. *See Harris v. Pfizer, Inc.*, No. 1:21-cv-06789 (S.D.N.Y.), ECF No. 1. The case was assigned to Judge Denise L. Cote. Ms. Harris, and another plaintiff who is a New Jersey resident, filed an amended complaint asserting claims under New York and New Jersey law. *Id.*, ECF No. 24. In December 2021, Pfizer moved to dismiss the amended complaint pursuant to Rule 12(b)(6). *Harris v. Pfizer, Inc.*, No. 1:21-cv-06789, 2022 WL 488410, at *1 (S.D.N.Y. Feb. 16, 2022).

Several weeks after Bursor & Fisher, P.A. filed *Harris*, Honik LLC filed seven other class action complaints in six other districts and a second case in the S.D.N.Y. Honik LLC selectively served Pfizer in some actions but not others after receiving judge assignments. The sixth action filed by Honik LLC was on behalf of plaintiff Juan Abreu and filed in the S.D. Fla. *See Abreu v. Pfizer, Inc.*, No. 0:21-CV-62122 (S.D. Fla.), ECF No. 1.

Recognizing the efficiencies to be gained through coordination, the parties met and conferred about a potential venue for the actions. Plaintiffs' counsel stated that their preferred venue was the S.D. Fla., while Pfizer preferred to seek transfer of the cases under Section 1404 to the S.D.N.Y., the venue where the first action was filed and the only district in which there would be jurisdiction over all cases. In light of the parties' disagreement over the appropriate venue, the parties agreed to litigate Pfizer's Section 1404 transfer motion in *Abreu* first, because the outcome of that motion would inform venue in the other actions. Plaintiffs would not agree to stay Pfizer's deadline to respond to the *Abreu* complaint while they were litigating the transfer motion, so Pfizer also filed a motion to dismiss pursuant to Rule 12(b)(6). *See id.*, ECF Nos. 9 & 16. The parties further agreed to stay all of the other then-filed actions except for *Harris* (where Pfizer had a pending motion to dismiss and also had answered) "to avoid unnecessary and duplicative motion practice on motions to transfer and motions to dismiss and potentially inconsistent rulings," as well as conserve judicial resources. *See, e.g., MSP Recovery Claims Series 44, LLC v. Pfizer Inc.*, No. 1:21-cv-23676 (S.D. Fla.), ECF No. 10, at 2.[3]

[3] After the Bursor & Fisher, P.A. and Honik LLC cases, two other plaintiffs' counsel filed cases in the S.D. Fla. and the Northern District of Illinois. *See MSP Recovery Claims Series 44, LLC v. Pfizer Inc.*, No. 1:21-cv-23676 (S.D. Fla.), ECF No. 1; *Spence v. Pfizer Inc.*, 1:21-cv-6324 (N.D. Ill.), ECF No. 1. These new plaintiffs and their counsel also agreed to stays pending the outcome of the Section 1404 transfer motion in *Abreu*. See *MSP Recovery Claims*, No. 1:21-cv-23676 (S.D. Fla.), ECF No. 10; *Spence v. Pfizer Inc.*, 1:16-cv-1806 (N.D. Ill.), ECF No. 9.

On February 16, 2022, there were two significant rulings. In *Harris*, Judge Cote in the S.D.N.Y. granted Pfizer's motion to dismiss with prejudice. 2022 WL 488410, at *9. In *Abreu*, Magistrate Judge Goodman in the S.D. Fla. – to whom Judge Federico A. Moreno had referred all pretrial motions – recommended transfer of the case to the S.D.N.Y. *See Abreu v. Pfizer Inc.*, No. 0:21-CV-62122, 2022 WL 481184 (S.D. Fla. Feb. 16, 2022). The very next day, the plaintiff in another action filed by Honik LLC in the S.D.N.Y. before Judge Cote voluntarily dismissed her case. *See Webb v. Pfizer Inc.*, No. 1:21-CV-8244 (S.D.N.Y. Feb. 17, 2022), ECF No. 16. None of the other plaintiffs with lawsuits filed by Honik LLC voluntarily dismissed their cases.

On March 2, 2022, the plaintiff in *Abreu* filed a motion for reconsideration, asking Judge Moreno to overrule Magistrate Judge Goodman's transfer recommendation because the two cases pending there, *Harris* and *Webb,* had been dismissed. *See Abreu v. Pfizer Inc.*, No. 0:21-CV-62122 (S.D. Fla.), ECF No. 43. Judge Moreno heard oral argument on the motion, and allowed the parties to submit additional briefing on whether transfer was still appropriate. *See id.*, ECF No. 52. Judge Moreno also requested that Magistrate Judge Goodman provide an updated report and recommendation supplementing his prior opinion. *Id*. at 1.

In April 2022, in the midst of the *Abreu* transfer briefing, Movant County of Monmouth filed the then last-filed of the Related Actions.[4] Consistent with the parties' approach in the other actions, Pfizer requested a stay of the action pending resolution of its then-pending transfer motion in *Abreu*. County of Monmouth did not consent. As a result, on July 5, while the transfer motion was still pending in *Abreu,* Pfizer filed both a motion to dismiss and motion to

[4] Since the filing of Movant's Motion, two new consumer class action lawsuits asserting similar claims have been filed. *See Lima v. Pfizer Inc.*, No. 0:22-cv-02243 (D. Minn.), ECF No. 1; *Baptiste v. Pfizer Inc.*, No. 2:22-cv-03647 (E.D. Pa.), ECF No. 1. However, when Movant filed the present Motion, there had not been any new lawsuits filed for more than five months.

transfer to the S.D.N.Y. *See County of Monmouth v. Pfizer Inc.*, No. 3:22-cv-02050 (D.N.J.), ECF Nos. 7 & 8.

On June 22, 2022, Magistrate Judge Goodman issued a second Report and Recommendation, once again recommending transfer of *Abreu* to the S.D.N.Y. *See Abreu v. Pfizer, Inc.*, No. 21-cv-62122, 2022 WL 2355541 (S.D. Fla. June 22, 2022). In that 53-page decision, Magistrate Judge Goodman found that despite the dismissal by Judge Cote of *Harris* and voluntary dismissal of *Webb* by Honik LLC, the first-filed rule still favored transfer. *Id.* at *23. He also found that, independent of the first-filed rule, transfer was warranted under Section 1404. *Id*. In reaching this decision, Magistrate Judge Goodman determined that Pfizer had "establish[ed] that among the loci of operative facts, New York is home to a considerable amount." *Id.* at *16. He further found that "Plaintiff's counsel is forum shopping," *id.* at *13, as evidenced by the immediate dismissal of *Webb* after the dismissal of *Harris* on the merits and after the recommendation to transfer *Abreu*, even though it was stayed. *Id.* at *22. Accordingly, Magistrate Judge Goodman held that "both the first-filed rule and 28 U.S.C. § 1404, the interests of justice, as contemplated by this individual factor and the broader scope of § 1404, weigh in favor of transfer." *Id.* at *23.

On August 16, 2022, Judge Moreno adopted Magistrate Judge Goodman's second Report and Recommendation in full and transferred *Abreu* to the S.D.N.Y. *See Abreu v. Pfizer Inc.*, No. 0:21-CV-62122, 2022 WL 3372104 (S.D. Fla. Aug. 16, 2022). On August 24, the plaintiff filed for reconsideration. The following day, Judge Cote ordered the parties to advise her when Judge Moreno rendered a decision on the motion for reconsideration, *see Abreu v. Pfizer, Inc.*, No. 22-cv-1433 (DLC) (S.D.N.Y.), ECF No. 47, which Judge Moreno denied on August 29. *See Abreu*, No. 0:21-CV-62122, ECF No. 84. Following Judge Moreno's ruling, on August 31, Pfizer

informed plaintiffs' counsel and Judge Cote that it intended to seek transfer of all the actions under Section 1404 and would be filing motions to lift the stays for the limited purpose of filing its Section 1404 transfer motions on a rolling basis over the next 30 days. That same day, Judge Cote responded by ordering the parties to submit a status report by October 14. *See Abreu v. Pfizer Inc.*, 1:22-cv-01433 (S.D.N.Y.), ECF No. 49.

Two weeks after Judge Moreno's August 16 decision transferring *Abreu* and mere hours after Pfizer had informed Judge Cote and other plaintiffs' counsel that Pfizer intended to seek Section 1404 transfer of the Related Actions, *Abreu*'s counsel informed Pfizer and Judge Cote that Movant had filed the present Motion seeking centralization of the Related Actions in an MDL before Judge Michael A. Shipp in the District of New Jersey, notwithstanding that Pfizer's motion to transfer that case under Section 1404 had been pending for nearly two months. Movant then changed its position on a stay of its action and requested one pending a decision by the Panel. *See County of Monmouth v. Pfizer Inc.*, No. 3:22-cv-02050 (D.N.J.), ECF No. 13.

ARGUMENT

I. PLAINTIFF'S MOTION SHOULD BE DENIED AT THIS TIME.

The Panel has held repeatedly that "centralization under Section 1407 should be the last solution after considered review of all other options." *In re Best Buy Co., Inc., Ca. Song-Beverly Credit Card Act Litig.*, 804 F. Supp. 2d 1376, 1378 (J.P.M.L. 2011); *see also In re Gerber Probiotic Prods. Mktg. & Sales Practices Litig.*, 899 F. Supp. 2d 1378, 1379 (J.P.M.L. 2012) (same); *In re Hudson's Bay Co. Customer Data Sec. Breach Litig.*, 326 F. Supp. 3d 1372, 1373 (J.P.M.L. 2018) (same); *In re GEICO Customer Data Sec. Breach Litig.*, 568 F. Supp. 3d 1406, 1407 (J.P.M.L. 2021) (same). Consistent with that edict, in its Notice of Filing, the Panel specifically instructed the parties here to "address what steps they have taken to pursue alternatives to centralization (including, but not limited to, engaging in informal coordination of

discovery and scheduling, and seeking Section 1404 transfer of one or more of the subject cases)." *See* MDL No. 3050, *In re: Chantix (Varenicline) Mtkg., Sales Practices & Prods. Liab. Litig. (No. II)*, ECF No. 3.

The Panel also has emphasized repeatedly that "where 'a reasonable prospect' exists that resolution of Section 1404 motions could eliminate the multidistrict character of a litigation, transfer under Section 1404 is preferable to [Section 1407] centralization." *In re Gerber*, 899 F. Supp. 2d 1378 at 1380; *see also In re 3M Co. Lava Ultimate Prods. Liab. Litig.*, 222 F. Supp. 3d 1347, 1347–48 (J.P.M.L. 2016) (same); *In re Allianz Structured Alpha Funds Litig.*, 544 F. Supp. 3d 1361, 1362 (J.P.M.L. 2021) (same); *In re Gen. Motors LLC Chevrolet Bolt EV Battery Prods. Liab. Litig.*, 532 F. Supp. 3d 1413, 1414–15 (J.P.M.L. 2021) (same). As the Panel has explained, centralization under Section 1404 "produces significant advantages" over Section 1407 because "transfer is for all purposes, including trial," whereas "[c]entralization under Section 1407 is not permanent" and "is limited to pretrial proceedings only." *In re Gerber*, 899 F. Supp. 2d 1378 at 1380. "Section 1404 may moot the multidistrict character of a litigation and allow a [coordinated] proceeding in one court with jurisdiction over the pretrial, trial, and post-trial aspects of the litigation." *Id*. For this reason, the Panel has denied requests for centralization under Section 1407 where Section 1404 transfer efforts are in process. *See, e.g., id.* at 1379 (denying centralization where "resolution of Section 1404 motions could eliminate the multidistrict character" of 10 actions pending in 5 districts); *In re Baby Food Mktg., Sales Practices & Prods. Liab. Litig.*, 544 F. Supp. 3d 1375, 1378 (J.P.M.L. 2021) (denying centralization where motions to transfer were pending because "[w]e believe it is better to allow the parties' attempts to self-organize play out before centralizing any part of this litigation."); *In re Allianz*, 544 F. Supp. 3d at 1362 (denying centralization "[e]ven where a Section 1404 transfer

motion is contested" because "a prospect nonetheless exists, particularly where few districts are involved"); *In re Gen. Motors LLC Chevrolet Bolt EV Battery*, 532 F. Supp. 3d at 1415 (denying centralization where "there is at least a reasonable prospect that the courts . . . will grant Section 1404 transfer . . . where five related actions are and defendant is headquartered").

Here, Pfizer agrees that litigating the actions in a single district court is appropriate for these Related Actions given the similar factual questions and legal claims they raise. To this end, Pfizer has worked cooperatively with plaintiffs' counsel, resulting in the parties agreeing to stay almost all of the actions while they first litigated transfer of *Abreu* pursuant to the first-filed rule and Section 1404. Indeed, allowing Section 1404 transfer to play out here likely would result in ***greater efficiency*** than MDL coordination, since the S.D.N.Y. could oversee the Related Actions for all purposes, whereas an MDL would be limited only to pretrial proceedings. *See In re Gerber*, 899 F. Supp. 2d at 1379-80.

Thus far, Section 1404 transfer is underway and working effectively. Judge Moreno recently transferred *Abreu* to the S.D.N.Y. In *County of Monmouth*, the parties are actively briefing Section 1404 transfer. And now Pfizer is seeking to lift the stays in the other Related Actions for the limited purpose of filing similar motions to transfer to the S.D.N.Y. One of those transfer motions has been filed to date.

There is no reason to believe at this time that transfer via the first-filed rule and Section 1404 will be ineffective. If Judge Shipp denies the transfer motion in *County of Monmouth*, or if another district court does, then "the parties may file another Section 1407 motion, and the Panel will revisit the question of centralization at that time." *In re Gerber*, 899 F. Supp. 2d at 1381 (citing *In re Glaceau VitaminWater Mktg. & Sales Practices Litig. (No. II)*, 764 F. Supp. 2d 1349, 1350 (J.P.M.L. 2011)). Further, the prospect that additional related actions may be filed in

other districts is low given that no new actions had been filed in the last five months until late last week, and even then, only two new actions were filed and one in the same district as another action. Further, "[t]he Panel has been 'disinclined to take into account the mere possibility of future filings in [its] centralization calculus.'" *In re Gen. Motors LLC Chevrolet Bolt EV Battery*, 532 F. Supp. 3d at 1415 (quoting *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 959 F. Supp. 2d 1375, 1376 (J.P.M.L. 2013)).

Movant's reliance on the Panel's prior decisions coordinating actions involving "other products due to nitrosamine or other carcinogenic contamination" is inapposite. Pl.'s Mot. at 2, 4, 9. Unlike here, those actions involved personal injury claims in addition to consumer class actions, dozens of plaintiffs' counsel, 17 or more related actions, and, in some instances, multiple defendants. *See In re: Valsartan N-Nitrosodimethylamine (NDMA) Contamination Prods. Liab. Litig.*, 363 F. Supp. 3d 1378, 1382 (J.P.M.L. 2019) ("There are presently a total of 40 related actions pending in 22 districts, which involve over a dozen distinct slates of plaintiffs' counsel and some 20 defendants, most of whom do not share counsel."); *In re Zantac (Ranitidine) Prod. Liab. Litig.*, 437 F. Supp. 3d 1368, 1368 (J.P.M.L. 2020) (identifying 9 related actions "asserting personal injury claims" and 6 related actions "of putative classes of consumers seeking refunds and other economic damages," in addition to "126 related actions pending in 21 districts" and multiple defendants); *In re Johnson & Johnson Aerosol Sunscreen Mktg., Sales Pracs. & Prod. Liab. Litig.*, 568 F. Supp. 3d 1412, 1413–14 (J.P.M.L. 2021) (identifying 17 related actions, 5 product lines at issue, consumer class action and personal injury claims, and multiple defendants); *In re: Procter & Gamble Aerosol Prods. Mktg. & Sales Pracs. Litig.*, MDL No. 3025, 2022 WL 1053652, at *1–2 (J.P.M.L. Apr. 7, 2022) (identifying 25 related actions and at least 4 product lines at issue). In stark contrast, here there is a single defendant, a single product

at issue, no personal injury claims, only eleven Related Actions, and seven plaintiffs' counsel who have stated that they are informally coordinating.

Indeed, the only apparent basis for Movant's Motion is that Movant does not like the forum to which the Section 1404 transfer process seems destined, presumably because Judge Cote previously dismissed claims under both New York and New Jersey law in *Harris*. *See* 2022 WL 488410, at *9. However, "the Panel does not consider '[t]he prospect of an unfavorable ruling by the transferee court or the possibility that another district judge may be more favorably disposed to a litigant's contention . . . in exercising its discretion under Section 1407.'" *In re Eliquis (Apixaban) Prods. Liab. Litig.*, 282 F. Supp. 3d 1354, 1356 n. 4 (J.P.M.L. 2017) (quoting *In re: Libor–Based Fin. Instruments Antitrust Litig.*, MDL No. 2262, Doc. No. 226, Transfer Order, at 2 (J.P.M.L. June 6, 2013)); *see also In re Glenn W. Turner Enters. Litig.*, 368 F. Supp. 805, 806 (J.P.M.L. 1973) (same). Here, where the Section 1404 transfer process is well underway and working effectively, Movant's Motion should be denied at this time.

II. ALTERNATIVELY, IF THE PANEL FINDS CENTRALIZATION WARRANTED NOW UNDER SECTION 1407, THE S.D.N.Y. IS THE PROPER FORUM.

For the reasons stated above, Pfizer does not believe centralization under Section 1407 is warranted at this time. However, if the Panel disagrees, then the S.D.N.Y. is the most appropriate forum for transfer of the Related Actions.

In determining the most appropriate transferee forum under Section 1407, the Panel considers (among other things) the location of parties, witnesses, and documents; the convenience of the parties and witnesses; the progress achieved in the pending actions; the resources and experience of the transferee forum; and the preference of the parties. *See In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 249 F. Supp. 3d 1357, 1360 (J.P.M.L. 2017) (ordering transfer and considering parties' convenience, status of pending

actions, and location); *In re Sprint Premium Data Plan Mktg. & Sales Practices Litig.*, 777 F. Supp. 2d 1349, 1351 (J.P.M.L. 2011) (a district is an "appropriate transferee district" if it "has a great deal of experience serving as a transferee court yet has a manageable MDL docket"). All of these factors weigh in favor of selecting the S.D.N.Y. as the transferee forum.

First, the S.D.N.Y. is the location of the first-filed action, *Harris*, the most advanced among the Related Actions.[5] There, Judge Cote already ruled on many of the claims under New York and New Jersey law. *See Harris*, 2022 WL 488410. And, due to the transfer of *Abreu*, she will be determining those claims under Florida law, as well. "[I]t is appropriate to give 'the first-filed criterion some weight in selecting a transferee district.'" *In re Prudential Ins. Co. of Am. SGLI/VGLI Contract Litig.*, 763 F. Supp. 2d 1374, 1375 (J.P.M.L. 2011) (quoting *In re: Halftone Color Separations ('809) Pat. Litig.*, 547 F. Supp. 2d 1383, 1384 (J.P.M.L. 2008)). The Panel often selects a transferee forum in the location of the first-filed action, which, as a result of being filed first, often also is the most advanced of the related actions, as is the case here. *See, e.g.*, *In re GMAC Ins. Mgmt. Corp. Overtime Pay Litig.*, 342 F. Supp. 2d 1357, 1358 (J.P.M.L. 2004) (centralizing the related actions in the district where "the first-filed and most advanced action is pending"); *In re Pantopaque Prod. Liab. Litig.*, 787 F. Supp. 229, 230 (J.P.M.L. 1992) (same); *In re: Bank of Am. Credit Prot. Mktg. & Sales Pracs. Litig.*, 804 F. Supp. 2d 1372, 1373 (J.P.M.L. 2011) (same).

Second, the S.D.N.Y. has a meaningful nexus to the parties, witnesses, and documents. Pfizer's headquarters are in New York—and thus many of the witnesses and relevant documents are located in or near the S.D.N.Y. *See Abreu*, 2022 WL 2355541, at *15–16 (finding that "it

[5] In *Abreu*, Magistrate Judge Goodman found that the dismissal of *Harris* on the merits did not preclude the application of the first-filed rule and transferred the case to the S.D.N.Y. pursuant to both the first-filed rule and Section 1404. *See* 2022 WL 2355541, at *7–24.

appears that much of Defendant's decision-making concerning the marketing, testing, and regulatory compliance occurred in New York or the New York area"). The Panel often selects a transferee forum where the defendant is headquartered. *See, e.g.*, *In re Profemur Hip Implant Prod. Liab. Litig.*, 481 F. Supp. 3d 1350, 1353 (J.P.M.L. 2020) (centralizing related actions in the district court "located near the Wright and Microport defendants' Memphis headquarters, where relevant documents and witnesses may be found"); *In re Farxiga (Dapagliflozin) Prod. Liab. Litig.*, 273 F. Supp. 3d 1380, 1382 (J.P.M.L. 2017) (centralizing related actions in the S.D.N.Y. because the defendant "is headquartered in New York, and thus many witnesses and relevant documents are likely to be found in or near the district"); *In re: Procter & Gamble Aerosol Prods.*, 2022 WL 1053652, at *2 (centralizing related actions where "P&G has its headquarters" because "common witnesses and other evidence likely will be located in or near this district").

Third, the S.D.N.Y. is the only forum that has jurisdiction over all of the Related Actions. Pfizer's principal place of business is in New York, making it subject to general personal jurisdiction in the S.D.N.Y. Thus, it is the only forum where all of the Related Actions could have been brought.

Finally, the S.D.N.Y. has the resources and expertise to manage coordinated litigation. Judge Cote is an experienced MDL judge who is not currently overseeing an MDL. As the Panel has recognized previously, "Judge Denise L. Cote . . . is an experienced transferee judge with the willingness and ability to manage this litigation. We are confident she will steer this litigation on a prudent course." *In re Eliquis (Apixaban)*, 282 F. Supp. 3d at 1356.

CONCLUSION

Pfizer respectfully requests that the Panel deny Movant's Motion. In the alternative, if the Panel believes that centralization is warranted now, Pfizer requests that the Panel transfer the

Related Actions and any subsequently filed cases raising similar claims to the Southern District of New York for coordinated pretrial proceedings before the Honorable Denise L. Cote.

Dated: September 22, 2022

Respectfully submitted,

DLA PIPER LLP (US)

/s/ Loren H. Brown

Loren H. Brown
Colleen Carey Gulliver
1251 Avenue of the Americas
New York, New York 10020-1104
Phone: (212) 335-4500
Facsimile: (212) 335-4501
loren.brown@us.dlapiper.com
colleen.gulliver@us.dlapiper.com

Matthew A. Holian
Jessica C. Wilson
33 Arch Street, 26th Floor
Boston, MA 02110-1447
T: (617) 406-6009
F: (617) 406-6109
matt.holian@us.dlapiper.com
jessica.wilson@us.dlapiper.com

Attorneys for Pfizer Inc.

EXHIBIT 1

Health Consequences of Smoking, Surgeon General fact sheet

This is the 32nd tobacco-related Surgeon General's report issued since 1964. It highlights 50 years of progress in tobacco control and prevention, presents new data on the health consequences of smoking, and discusses opportunities that can potentially end the smoking epidemic in the United States. Scientific evidence contained in this report supports the following facts:

The century-long epidemic of cigarette smoking has caused an enormous, avoidable public health catastrophe in the United States.

- Since the first Surgeon General's report on smoking and health was published 50 years ago, more than 20 million Americans have died because of smoking.
- If current rates continue, 5.6 million Americans younger than 18 years of age who are alive today are projected to die prematurely from smoking-related disease.
- Most of the 20 million smoking-related deaths since 1964 have been adults with a history of smoking; however, 2.5 million of those deaths have been among nonsmokers who died from diseases caused by exposure to secondhand smoke.
- More than 100,000 babies have died in the last 50 years from Sudden Infant Death Syndrome, complications from prematurity, complications from low birth weight, and other pregnancy problems resulting from parental smoking.
- The tobacco epidemic was initiated and has been sustained by the tobacco industry, which deliberately misled the public about the risks of smoking cigarettes.

Despite significant progress since the first Surgeon General's report, issued 50 years ago, smoking remains the single largest cause of preventable disease and death in the United States.

- Smoking rates among adults and teens are less than half what they were in 1964; however, 42 million American adults and about 3 million middle and high school students continue to smoke.
- Nearly half a million Americans die prematurely from smoking each year.
- More than 16 million Americans suffer from a disease caused by smoking.
- On average, compared to people who have never smoked, smokers suffer more health problems and disability due to their smoking and ultimately lose more than a decade of life.
- The estimated economic costs attributable to smoking and exposure to tobacco smoke continue to increase and now approach $300 billion annually, with direct medical costs of at least $130 billion and productivity losses of more than $150 billion a year.

The scientific evidence is incontrovertible: inhaling tobacco smoke, particularly from cigarettes, is deadly. Since the first Surgeon General's Report in 1964, evidence has linked smoking to diseases of nearly all organs of the body.

- In the United States, smoking causes 87 percent of lung cancer deaths, 32 percent of coronary heart disease deaths, and 79 percent of all cases of chronic obstructive pulmonary disease (COPD).
- One out of three cancer deaths is caused by smoking**.**
- This report concludes that smoking causes colorectal and liver cancer and increases the failure rate of treatment for all cancers.

- The report also concludes that smoking causes diabetes mellitus, rheumatoid arthritis and immune system weakness, increased risk for tuberculosis disease and death, ectopic (tubal) pregnancy and impaired fertility, cleft lip and cleft palates in babies of women who smoke during early pregnancy, erectile dysfunction, and age-related macular degeneration.
- Secondhand smoke exposure is now known to cause strokes in nonsmokers.
- This report finds that in addition to causing multiple serious diseases, cigarette smoking diminishes overall health status, impairs immune function, and reduces quality of life.

Smokers today have a greater risk of developing lung cancer than did smokers in 1964.

- Even though today's smokers smoke fewer cigarettes than those 50 years ago, they are at higher risk of developing lung cancer.
- Changes in the design and composition of cigarettes since the 1950s have increased the risk of adenocarcinoma of the lung, the most common type of lung cancer.
- Evidence suggests that ventilated filters may have contributed to higher risks of lung cancer by enabling smokers to inhale more vigorously, thereby drawing carcinogens contained in cigarette smoke more deeply into lung tissue.
- At least 70 of the chemicals in cigarette smoke are known carcinogens. Levels of some of these chemicals have increased as manufacturing processes have changed.

For the first time, women are as likely to die as men from many diseases caused by smoking.

- Women's disease risks from smoking have risen sharply over the last 50 years and are now equal to men's for lung cancer, COPD, and cardiovascular diseases. The number of women dying from COPD now exceeds the number of men.
- Evidence also suggests that women are more susceptible to develop severe COPD at younger ages.
- Between 1959 and 2010, lung cancer risks for smokers rose dramatically. Among female smokers, risk increased 10-fold. Among male smokers, risk doubled.

Proven tobacco control strategies and programs, in combination with enhanced strategies to rapidly eliminate the use of cigarettes and other combustible, or burned, tobacco products, will help us achieve a society free of tobacco-related death and disease.

- The goal of ending tobacco-related death and disease requires additional action.
- Evidence-based tobacco control interventions that are effective continue to be underused. What we know works to prevent smoking initiation and promote quitting includes hard-hitting media campaigns, tobacco excise taxes at sufficiently high rates to deter youth smoking and promote quitting, easy-to-access cessation treatment and promotion of cessation treatment in clinical settings, smoke-free policies, and comprehensive statewide tobacco control programs funded at CDC-recommended levels.
- Death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other burned tobacco products. Rapid elimination of their use will dramatically reduce this public health burden.
- New "end-game" strategies have been proposed with the goal of eliminating tobacco smoking. Some of these strategies may prove useful for the United States, particularly reduction of the nicotine yield of tobacco products to non-addictive levels.

OSG Headquarters

Office of the Surgeon General
U.S. Department of Health & Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201
E-mail: surgeongeneral@hhs.gov
Phone: 202-401-7529

EXHIBIT 2

News & Events

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
P06-67
May 11, 2006

Media Inquiries:
Laura Alvey, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Approves Novel Medication for Smoking Cessation

The U.S. Food and Drug Administration (FDA) announced today the approval of Chantix (varenicline tartrate) tablets, to help cigarette smokers stop smoking. The active ingredient in Chantix, varenicline tartrate, is a new molecular entity that received a priority FDA review because of its significant potential benefit to public health.

Chantix acts at sites in the brain affected by nicotine and may help those who wish to give up smoking in two ways: by providing some nicotine effects to ease the withdrawal symptoms and by blocking the effects of nicotine from cigarettes if they resume smoking.

"Tobacco use, particularly cigarette smoking, is the single most preventable cause of death in the United States and is responsible for a growing list of cancers as well as chronic diseases including those of the lung and heart," said Scott Gottlieb, MD, Deputy Commissioner for Medical and Scientific Affairs. "The agency is committed to helping facilitate the development of products to help people quit smoking and improve their overall quality of life."

According to the Centers for Disease Control and Prevention (CDC), an estimated 44.5 million adults in the United States smoke cigarettes and more than 8.6 million of them have at least one serious illness caused by smoking.

"Cigarette smoking is a very difficult habit to break due in large part to nicotine dependence or addiction" said Dr. Steven Galson, Director of FDA's Center for Drug Evaluation and Research. "Chantix therapy has proven to be effective in smokers motivated to quit and will provide another tool for physicians to use for the millions of smokers who want to quit."

The effectiveness of Chantix in smoking cessation was demonstrated in six clinical trials, which included a total of 3659 chronic cigarette smokers who were treated with varenicline. Five of the six studies were randomized, controlled clinical trials in which Chantix was shown to be superior to placebo in helping people quit smoking. These smokers had previously averaged 21 cigarettes a day for approximately 25 years. In two

of the five placebo-controlled studies, Chantix-treated patients were also more successful in giving up smoking than patients treated with Zyban (bupropion).

The approved course of Chantix treatment is 12 weeks. Patients who successfully quit smoking during Chantix treatment may continue with an additional 12 weeks of Chantix treatment to further increase the likelihood of long-term smoking cessation.

In clinical trials, the most common adverse effects of Chantix were nausea, headache, vomiting, flatulence (gas), insomnia, abnormal dreams, and dysgeusia (change in taste perception).

Chantix is manufactured and distributed by Pfizer, Inc., New York, NY.

#

RSS Feed for FDA News Releases [what is RSS?]

EXHIBIT 3

COMPANY ANNOUNCEMENT

Pfizer Issues a Voluntary Nationwide Recall for Twelve Lots of CHANTIX® (Varenicline) Tablets Due to N-Nitroso Varenicline Content

More Recalls, Market Withdrawals, & Safety Alerts (/safety/recalls-market-withdrawals-safety-alerts)

Summary

Company Announcement Date:

July 16, 2021

FDA Publish Date:

July 19, 2021

Product Type:

Drugs

Reason for Announcement:

N-Nitroso Varenicline content above ADI level

Company Name:

Pfizer

Brand Name:

CHANTIX

Product Description:

Smoking cessation treatment

Company Announcement

Pfizer is voluntarily recalling two lots of Chantix 0.5mg Tablets, two lots of Chantix 1 mg Tablets, and eight lots of a Chantix kit of 0.5mg/1 mg Tablets to the patient (consumer/user) level due to the presence of a nitrosamine, N-nitroso-varenicline, above the Pfizer established Acceptable Daily Intake (ADI) level.

Long-term ingestion of N-nitroso-varenicline may be associated with a theoretical potential increased cancer risk in humans, but there is no immediate risk to patients taking this medication. The health benefits of stopping smoking outweigh the theoretical potential cancer risk from the nitrosamine impurity in varenicline.

Nitrosamines are common in water and foods, including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines. These impurities may increase the risk of cancer if people are exposed to them above acceptable levels over long periods of time.[i]

Chantix is a treatment to help patients quit smoking and is intended for short term use. People who smoke cigarettes are 15 to 30 times more likely to get lung cancer than people who do not smoke.[ii] Smoking is also associated with many other cancers.[iii] CHANTIX has a safety profile that has been established over 15 years of marketing authorization and through a robust clinical program. Pfizer believes the benefit/risk profile of CHANTIX remains positive. Patients currently taking Chantix should consult with their doctor to confirm if they received an affected lot, and if appropriate, about alternative treatment options. To date, Pfizer has not received any reports of adverse events that have been related to this recall.

The NDC, Lot Number, Expiration Date, and Configuration details for Chantix Tablets is indicated in the table below and photos of the products can be found at the end of this press release. The product lots were distributed nationwide to wholesalers and Distributors in the United States and Puerto Rico from June 2019 to June 2021.

Product	NDC	Lot Number	Expiration Date	Presentation	Configuration/Count
Chantix (varenicline) Tablets, 0.5 mg	0069-0468-56	00019213	2022 JAN	Bottles	56 tablets/bottle
Chantix (varenicline) Tablets, 0.5 mg	0069-0468-56	EC6994	2023 MAY	Bottles	56 tablets/bottle
Chantix (varenicline) Tablets, 1 mg	0069-0469-56	EA6080	2023 MAR	Bottles	56 tablets/bottle
Chantix (varenicline) Tablets, 1 mg	0069-0469-56	EC9843	2023 MAR	Bottles	56 tablets/bottle
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	00020231	2021 SEP	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	00020232	2021 NOV	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets

Top ()

Product	NDC	Lot Number	Expiration Date	Presentation	Configuration/Count
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	00020357	2021 DEC	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	00020358	2022 JAN	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	00020716	2022 JAN	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	ET1600	01/2023	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	ET1607	01/2023	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets
Chantix (varenicline) Tablets, 0.5/1 mg	0069-0471-03	ET1609	01/2023	Cartons containing 2 blister packs	Carton containing one blister pack of 11 0.5 mg tablets and one blister pack containing 42 1 mg tablets

Pfizer places the utmost emphasis on patient safety and product quality at every step in the manufacturing and supply chain process. Pfizer has notified their direct consignees by letter to arrange for return of any recalled product.

Wholesalers and distributors with an existing inventory of the lots, listed in the table above, should stop use and distribution and quarantine the product immediately.

If you have further distributed the recalled product, please notify any accounts or additional locations which may have received the recalled product from you. Please conduct a sub-recall to those accounts and communicate this recall information immediately. Please request they immediately cease distribution of the affected product and promptly contact Stericycle at 888-276-6166 (Mon.-Fri. 8:00 am - 5:00 pm ET) to obtain a Business Reply Card (BRC) to initiate the return process.

If you received free product through the Pfizer Patient Assistance Program (PAP) or the Pfizer Institutional Patient Assistance Program (IPAP), please check your stock immediately against the table above. If you have any of the affected product lots in your inventory, please follow the instructions above for returning the product to Stericycle Inc. Additionally, if you are aware of any patients to whom you dispensed the affected lots who still may have the product in their possession, please ask them to return the product to you and then follow the instructions above for returning the product to Stericycle Inc. To request replacement product for any Pfizer PAP or Pfizer IPAP product you return, please contact 833-203-2776 (Mon.-Fri. 8:00 am – 6:00 pm ET).

As communicated by FDA, there is no immediate risk to patients taking Chantix.[iv] Patients who are taking this product should consult with their health care provider or pharmacy to determine if they have the affected product lots. Patients with the affected lots should contact Stericycle Inc. at 888-276-6166 (Mon.-Fri. 8:00 am - 5:00 pm ET) for instructions on how to return their product and obtain reimbursement for their cost.

Healthcare Professionals with questions regarding this recall can contact Pfizer using the below information.

*	*	*
Pfizer Medical Information	800-438-1985, option 3 (Mon.-Fri. 9 am-5 pm ET) www.pfizermedinfo.com (http://www.pfizermedinfo.com/) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)	For medical questions regarding the product
Pfizer Drug Safety	800-438-1985, option 1 (24 hours a day; 7 days a week)	To report adverse events and product complaints

Contact Center Contact Information Area of Support

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- Complete and submit the report Online (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda)
- Regular Mail or Fax: Download form (/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting) or call 1- 800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

This recall is being conducted with the knowledge of the U.S. Food and Drug Administration.

References:

Top ()

[i] https://www.fda.gov/drugs/drug-safety-and (https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications)availability/information-about-nitrosamine-impurities-medications (https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications)

[ii] U.S. Centers for Disease Control and Prevention. What Are the Risk Factors for Lung Cancer? https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm (https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm)Updated September 2020. Accessed June 2021.

[iii] U.S. Department of Health and Human Services. Smoking and Cancer (Fact Sheet). Atlanta, GA: US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

[iv]https://www.fda.gov/drugs/drug-safety-and-availability/fda (https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-health-care-professionals-and-patients-voluntary-recall-varenicline-chantix-warehouse)alerts-health-care-professionals-and-patients-voluntary-recallvarenicline-chantix-warehouse (https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-health-care-professionals-and-patients-voluntary-recall-varenicline-chantix-warehouse)

Expanded Press Release (/safety/recalls-market-withdrawals-safety-alerts/pfizer-expands-voluntary-nationwide-recall-include-four-additional-lots-chantixr-varenicline-tablets)

Company Contact Information

Consumers:
Stericycle
888-276-6166

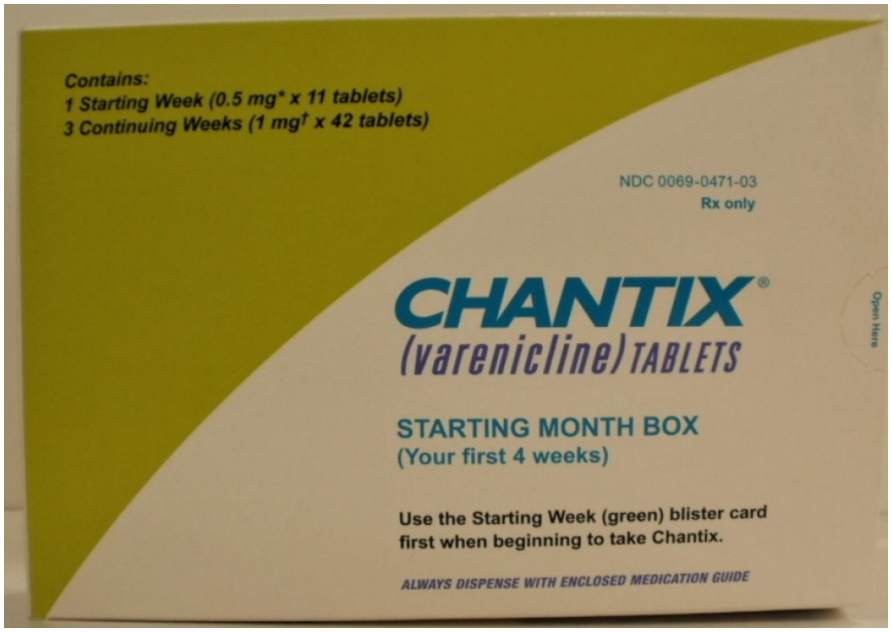
Media:
Eamonn Nolan
212-733-4626
Eamonn.Nolan@pfizer.com (mailto:Eamonn.Nolan@pfizer.com)

Product Photos

Top ()

Top ()

Top ()



Top ()

EXHIBIT 4

Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2021
Pharmaceutical Quality/ Manufacturing Standards/
Current Good Manufacturing Practice (CGMP)

Revision 1

Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2021
Pharmaceutical Quality/ Manufacturing Standards/
Current Good Manufacturing Practice (CGMP)

Revision 1

Preface

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see Section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2) and (g)(3)). FDA made this determination because of the importance of providing timely information to manufacturers regarding risk assessments, testing, and other appropriate actions they should take to reduce and mitigate nitrosamine impurities in active pharmaceutical ingredients (APIs)[1] and drug products. This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1530 and complete title of the guidance in the request.

[1] The term *API* used throughout this guidance should be interpreted to mean drug substance, the active ingredient in a drug product. See 21 CFR 210.3(b)(7) (defining *active ingredient*) and 314.3 (defining *drug substance*).

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Control of Nitrosamine Impurities in Human Drugs Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance recommends steps manufacturers of APIs and drug products should take to detect and prevent unacceptable levels of nitrosamine[2] impurities in pharmaceutical products.[3] The guidance also describes conditions that may introduce nitrosamine impurities. The recent unexpected finding of nitrosamine impurities, which are probable human carcinogens, in drugs such as angiotensin II receptor blockers (ARBs),[4] ranitidine,[5] nizatidine,[6] and metformin,[7] has made clear the need for a risk assessment strategy for potential nitrosamines in any pharmaceutical product at risk for their presence. This document revises the guidance of the same title issued in September 2020. This revision extends the time period for preparing initial risk assessments to March 31, 2021 (i.e., within 7 months of publication of the original guidance).

[1] This guidance has been prepared by the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2020-D-1530 (available at https:/regulations.gov/docket/FDA-2020-D-1530) (see the instructions for submitting comments in the docket).

[2] The term *nitrosamine* as used in this guidance means *N-nitrosamine*.

[3] New drug application (NDA) and abbreviated new drug application (ANDA) holders or sponsors, drug master file (DMF) holders, and owners of marketed products that are not the subject of approved NDAs or ANDAs (such as compounded products or products marketed under an over-the-counter (OTC) drug monograph) who are not also the manufacturer of the drug products and APIs should work with their contract manufacturers to take the steps recommended in this guidance. This applies to drug products currently available on the U.S. market as well as those with pending applications.

[4] The first nitrosamine detected in ARBs was N-nitrosodimethylamine (NDMA), which is a genotoxic and carcinogenic agent in animals and is classified as probably carcinogenic to humans (Class 2A carcinogen) by the World Health Organization's (WHO's) International Agency for Research on Cancer (IARC). Other nitrosamines, including N-nitrosodiethylamine (NDEA) and N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), have also been detected in various ARB products.

[5] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine

[6] See footnote 5.

[7] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin

The discovery of nitrosamines in some types of drug products led FDA and other international regulators to conduct a detailed analysis of these impurities in affected APIs and drug products.[8,9] Based on the Agency's current understanding, this guidance discusses potential root causes of nitrosamine formation and advises API and drug product manufacturers that they should (1) conduct risk assessments of their approved or marketed products and products with pending applications, and (2) take appropriate actions to reduce or prevent the presence of nitrosamines in APIs and drug products.

Although nitrosamine impurities have been found in only some drug products, and batches of those products have been recalled when there were unacceptable levels[10] of these impurities, nitrosamine impurities might exist in other APIs and drug products due to use of vulnerable processes and materials that may produce nitrosamine impurities. Therefore, the recommendations made in this guidance apply to all chemically synthesized APIs. They also apply to drug products containing chemically synthesized APIs and to drug products at risk due to other factors described in this guidance (see sections II.B and C), and not just to the drug products that have been identified in FDA announcements.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA has been investigating the presence of nitrosamine impurities in certain drug products. Since 2018, several drug products including ARBs, ranitidine, nizatidine, and metformin have been found to contain unacceptable levels of nitrosamines.

In June 2018, FDA was informed of the presence of an impurity identified as N-nitrosodimethylamine (NDMA) in the ARB valsartan.[11] Through investigation, the Agency determined that numerous lots of valsartan and a few other ARB drug products from different manufacturers contained unacceptable levels of nitrosamines. The drug product manufacturers

[8] Other regulators with which FDA has been collaborating include the European Medicines Agency (EMA), European Directorate for the Quality of Medicines and Healthcare (EDQM), Health Canada (HC), Therapeutic Goods Administration (TGA, Australia), Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency (PMDA/MHLW, Japan), Health Sciences Authority, Singapore (HSA, Singapore), and Swissmedic (Switzerland).

[9] FDA's validated laboratory methods used in assaying nitrosamine impurities in various drugs as well as the analytical results for various drugs and batches are available at https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current, https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine, and https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin.

[10] See Table 1 in section III.A. of this guidance.

[11] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current

voluntarily recalled the affected batches of these drug products,[12] which led to a drug shortage in some of the affected products.[13] In addition, FDA evaluated processes that use common amines in API synthesis and learned that common synthetic pathways could also introduce other types of nitrosamine impurities besides NDMA.

In September 2019, FDA learned that some common heartburn products (ranitidine, commonly known as Zantac, and nizatidine, commonly known as Axid) contained unacceptable levels of NDMA.[14] FDA recommended that manufacturers voluntarily recall ranitidine and nizatidine products with NDMA levels above what the Agency considers acceptable.[15, 16] Recently, preliminary findings from FDA stability testing raised concerns that NDMA levels in some ranitidine products stored at room temperature can increase with time to unacceptable levels. FDA's preliminary results using accelerated stability testing demonstrated that elevated levels of NDMA were measured in all products after 2 weeks. FDA's testing suggests that NDMA levels increase with storage time. On April 1, 2020, FDA requested that all ranitidine products be withdrawn from the U.S. market.

In December 2019, FDA became aware that some metformin diabetes medicines in other countries were reported to have NDMA. In light of this information, FDA acquired samples of metformin to test for NDMA. By February 2020, the Agency had identified NDMA in some samples but did not find levels exceeding the acceptable intake limit. In May 2020, further FDA testing revealed that certain lots of metformin extended-release formulation contained NDMA above the Agency's recommended acceptable intake limit. Based on that testing, FDA requested that identified applicants voluntarily recall these lots of the extended-release metformin. FDA continues to investigate possible NDMA impurities in metformin and other drug products and will advise companies on appropriate action.

Because the nitrosamine impurity issue extends beyond the U.S. drug supply, FDA and other regulatory authorities have partnered to share information, coordinate inspection efforts, communicate effective analytical methods to detect and identify various nitrosamines, and to develop rapid solutions to ensure the safety and quality of the drug supply.

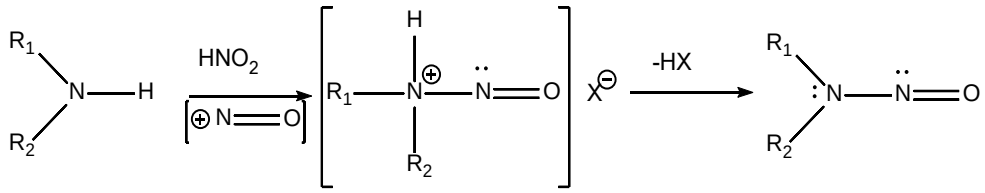
A. Nitrosamine Impurities

The term *nitrosamine* describes a class of compounds having the chemical structure of a nitroso group bonded to an amine ($R^1N(-R^2)-N=O$), as shown in Figure 1. The compounds can form by a

[12] For a list of recalled products, see FDA's Recalls, Market Withdrawals, & Safety Alerts web page at https://www.fda.gov/node/360167.
[13] See FDA's public web page on drug shortages at https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages and FDA's list of recalled ARB products at https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and.
[14] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
[15] https://www.fda.gov/news-events/press-announcements/statement-new-testing-results-including-low-levels-impurities-ranitidine-drugs
[16] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current

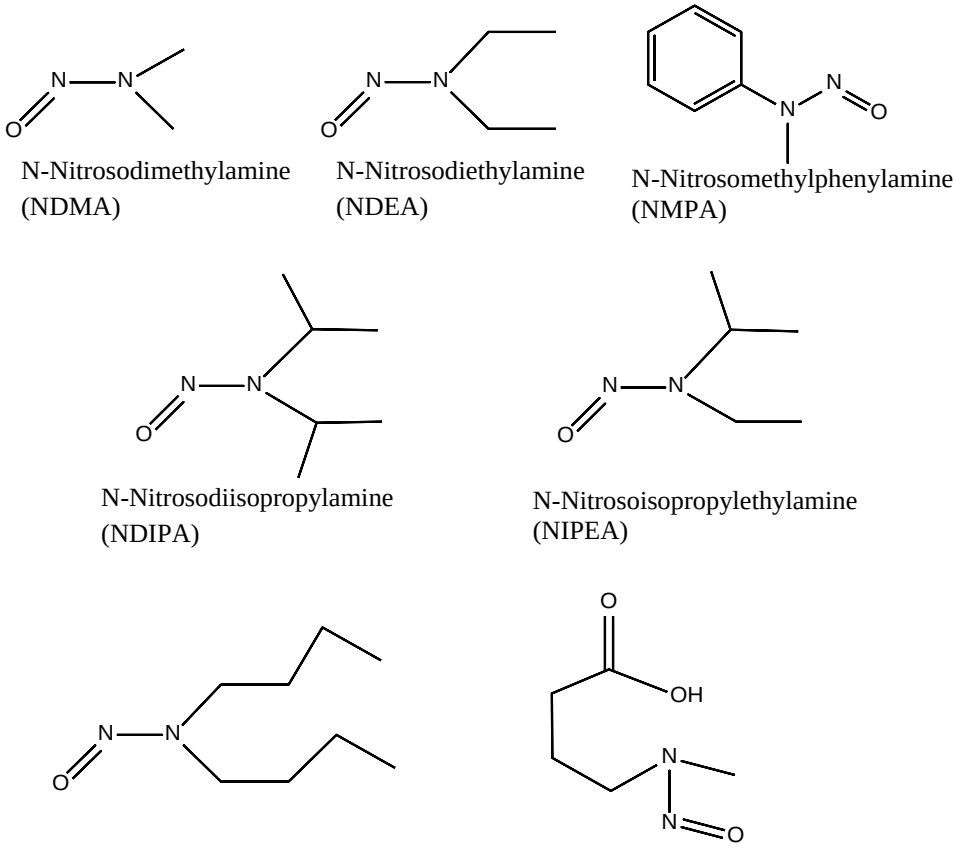
nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions).

Figure 1. Representative Reaction to Form Nitrosamines



FDA has identified seven nitrosamine impurities that theoretically could be present in drug products: NDMA, N-nitrosodiethylamine (NDEA), N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), N-nitrosoisopropylethyl amine (NIPEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA), and N-nitrosomethylphenylamine (NMPA) (Figure 2). Five of them (NDMA, NDEA, NMBA, NIPEA, and NMPA) have actually been detected in drug substances or drug products.

Figure 2. Chemical Structures of Seven Potential Nitrosamine Impurities in APIs and Drug Products



Nitrosamine compounds are potent genotoxic agents in several animal species and some are classified as probable or possible[17] human carcinogens by the International Agency for Research on Cancer (IARC).[18] They are referred to as "cohort of concern" compounds in the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018).[19] The guidance recommends control of any known mutagenic carcinogen, such as nitroso-compounds, at or below a level such that there would be a negligible human cancer risk associated with the exposure to potentially mutagenic impurities. Following the discovery of nitrosamine contaminants in ARBs, FDA published interim acceptable limits for these impurities.[20] FDA recommended that manufacturers take action to quantify nitrosamine levels in their drugs and to reduce or remove these impurities when above the interim limit; FDA has used the interim limits to guide immediate decision-making for additional evaluation and product recalls[21] while balancing the risks of potential long-term carcinogen exposure with disruption to clinical management of patients.

B. General Root Causes for the Presence of Nitrosamine Impurities in APIs

Recent information gathered by FDA suggests several general root causes of the presence of nitrosamine impurities in APIs:

1. General Conditions That Lead to Nitrosamine Formation

Formation of nitrosamines is possible in the presence of secondary, tertiary, or quaternary amines[22] and nitrite salts[23] under acidic reaction conditions. Under these conditions, nitrite salts may form nitrous acid, which can react with an amine to form a nitrosamine (see Figure 1). There is a greater risk of nitrosamine formation if nitrous acid is used to quench residual azide (a reagent commonly used in tetrazole ring formation or introduction of azide functional group into a molecule) in the presence of precursor amines.

Nitrites used as reagents in one step can carry over into subsequent steps, despite purification operations, and react with amines to generate nitrosamine impurities. Therefore, whenever nitrite salts are present, carryover into subsequent steps cannot be ruled out. In general, processes that use nitrites in the presence of secondary, tertiary, or quaternary amines are at risk of generating nitrosamine impurities.

---

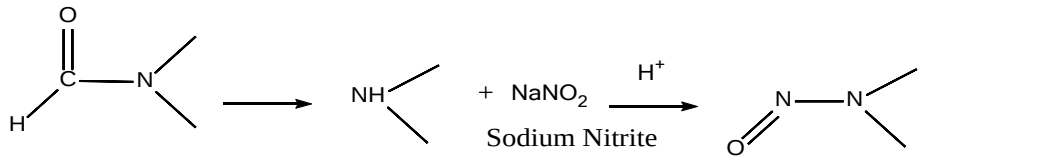
[17] NDBA is classified as possibly carcinogenic (2B) by IARC.
[18] https://monographs.iarc.fr/list-of-classifications
[19] The Agency updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[20] See the 2/28/2019 announcement at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan.
[21] https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
[22] Secondary and tertiary amines may be present as impurities or degradants of quaternary ammonium salts.
[23] Secondary, tertiary, and quaternary amines and nitrite also can be called nitrosamine precursors.

2. Sources of Secondary, Tertiary, and Quaternary Amines That Can Form Nitrosamines

Amines may be present in a manufacturing process for a variety of reasons. The API (or API degradants), intermediates, or starting materials may contain secondary or tertiary amine functional groups. Tertiary and quaternary amines may also be added intentionally as reagents or catalysts. All of these types of amines can react with nitrous acid or other nitrosating agents to form nitrosamines.[24, 25, 26]

Amide solvents, which are susceptible to degradation under certain reaction conditions, are another source of secondary amines. For example, under high reaction temperatures for an extended reaction period, N,N-dimethylformamide can degrade into dimethylamine, which can react with nitrous acid to form NDMA (see Figure 3). N-methylpyrrolidone, N,N-dimethylacetamide, and N,N-diethylacetamide also have similar degradation pathways to form secondary amines that can react with nitrous acid to form nitrosamine impurities. Secondary amines could also be present as impurities in amide solvents. For example, dimethylamine, which can react with nitrous acid to form NDMA, may exist as an impurity in N,N-dimethylformamide.

Figure 3. Formation of NDMA From N,N-Dimethylformamide



Tertiary and quaternary amines used as reagents in the synthesis of APIs may contain other amine impurities. Tertiary amines, such as triethylamine, have been shown to contain low levels of other secondary amines (such as dipropylamine and isopropylethylamine). Secondary and tertiary amines may be present as impurities or degradants formed by dealkylation of quaternary amines. For example, a common phase-transfer catalyst, tetrabutylammonium bromide, may contain tributyl- and dibutylamine impurities. The amine impurity level that may lead to nitrosamine contamination of the API is process dependent and should be determined by each API manufacturer.

This list of the aforementioned sources is not exhaustive, as amine reagents can be used to mediate a wide range of synthetic transformations. Manufacturers should evaluate other reagents containing amine functional groups for potential risk of nitrosamine formation.

[24] Smith, PAS and RN Loeppky, 1967, Nitrosative cleavage of tertiary amines, J Am Chem Soc, 89(5): 1147–1157
[25] Fiddler, W, JW Pensabene, RC Doerr, and AE Wasserman, 1972, Formation of N-nitrosodimethylamine from naturally occurring quaternary ammonium compounds and tertiary amines, Nature, 236: 307
[26] Gillatt, PN, RJ Hart, CL Walters, and PI Reed, 1984, Susceptibilities of drugs to nitrosation under standardized chemical conditions, Food Chem Toxicol, 22(4): 269–274

3. Contamination in Vendor-Sourced Raw Materials

Nitrosamine impurities can be introduced when vendor-sourced materials, including starting materials and raw materials, are contaminated. The Agency has observed the following contaminations due to this root cause:

- Nitrosamine contamination has occurred when fresh solvents (*ortho*-xylene, toluene, and methylene chloride) were contaminated during shipment from vendors (e.g., during transfer between storage vessels).

- Sodium nitrite is a known impurity in some starting materials (such as sodium azide) and may be present and react with amines under acidic conditions to form nitrosamines. Nitrate-containing raw materials, such as potassium nitrate, may contain nitrite impurities. The amount of nitrite impurity that can be tolerated is process dependent and should be determined by each API manufacturer.

- Secondary or tertiary amines have been reported as impurities in some raw materials (see details in section II.B.2 in this guidance) and in fresh solvents such as toluene.

- Starting materials or outsourced intermediates may be at risk through cross-contamination if they are manufactured at sites where nitrosamine impurities are produced in other processes.

Awareness of the supply chain of raw materials is an important factor in preventing contamination. For example, API producers may not be aware of nitrosamine contamination in raw or starting materials they have sourced from vendors; a producer whose manufacturing process is not normally susceptible to nitrosamine formation may not realize that vendor-sourced material may have had impurities introduced during production or transport.

4. Recovered Solvents, Catalysts, and Reagents as Sources of Contamination

Recovered materials such as solvents, reagents, and catalysts may pose a risk of nitrosamine impurities due to the presence of residual amines (such as trimethylamine or diisopropylethylamine). If the recovery process involves a quenching step (i.e., nitrous acid used to decompose residual azide), nitrosamines could form during solvent recovery. These nitrosamines may be entrained if they have boiling points or solubility properties[27] similar to the recovered materials, depending on how recovery and subsequent purification takes place (e.g., aqueous washes or distillation). This further increases the risk of contamination in material recovery. For these reasons, some drug products using APIs manufactured by certain "low" risk processes[28] were found to be contaminated. The Agency has observed the following contaminations due to this root cause:

[27] NDMA and NDEA have boiling points of 151–153°C and 175–177°C, respectively (https://pubchem.ncbi.nlm.nih.gov). Both are miscible with water and soluble in organic solvents.
[28] "Low" risk processes are those deemed not normally susceptible to nitrosamine formation.

- A manufacturing site may produce the same API by more than one synthetic process that uses common solvents. If any of those synthetic processes produces nitrosamines or contains precursor amines, the solvents sent for recovery are at risk. The use of recovered solvents that are comingled from different processes or across manufacturing lines without control and monitoring can introduce nitrosamine impurities. If a recovered solvent is contaminated in this way and then used to manufacture an API, the API will be contaminated even if the synthetic route is not normally susceptible to nitrosamine formation.

- Recovery of raw materials (e.g., solvents, reagents, and catalysts) is often outsourced to third-party contractors. Process outsourcing can pose a risk if the third-party recovery facility does not receive enough specific information on the contents of the materials they are processing and relies solely on routine recovery processes.

- Raw materials can be contaminated if adequate cleaning of equipment between customers, or between different materials, is not carried out or is not validated as capable of removing each impurity of concern. It was reported that *ortho*-xylene and toluene were contaminated during recovery due to inadequate cleaning and to use of shared storage equipment between different customers. Inadequate and unvalidated cleaning procedures can also lead to cross-contamination if precautions to avoid nitrosamine contamination are not in place before materials from different customers are combined for recovery. For example, the catalyst tri-N-butyltin chloride (used as a source of tri-N-butyltin azide) was contaminated at a third-party contractor facility due to the combination of this catalyst from different customers.

5. Quenching Process as a Source of Nitrosamine Contamination

There is a risk of nitrosamine formation when a quenching step is performed directly in the main reaction mixture (i.e., when nitrous acid is added to the reaction mixture to decompose residual azide). This allows nitrous acid to come into direct contact with residual amines in the raw materials used in the manufacturing process. The nitrosamine impurities could be carried to the subsequent steps if there are not adequate removal or purification operations in place, or if the operations are not optimized for removing specific impurities of concern. This can contaminate the entire downstream process once they are introduced. Even if the quenching process is conducted outside of the main reaction mixture (see section II.B.4 in this guidance), there is a risk if contaminated recovered materials are introduced into the main process.

6. Lack of Process Optimization and Control

Another potential source of formation of nitrosamine impurities is lack of optimization of the manufacturing process for APIs when reaction conditions such as temperature, pH, or the sequence of adding reagents, intermediates, or solvents are inappropriate or poorly controlled. FDA has seen instances in which reaction conditions varied widely between batches and even between different processing equipment in the same facility for the same API.

The multiple root causes of nitrosamine contamination listed above can occur within the same API process. Therefore, multiple strategies may be necessary to identify all potential sources of

contamination. Typical routine tests (e.g., HPLC) for API purity, identity, and known impurities are unlikely to detect the presence of nitrosamine impurities. Further, each failure mode could result in different nitrosamines in different amounts across batches from the same process and the same API producer, with contamination detected in some batches but not all.

C. Nitrosamine Impurities in Drug Products From Sources Other Than API Contamination

Nitrites are common nitrosating impurities that have been reported in many excipients at ppm levels. Nitrite impurities are found in a range of commonly used excipients, which may lead to nitrosamine impurities forming in drug products during the drug product manufacturing process and shelf-life storage period. The supplier qualification program[29] should take into account that nitrite impurities vary across excipient lots and may vary by supplier. Drug product manufacturers should also be aware that nitrite and nitrosamine impurities may be present in potable water.

Some drug products may undergo degradation pathways that form nitrosamine impurities; this could potentially occur during drug product storage.

III. RECOMMENDATIONS

Because nitrosamines are probable or possible human carcinogens, FDA recommends that manufacturers consider the potential causes of nitrosamine formation described in this guidance as well as any other pathways observed and evaluate the risk for nitrosamine contamination or formation in their APIs and drug products. Manufacturers should prioritize evaluation of APIs and drug products based on factors such as maximum daily dose, duration of treatment, therapeutic indication, and number of patients treated.[30] As new information becomes available and FDA's understanding of nitrosamines in drugs evolves, the Agency may recommend that certain drug products become higher priorities for risk assessment.

Manufacturers should refer to the ICH guidance for industry *Q9 Quality Risk Management* (June 2006) for details related to quality risk identification, analysis, and management. Manufacturers of APIs and drug products should take appropriate measures to prevent unacceptable levels of nitrosamine impurities in their products.

[29] In accordance with the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009), the manufacturer's pharmaceutical quality system extends to control of the quality of purchased materials. The supplier qualification program is a manufacturer's system (e.g., audits, material evaluations, qualification) for selecting material suppliers who can provide materials using a defined and approved supply chain.

[30] For example, a drug product with a maximum daily dose (MDD) of 2000 mg with the same detected level of the same type of nitrosamine would pose a greater risk than a drug product with a maximum daily dose of 200 mg. A drug product intended for only short-term use (e.g., a 7-day course of an antibiotic) poses less risk than a drug product intended for chronic use.

A. Acceptable Intake Limits

FDA recommends the following acceptable intake (AI)[31] limits for the nitrosamine impurities NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA (Table 1). We further recommend that manufacturers use these AIs when determining limits for nitrosamine impurities in APIs and drug products.[32]

Table 1. AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

[1] The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA,NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. Appendix B includes a description of the AI derivation for NDMA, which is an example of how FDA applied ICH M7(R1) to set a limit.
[2] The conversion of AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

These limits are applicable only if a drug product contains a single nitrosamine. If more than one of the nitrosamine impurities identified in Table 1 is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the AI for the most potent nitrosamines) based on the maximum daily dose (MDD), the manufacturer should contact the Agency for evaluation. For drug products with an MDD of less than 880 mg/day, a recommended limit for total nitrosamines of 0.03 ppm is not more than 26.5 ng/day and is considered acceptable. For drug products with an MDD above 880 mg/day, the limit for total nitrosamines should be adjusted so as not to exceed the recommended limit of 26.5 ng/day.[33]

If nitrosamines without published AI limits are found in drug products, manufacturers should use the approach outlined in ICH M7(R1) to determine the risk associated with the nitrosamine and contact the Agency about the acceptability of any proposed limit.[34]

Generally, sensitive methods with limits of quantitation (LOQ) in the parts-per-billion (ppb) range are needed to meet the low AIs recommended for nitrosamines. Manufacturers of APIs and drug

[31] The term *acceptable intake (AI)* is used in ICH M7(R1) to indicate the threshold of toxicological concern (TTC) considered for the impurity to be associated with negligible risk of carcinogenicity or other toxic effects. FDA announcements regarding limits for nitrosamines used the term *acceptable daily intake (ADI)*. For the purposes of this guidance, the term *AI* is used rather than *ADI*.
[32] API manufacturers should control nitrosamine impurities to ensure that the drug products in which the APIs are used will meet the recommended AI limits.
[33] Manufacturers should contact CDER-OPQ-Inquiries@fda.hhs.gov if multiple nitrosamine impurities are detected in an API or drug product in which the total nitrosamine level exceeds 26.5 ng/day based on MDD. Inquiries submitted to this mailbox will be routed to the appropriate FDA office.
[34] See footnote 33 for contact information.

products should use methods with LOQs at or below 0.03 ppm.[35] Manufacturers should establish methods for which the LOQ and limit of detection (LOD) are as low as reasonably practical for products for which the maximum daily dose is high (e.g., greater than 1 g). If more than one nitrosamine listed in Table 1 is detected, then the analytical method should be validated for LOQs below 0.03 ppm to accurately quantify a total nitrosamine level of not more than 26.5 ng/day. For example, if the MDD is 1200 mg, the LOQ should be below 0.02 ppm. FDA's public webpage includes validated analytical test methods recommended for detecting nitrosamine impurities in several different APIs and products.[36, 37]

API and drug product manufacturers should take the following steps to mitigate nitrosamine impurities in their products:

1. Assess the risk of nitrosamine impurities in APIs, marketed products, and products under approved and pending applications. Risk assessments should be conducted in a timely manner based on the prioritization of drugs.[38] Manufacturers do not need to submit risk assessment documents to the Agency, but they should retain these documents so that they are available if requested.

2. Conduct confirmatory testing[39] when there is any risk for the presence of nitrosamine impurities. Due to nitrosamines' physiochemical properties (low molecular weights, some volatility and high toxicity), the analytical methods for nitrosamines need to have specificity, excellent chromatographic separation, and highly sensitive detection capability.

3. Report changes implemented to prevent or reduce nitrosamine impurities in APIs and drug products to FDA. This includes submission of any drug master file (DMF) amendments in accordance with 21 CFR 314.420(c) and changes to approved applications as required under 21 CFR 314.70 and 314.97 and pending applications under 21 CFR 314.60 and 314.96.

[35] The LOQ may be considered the reporting threshold for nitrosamine impurities (i.e., the limit above which an impurity should be reported in the certificate of analysis).
[36] FDA-recommended analytical methods for detecting nitrosamine impurities can be found at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine, at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin, and in the 12/12/2018 update at https://www.fda.gov/Drugs/DrugSafety/ucm613916.htm.
[37] Manufacturers or laboratories are encouraged to make validated test methods publicly available (e.g., by posting on the method developer's website) to facilitate faster testing of other similar products. FDA also accepts requests to post privately developed methods at FDA's website if FDA's review of the method protocol finds it is scientifically sound, and if the method owner provides written authorization for posting by FDA. The manufacturers or laboratories should send their test methods to CDER-OPQ-Inquiries@fda.hhs.gov.
[38] In accordance with quality management principles, manufacturers should consider manufacturing changes and shifts over the product lifecycle that may impact the potential for nitrosamine impurities, including new sources of raw materials or excipients. Risks should be reassessed periodically (see ICH Q9).
[39] Testing using appropriately validated methods may be conducted by the API manufacturer or by a qualified laboratory.

B. Recommendations to API Manufacturers

While nitrosamines are not expected to form during the manufacture of the vast majority of APIs, all manufacturers of chemically synthesized APIs should take appropriate actions to mitigate the risk of nitrosamine contamination for APIs where there is a potential for nitrosamine impurities.

API manufacturers should review their API manufacturing processes and perform risk assessments to identify the potential for nitrosamine impurities. If a risk of nitrosamine impurities is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods. If the risk assessment determines that there is no potential for nitrosamine impurities, there is no need to take further action. If a nitrosamine impurity is detected, API manufacturers should investigate the root cause. They should implement changes in the manufacturing process to reduce or prevent nitrosamine impurities.[40]

1. Mitigating the Presence of Nitrosamine Impurities in APIs

FDA recommends that API manufacturers take the following actions:

- API manufacturers should optimize the design of the manufacturing process for APIs during route of synthesis (ROS) development to minimize or prevent the formation of nitrosamine impurities. API manufacturers should refer to the recommendations in ICH M7(R1) and the ICH guidances for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016) and *Q11 Development and Manufacture of Drug Substances* (November 2012) in this respect. The following factors should be considered during process development:
    - Avoiding reaction conditions that may produce nitrosamines whenever possible; when not possible, demonstrating that the process is adequately controlled and is capable of consistently reducing nitrosamine impurities through appropriate and robust fate and purge studies.
    - Using bases other than secondary, tertiary, or quaternary amines (when possible) if ROS conditions may form nitrosamines.
    - Using caution when the ROS involves the use of amide solvents (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, and N-methylpyrrolidone).
    - Replacing nitrites with other quenching agents for azide decomposition processes.
    - Optimizing and consistently controlling the sequences of reactions, processes, and reaction conditions (such as pH, temperature, and reaction time).
    - Designing a manufacturing process that facilitates the purge of nitrosamine impurities in the subsequent processing steps.

[40] See section V in this guidance for reporting changes to approved applications and DMFs.

- API manufacturers should consider removing quenching steps (when there is a risk of nitrosamine formation, e.g., using nitrous acid to decompose residual azide) from the main reaction mixture to reduce the risk of nitrosamine formation. The API, or an intermediate formed through a reaction using an azide salt, can be separated from the mother liquor into the organic phase. The aqueous waste phase separated from the organic phase should then be quenched with nitrous acid without contacting the API, its intermediate, or solvents intended for recovery.

- API manufacturers should audit their supply chains and monitor them for any at-risk raw materials, starting materials, and intermediates.[41] API manufacturers should maintain records including the name of the raw material manufacturer and its supplier,[42] roles of the actual manufacturers of such materials, and any repackers and distributors who handle the materials before API manufacture. When appropriate, API manufacturers should establish controls and consider additional specifications for at-risk materials to prevent nitrosamine contamination.

- To avoid cross-contamination when recovered materials such as solvents, reagents, and catalysts are used in the manufacturing process, recovered material should be used only in the same step or in an earlier step (if there is sufficient purification) of the same process from which it was collected. The recovered materials should meet appropriate standards before reuse. If the recovery of materials is outsourced to third-party contractors, the API manufacturer should audit the contractors' validation of cleaning procedures. API manufacturers should follow recommendations in ICH Q7 for ensuring that cross-contamination with nitrosamine or nitrosamine precursors can be prevented. API manufacturers should also verify with their suppliers whether the purchased materials used in their processes are recovered.

- API manufacturers should be aware that potable water used in API manufacture may contain low levels of nitrite and even nitrosamines from environmental contamination.[43] The existence of nitrites in processing water may lead to nitrosamine contamination in API manufacture. Therefore, to avoid unacceptable levels of nitrosamine impurities in APIs, API manufacturers should analyze nitrite and nitrosamine levels in water and use water that has been purified to remove unacceptable impurities.

  If a nitrosamine is introduced to the API through exogenous sources[44] that can be avoided, manufacturers should eliminate the source of contamination.

- API batches may be reprocessed or reworked to control the level of nitrosamine impurities as provided in ICH Q7 for amending and controlling such operations. If a batch is found to

[41] For a description of "at-risk materials," see section II.B in this guidance.
[42] ICH Q7
[43] See the latest version of the WHO's *Guidelines for Drinking-Water Quality* at https://www.who.int/water_sanitation_health/water-quality/guidelines/en/.
[44] Exogenous sources, for the purposes of this guidance, refer to materials such as solvents and raw materials used in synthesis or processing that may introduce contamination.

contain nitrosamine and is reprocessed or reworked in any way, these operations should be conducted under oversight of the quality unit.

2. *Control of Nitrosamine Impurities in APIs*

If a nitrosamine impurity is detected above the LOQ, the API manufacturer should develop a strategy to ensure that the nitrosamine level remains within the AI limit. Manufacturers should develop an appropriate control strategy, which should include specification limits, to ensure that the nitrosamine level reliably remains well below the AI limit in the API. Given existing uncertainties regarding nitrosamine impurities and their presence in drugs, for APIs with an impurity detected above the LOQ or at-risk APIs, testing of each batch on release should be conducted. Alternate approaches (e.g., upstream test of an intermediate) should be supported by sufficient process understanding and evidence of adequate statistical control and should be submitted to FDA in a supplement prior to implementation.[45]

Any API batch found to contain levels of nitrosamine impurities above the recommended AI should not be released by the API manufacturer for distribution unless, with prior FDA agreement, the API is needed to prevent or mitigate a shortage of a drug.

C. Recommendations to Drug Product Manufacturers

Drug product manufacturers should conduct risk assessments to determine the potential for nitrosamine impurities in drug products. A risk assessment should involve collaboration with the API manufacturer to aid in the identification of the API ROS or other process conditions of the API's manufacture that put the drug product at risk for nitrosamine impurities. The risk assessment should also include evaluation of any pathway (including degradation) that may introduce nitrosamines during drug product manufacture or storage. If the risk assessment determines that there is no potential for nitrosamine impurities, there is no need to take further action.

If a risk of nitrosamines in a drug product is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods.[46] If a nitrosamine impurity is detected, manufacturers should investigate the root cause and implement changes in the manufacturing process to mitigate or reduce nitrosamine impurities.[47]

1. *Control of Nitrosamine Impurities in Drug Products*

Drug product manufacturers must test representative samples of all incoming components, including lots of at-risk API, prior to use, as required under 21 CFR 211.84.[48] To meet the CGMP

[45] All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (see 21 CFR 314.70(b)(2)) and the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004)).

[46] Testing using appropriately validated methods may be conducted by the API manufacturer or by a qualified laboratory.

[47] See section V in this guidance for reporting changes to approved applications and DMFs.

[48] At-risk APIs include APIs with secondary, tertiary, and quaternary amine functional groups. They also include any API with an ROS using at-risk materials (see section II.B in this guidance).

regulations in 21 CFR 211 subpart E and be consistent with the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009), drug product manufacturers should continue testing API lots until they have verified that the API supplier can consistently manufacture API without unacceptable levels of nitrosamine.

Drug product manufacturers, when designing their control strategy, should evaluate whether nitrites could be present during manufacturing processes where at-risk APIs are used. They should also evaluate whether nitrosamines could form in a finished drug product over the drug product's shelf life. If a nitrosamine is introduced to the drug product through exogenous sources that can be avoided, manufacturers should eliminate the source of contamination.

If a nitrosamine impurity is detected above the LOQ, the manufacturer should develop a strategy to ensure that the nitrosamine level remains within the AI limit. The control strategy should include specification limits for the identified nitrosamine. Such a control strategy is also recommended when the introduction of nitrosamine is inherent due to the API structure, the API ROS, or the manufacturing process of the API or drug product. Given existing uncertainties regarding nitrosamine impurities and their presence in drugs, testing of each batch on release should be conducted. Alternate approaches should be supported by sufficient process understanding and evidence of adequate statistical control and should be submitted to FDA in a supplement prior to implementation.[49]

If drug product batches with unacceptable levels of nitrosamine impurities are already in distribution, drug product manufacturers should contact FDA so the Agency can determine the regulatory action for the specific drug products. Any drug product batch found to contain levels of nitrosamine impurities at or above the recommended AI should not be released by the drug product manufacturer for distribution. Manufacturers should contact the Agency if a recall is initiated.[50] Under section 501 of the Food, Drug, and Cosmetic Act (FD&C Act),[51] a drug that is not manufactured, processed, packed, or held in conformity with CGMP to ensure that the drug meets certain quality and purity standards is considered adulterated. FDA may exercise regulatory discretion when warranted to prevent or mitigate a shortage of a drug.

IV. MAINTAINING THE DRUG SUPPLY

If any manufacturing changes or recalls are likely to lead to a disruption in the drug supply, manufacturers should immediately contact CDER's Drug Shortage Staff at drugshortages@fda.hhs.gov; FDA can work with manufacturers to mitigate the risk of nitrosamine impurities in APIs and drug products while avoiding interruptions in the drug supply. Contacting the Drug Shortage Staff can assist manufacturers in meeting any obligations to report discontinuances or interruptions in their drug manufacture under section 506C of the FD&C Act and implementing regulations under 21 CFR 314.81(b)(3)(iii). It also allows FDA to consider, as

[49] All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (see 21 CFR 314.70(b)(2)(i)) and the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004)).

[50] Manufacturers can contact the recall coordinator assigned to the product type and location. Contact information for recall coordinators is available at https://www.fda.gov/safety/industry-guidance-recalls/ora-recall-coordinators.

[51] See 21 U.S.C. 351.

soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on the affected products.

V. REPORTING CHANGES TO FDA

Drug manufacturers must report changes implemented to prevent or reduce nitrosamine impurities in accordance with FDA regulations (21 CFR 314.60, 314.70, 314.96, and 314.97).

If an API DMF holder makes process changes in the ROS as a result of the risk assessment and confirmatory testing, the DMF holder must submit amendments and inform each drug product manufacturer that references the DMF (including pending and approved applications), in accordance with 21 CFR 314.420(c). If the API is manufactured by the applicant and not covered by a DMF, the manufacturer must report such ROS changes in the application in accordance with 21 CFR 314.70 and 21 CFR 314.97. If a batch of API is found to contain a nitrosamine and is reprocessed or reworked in any way, these operations should be reported in the DMF or application (as applicable).

Although each DMF may contain only a single synthetic route, if a change in synthetic process is needed to avoid nitrosamine contamination and it is not possible to immediately stop using the original manufacturing process, the API manufacturer should submit both processes in the DMF and provide an estimate for the earliest feasible timeframe for the removal of the original process. The different synthetic processes should be identified by separate codes to designate batches manufactured through each process. If the original process cannot be discontinued within a reasonable timeframe, the new or revised process should be submitted in a separate DMF.

If changes to the drug product are needed to prevent nitrosamine formation, application holders must submit a supplement to notify FDA of any changes to conditions established in the approved applications beyond the variations already provided for in their applications, as required by 21 CFR 314.70 and 314.97. Holders of pending applications must update their applications through submission of an amendment according to 21 CFR 314.60 and 314.96. Section V of this guidance includes additional information on reporting changes in APIs and drug products.

A. Recommended Timeline for Risk Assessment, Confirmatory Testing, and Submission of Required Changes

FDA recommends different implementation timelines depending on the regulatory status of the drug product.[52]

[52] New drug application (NDA) and abbreviated new drug application (ANDA) holders or sponsors, drug master file (DMF) holders, and owners of marketed products that are not the subject of approved NDAs or ANDAs (such as compounded products or products marketed under an over-the-counter (OTC) drug monograph) who are not also the manufacturer of the drug products and APIs should work with their contract manufacturers to take the steps recommended in this guidance. This applies to drug products currently available on the U.S. market as well as those with pending applications.

1. Approved or Marketed Drug Products

To ensure the safety of the U.S. drug supply, manufacturers should conclude a risk assessment of approved or marketed products *within 7 months* of publication of the original guidance, with a recommended completion date of on or before March 31, 2021. Confirmatory testing should start as soon as the risk of nitrosamine is identified from the risk assessment and should begin immediately for products considered at high risk. To ensure the safety of the U.S. drug supply, confirmatory testing of drug products and submission of required changes in drug applications should be concluded *within 3 years* of publication of the original guidance, with a recommended completion date of on or before October 1, 2023. FDA acknowledges that the implementation timeline includes investigating the root cause of the contamination or formation, identifying changes that will eliminate the root cause (e.g., change in manufacturing process, change in supplier), and confirming that any proposed changes will minimize the risk of nitrosamine contamination or formation without otherwise adversely affecting product quality. The timelines also include activities conducted by API manufacturers (i.e., risk assessment and testing) to support the drug products in which they are used. FDA may request an expedited risk assessment, confirmatory testing, or other regulatory action based on information available to the Agency.

2. Pending Applications

a. Pre-Submission Stage

FDA recommends that applicants conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products and conduct confirmatory testing as needed prior to submission of an original application. However, the risk assessment and submission of confirmatory testing, if needed, and changes to the DMF or application may be submitted in an amendment if they are not available at the time of the original submission filing. Such an amendment should be submitted as quickly as possible after the original submission filing to minimize any potential adverse impact on the application assessment timeline.[53]

b. Applications Pending With the Agency

Applicants with pending applications should conduct the risk assessment expeditiously and inform FDA if confirmatory testing finds nitrosamine levels above the AI limit.[54] If a nitrosamine impurity is detected above the LOQ but is within the AI limit, the applicant should amend the application as appropriate. The Agency will work with the applicant to resolve issues during the review cycle or immediately after approval, and before distribution, if determined to be necessary by the Agency.[55]

[53] For NDA submissions, manufacturers should discuss the need for an amendment with the Agency at the pre-NDA stage.
[54] For NDAs, the applicant should contact the specific product's review division. For ANDAs, the applicant should contact the project manager specified for the ANDA.
[55] In certain cases, FDA may consult with CDER's Drug Shortage Staff to ensure adequate supply on the U.S. market.

FDA generally will adhere to review goals established as part of the Prescription Drug User Fee Act reauthorization for years 2018–2022 (PDUFA VI) and the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II).

APPENDIX A. ADDITIONAL RESOURCES

The recommendations on reporting changes in APIs and drug products in this guidance are in accordance with the FDA's current regulations and guidances. The following guidances[1] are generally relevant to API and drug product impurities, including reporting changes of controls for impurities and application submission information:[2]

- Guidance for industry *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
- Guidance for industry *SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)
- Guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale -Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (October 1997)
- Guidance for industry *Changes to an Approved NDA or ANDA* (April 2004)
- ICH guidance for industry *Q9 Quality Risk Management* (June 2006)
- ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009)
- ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012)
- Guidance for industry *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)
- ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016)
- ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018)
- Draft guidance for industry *Postapproval Changes to Drug Substances* (September 2018)[3]

[1] The Agency updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] This guidance is not intended to cover all of the current good manufacturing practice (CGMP) requirements that are relevant. The DMF and drug product reporting provisions are the main focus in this section of the guidance.
[3] When final, this guidance will represent FDA's current thinking on this topic.

APPENDIX B. FDA DETERMINATION OF ACCEPTABLE INTAKE LIMITS

Identification of the acceptable intake (AI) values listed in section III of this guidance follows the procedures recommended in the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018).[1] A compound-specific AI can be calculated based on rodent carcinogenicity potency data such as TD_{50} values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2) identified in the public literature. Linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is achieved by simply dividing the TD_{50} by 50,000. The AI (in mg/kg/day units) can then be converted to mg/day by multiplying by the human body weight (50 kg is the assumed body weight identified in the referenced guidance). Linear extrapolation from a TD_{50} value is considered appropriate to derive an AI for M7 Class 1 impurities (known mutagenic carcinogens) with no established threshold mechanism. In many cases, the carcinogenicity data are available from the Carcinogenicity Potency Database (CPDB). When the CPDB contains a pre-calculated TD_{50} value for a selected chemical, this value may be used to calculate the AI. Where carcinogenicity study data for an impurity are of lesser quality as described in ICH M7, a surrogate compound with carcinogenicity data may be used to derive an acceptable intake but should be scientifically justified.

A summary of the AI derivation for NDMA is provided as an example. NDMA was identified as a mutagenic carcinogen in several species and is listed as a probable human carcinogen by the Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) program. TD_{50} values for NDMA are 0.0959 mg/kg/day (rat, based on Peto et al.[2]) and 0.189 mg/kg/day (mouse) according to the CPDB.[3] For the AI calculation, the lower (more conservative) value of the rat is used. The resulting AI associated with a 1 in 100,000 cancer risk over 70 years of exposure is calculated by dividing the TD_{50} by 50,000 and then multiplying by 50 to account for a patient with a 50-kg body weight, resulting in 0.0000959 mg/day NDMA, or approximately 96 ng/day NDMA.

Hence, a daily lifelong intake of 96 ng/day NDMA corresponds to a theoretical cancer risk of 10^{-5} and therefore represents an AI when present as an impurity.

[1] The Agency updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] Peto, R, R Gray, P Brantom and P Grasso, 1991, Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine, Cancer Research, 51: 6452–6469

[3] Carcinogenicity Potency Database entry for N-nitrosodimethylamine (CAS 62-75-9) (NDMA) accessed at https://www.nlm.nih.gov/databases/download/cpdb.html

EXHIBIT 5

Information about Nitrosamine Impurities in Medications

On This Page

Latest Information

Losartan Valsartan and other ARBs (/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan)

Metformin (/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin)

Ranitidine (Zantac) (/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine)

Rifampin/Rifapentine (/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine)

Varenicline (Chantix) (/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix)

What You Should Know about Nitrosamine Impurities

FDA issues guidance,"Control of N-Nitrosamine Impurities in Human Drugs"

Update [2/24/2021] To ensure the safety of the U.S. drug supply, the guidance recommends that manufacturers should conclude the risk assessment of approved or marketed products, the first of three steps manufacturers should follow to mitigate nitrosamine impurities in their products, within 6 months of publication of the guidance. Through

Top ()

today's revision to the guidance, FDA extends the recommended timeframe for completion of risk assessments to March 31, 2021. Manufacturers do not need to submit risk assessment documents to the agency, but they should retain these documents so that they are available if requested.

[9/1/2020] FDA is announcing the availability of a guidance for industry, entitled "Control of N-Nitrosamine Impurities in Human Drugs (/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)." This guidance recommends steps manufacturers of active pharmaceutical ingredients and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products. The guidance also describes conditions that may introduce nitrosamine impurities.

What patients should know about nitrosamine impurities

- FDA has been investigating the presence of impurities, called nitrosamines, in some types of medications.
- Nitrosamines are common in water and foods, including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
- FDA, in collaboration with regulatory counterparts around the world, has set internationally-recognized acceptable daily intake limits for nitrosamines. If drugs contain levels of nitrosamines above the acceptable daily intake limits, FDA recommends these drugs be recalled by the manufacturer as appropriate.
- Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that contains nitrosamines at-or-below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer.
- Patients taking prescription medications with potential nitrosamine impurities should not stop taking their medications. Patients should talk to their health care professionals about concerns and other treatment options.
- Consumers taking over-the-counter medications with potential nitrosamine impurities may consider using other OTC products approved for their condition.
- Find information about medications that have been recalled due to potential nitrosamine impurities on the FDA recalls webpage (/safety/recalls-market-withdrawals-safety-alerts).
- The agency is working to determine the source of these impurities and will keep the public informed.

What health care professionals should know about nitrosamine impurities

- Health care professionals should continue to prescribe medications when clinically appropriate even though they may have low levels of nitrosamine impurities.
- Health care professionals can educate patients about alternative treatment options to medications with potential nitrosamine impurities if available and clinically appropriate.
- Find information about medications that have been recalled due to potential nitrosamine impurities on the FDA recalls webpage (/safety/recalls-market-withdrawals-safety-alerts). (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/mylan-initiates-voluntary-nationwide-recall-three-lots-nizatidine-capsules-usp-due-detection-trace)
- If a medication has been recalled, pharmacists may be able to dispense the same medication from a manufacturing lot that has not been recalled. Prescribers may also determine whether there is an alternative treatment option for patients.
- FDA will continue to investigate the presence of nitrosamine impurities in drugs and will communicate new information as it becomes available.

What industry should know about nitrosamine impurities

- Manufacturers are responsible for understanding their processes, which includes preventing the presence of unacceptable impurities. Manufacturers are also responsible for developing and using suitable methods to detect and limit unacceptable impurities, including any new impurities that may arise when they make changes to their manufacturing processes.
- FDA has published testing methods that can be used by industry to detect nitrosamine impurities.
- FDA, in collaboration with regulatory counterparts around the world, has set internationally-recognized acceptable daily intake limits for nitrosamines. If drugs contain levels of nitrosamines above the acceptable daily intake limits, FDA recommends these drugs be recalled by the manufacturer as appropriate or not be released for distribution to the market.
- The agency is working with industry to determine the source of these impurities, but there are multiple reasons why nitrosamines can be present in medicines.

Why are some drugs being recalled due to a potential nitrosamine impurity while others are not?

FDA, in collaboration with regulatory counterparts around the world, has set internationally-recognized acceptable daily intake limits for nitrosamines. Nitrosamines below this level are acceptable in drugs. If drugs contain levels of nitrosamines above the acceptable daily intake limit, FDA recommends these drugs be recalled by the manufacturer.

Some manufacturers have recalled certain drugs as a precautionary measure, while others have been recalled after testing positive for nitrosamine levels above the acceptable daily intake limits. Information about drugs that have been recalled due to potential nitrosamine impurities can be found on the FDA recalls webpage (/safety/recalls-market-withdrawals-safety-alerts/mylan-initiates-voluntary-nationwide-recall-three-lots-nizatidine-capsules-usp-due-detection-trace).

Top ()

What is the risk of taking a drug that contains nitrosamines?

FDA does not expect nitrosamines to cause harm when ingested at low levels. Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that contains nitrosamines at, or below, the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer.

Why are nitrosamine impurities present in drugs?

There are multiple reasons why nitrosamines can be present in drugs. FDA found the source of nitrosamines can be related to the drug's manufacturing process or its chemical structure or even the conditions in which they are stored or packaged. As foods and drugs are processed in the body, nitrosamines can also be formed. FDA continues to test and research possible sources for drugs found to contain nitrosamines.

Is the presence of nitrosamines in drugs a new problem? Why have there been so many recent reports of drugs containing nitrosamines?

FDA has ongoing assessment, surveillance, compliance and pharmaceutical quality efforts across every product area, and we will continue to work with drug manufacturers to ensure safe, effective and high-quality drugs for the American public. When we identify new and previously unrecognized risks to safety and quality, we react swiftly to resolve the problem, as we have done in responding to the recent findings of nitrosamines in certain medicines.

Today, we have better testing methods than ever before, and we know what to look for in products' chemical structures and manufacturing processes that may increase the risk of forming low levels of nitrosamines. Improved technology enables us to detect even trace amounts of impurities in drug products and may be the reason why more products have been found to have low levels of nitrosamines. The agency has strict standards for safety, effectiveness and quality, and our staff makes every effort to help keep the U.S. drug supply as safe as possible. We also work closely with international drug regulatory agencies so that we leverage resources and testing done outside the U.S. which can help inform testing of the U.S. drug supply. As our investigations and testing continues, along with the investigations done by other drug regulatory agencies, we may find low levels of nitrosamines in additional drugs.

Can we trust FDA and its approvals and drug surveillance?

FDA is committed to ensuring that the medicines Americans take are safe and effective. We continually gain new knowledge about drugs which allows us to identify and quickly address previously unknown risks to patients. When we identify drug quality lapses that pose potential risks for patients, we make every effort to understand the issues and provide our best recommendation to the public as quickly and accurately as possible. We will continue to investigate and work to ensure these types of impurities do not exceed acceptable limits so that patients can continue taking their medicines without concern.

Resources for You

- Stakeholder Questions for May 4th FDA-Industry Meeting to Discuss Nitrosamine Impurities in Pharmaceuticals (/media/150864/download)
- Video: A Message for Patients about ARBs (https://youtu.be/BLZMnHxyfqg) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) | Transcript (/drugs/drug-safety-and-availability/transcript-angiotensin-ii-receptor-blockers-arbs-message-patients)
- FDA Recalls – Recalls, Market Withdrawals, & Safety Alerts (/safety/recalls-market-withdrawals-safety-alerts)
- What to Know and Do About Possible Nitrosamines in Your Medication (/consumers/consumer-updates/what-know-and-do-about-possible-nitrosamines-your-medication)

Top ()

EXHIBIT 6

FDA Updates and Press Announcements on Nitrosamine in Varenicline (Chantix)

9/17/2021: UPDATE - Pfizer again expands voluntary Chantix recall

Update [9/17/2021] FDA is alerting patients and health care professionals that Pfizer is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/pfizer-expands-voluntary-nationwide-recall-include-all-lots-chantixr-varenicline-tablets-due-n) to include all lots of varenicline (Chantix) 0.5 mg and 1 mg tablets. Pfizer is recalling these lots due to the presence of unacceptable N-nitroso-varenicline levels.

To lessen the impact to patients from a drug shortage due to this ongoing recall, FDA will not object to certain manufacturers distributing varenicline tablets containing N-nitroso-varenicline above FDA's acceptable intake limit of 37 ng per day but below the interim acceptable intake limit of 185 ng per day until the impurity can be eliminated or reduced to acceptable levels.

The agency has temporarily exercised regulatory flexibility and discretion with respect to Apotex's distribution of Health Canada-approved Apo-Varenicline tablets in the U.S. containing N-nitroso-varenicline up to FDA's interim acceptable intake limit in order to help maintain adequate varenicline supply in the U.S. for the near term.

FDA reminds patients taking recalled varenicline to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different treatment. The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

8/23/2021: Laboratory testing results for nitrosamines in varenicline products

Go to Laboratory Tests | Varenicline (/drugs/drug-safety-and-availability/laboratory-analysis-varenicline-products)

8/18/2021: Pfizer voluntarily recalls additional lots of varenicline (Chantix)

Update [8/18/2021] Pfizer expanded its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/pfizer-expands-voluntary-nationwide-recall-include-four-additional-lots-chantixr-varenicline-tablets) of varenicline (Chantix) to include 4 additional lots (16 total) to the consumer level. Pfizer is recalling these lots due to the presence of N-nitroso-varenicline above the company's acceptable limit for this impurity.

FDA reminds patients taking recalled varenicline to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

7/19/2021: UPDATE - Pfizer expands its voluntary recall of Chantix

Update [7/19/2021] Pfizer expanded its voluntary recall (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/pfizer-issues-voluntary-nationwide-recall-twelve-lots-chantixr-varenicline-tablets-due-n-nitroso) of varenicline (Chantix) to 12 lots to the consumer level. Pfizer is recalling these lots due to the presence of N-nitroso-varenicline above the company's acceptable limit for this impurity.

Pfizer's recalled lots to date:

Lot number	Expiration date
00020231	9/2021
00020232	11/2021
00020357	12/2021
00020358	1/2022
00020716	1/2022
00019213	1/2022
ET1607	1/2023
ET1609	1/2023
EC6994	5/2023
**ET1600*	*1/2023*
**EA6080*	*3/2023*
**EC9843*	*3/2023*

**most recent additions*

FDA reminds patients taking recalled varenicline to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

7/16/2021: UPDATE - FDA not objecting to distribution of varenicline with nitrosamine below interim acceptable intake limit

EXHIBIT 7

FDA alerts health care professionals and patients to a voluntary recall of varenicline (Chantix) to the warehouse level

[**7/02/2021**] FDA is alerting patients and health care professionals to Pfizer's voluntary recall of nine lots of the smoking cessation drug, varenicline (brand name Chantix), to the warehouse level. The company is recalling varenicline because it may contain levels of a nitrosamine impurity, called N-nitroso-varenicline, above FDA's acceptable intake limit. N-nitroso-varenicline may be associated with a potential increased cancer risk in humans, but there is no immediate risk to patients taking this medication. An increased cancer risk would be associated with long-term use, and the health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.

Recalled lots:

Lot number	Expiration date
00020231	9/30/2021
00020232	11/30/2021
00020357	12/31/2021
00020358	1/31/2022
00020716	1/31/2022
00019213	1/31/2022
ET1607	1/31/2023
ET1609	1/31/2023
EC6994	5/31/2023

N-Nitroso-varenicline belongs to the nitrosamine class of compounds, some of which are classified as probable or possible human carcinogens (substances that could cause cancer), based on laboratory tests such as rodent carcinogenicity studies. Although there are no data available to directly evaluate the carcinogenic potential of N-nitroso-varenicline, information available on closely related nitrosamine compounds was used to calculate lifetime exposure limits for N-nitroso-varenicline.

Pfizer is recalling the varenicline lots currently stored in warehouses. FDA recommended Pfizer revise its recall to the consumer level in order to take into account the product currently on the market, but the company has not yet done so.

In addition to the voluntary recall, Pfizer is holding release of varenicline to the U.S. market until it can confirm N-nitroso-varenicline levels below what the company considers to be acceptable.

What patients should know:

- Continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option.
- Contact your health care professional if you are taking this medication and have questions about your health.

What health care professionals should know:

- FDA has determined the recalled varenicline poses an unnecessary risk to patients. Therefore, FDA recommends health care professionals consider other available treatment options for the patient's medical condition.
- If you have varenicline samples from this company, quarantine them, and do not provide them to patients.
- Contact Pfizer directly if you have questions regarding product return or disposal.

FDA is actively considering options to help mitigate a shortage of varenicline in the U.S. including working to identify an alternate supplier. The agency is continuing to investigate the presence of N-nitroso-varenicline in varenicline products and will provide more information as it becomes available.

We know impurities in medicines are of great concern to patients and consumers who rely on safe and effective medicines approved by FDA, and we are working with manufacturers and global regulators to provide clear and actionable information. In September 2020, FDA published a guidance for industry entitled "*Control of N-Nitrosamine Impurities in Human Drugs* (/media/141720/download)." This guidance recommends steps manufacturers of active pharmaceutical ingredients (APIs) and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products.

Today, we have better testing methods than ever before, and we have a better understanding of what to look for in products' chemical structure and manufacturing processes that may increase the risk of forming low levels of impurities. Improved technology enables us to detect even trace amounts of impurities in drug products and may be the reason why more products have been recently found to have detectable levels of nitrosamines.

FDA continues its ongoing review, surveillance, compliance and pharmaceutical quality efforts across every product area and will continue to work with drug manufacturers to ensure safe, effective and high-quality drugs for the American public.

Patients and health care professionals should report any adverse reactions with varenicline to FDA's MedWatch program (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home)

Top ()

- Download and complete the appropriate form (/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting), then submit it via fax at 1-800-FDA-0178

FDA-published testing method to provide an option for regulators and industry to detect nitrosamine impurities

The link below is to an FDA-published testing method to provide an option for regulators and industry to detect nitrosamine impurities in varenicline drug substances and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

- LC-ESI-HRMS method (/media/151470/download): A reverse phase LC method with HRMS detection for the determination of varenicline NDSRI in Chantix™ drug product or drug substance.

Top ()

EXHIBIT 8

Recalls Background and Definitions

Recalls are actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority.

- **Class I recall:** a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.
- **Class II recall:** a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
- **Class III recall:** a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.
- **Market withdrawal:** occurs when a product has a minor violation that would not be subject to FDA legal action. The firm removes the product from the market or corrects the violation. For example, a product removed from the market due to tampering, without evidence of manufacturing or distribution problems, would be a market withdrawal.
- **Medical device safety alert:** issued in situations where a medical device may present an unreasonable risk of substantial harm. In some case, these situations also are considered recalls.

BEFORE THE UNITED STATES JUDICIAL PANEL ON MULTIDISTRICT LITIGATION

IN RE: CHANTIX (VARENICLINE) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION (No. II)	**MDL No. 3050**

PROOF OF SERVICE

In compliance with Rule 4.1(a) of the Rules of Procedure for the United States Judicial Panel on Multidistrict Litigation, the undersigned hereby certifies that the foregoing Notice of Appearance was electronically filed on September 22, 2022 with the Clerk of the Panel and served on all counsel using the CM/ECF system.

Loren H. Brown
Loren H. Brown