May 24, 2021

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

Re: Valisure Citizen Petition on Benzene in Sunscreen and After-sun Care Products

Dear Sir or Madam:

The undersigned, on behalf of Valisure LLC ("Valisure" or "Petitioner"), submits this Citizen Petition ("Petition") pursuant to Sections 301(21 U.S.C. § 331), 501 (21 U.S.C. § 351), 502 (21 U.S.C. § 352), 505 (21 U.S.C. § 355), 601 (21 U.S.C. § 361), 602 (21 U.S.C. § 362), 702 (21 U.S.C. § 372), 704 (21 U.S.C. § 374), and 705 (21 U.S.C. § 375) of the Federal Food, Drug and Cosmetic Act (the "FDCA"), in accordance with 21 C.F.R. 10.20 and 10.30, to request the Commissioner of Food and Drugs ("Commissioner") to issue a regulation, request recalls, revise industry guidance, and take such other actions set forth below.

A. Action Requested

Sunscreens are considered drugs that are regulated by the U.S. Food and Drug Administration ("FDA").[1] Valisure has tested and detected high levels of benzene in specific batches of sunscreen products containing active pharmaceutical ingredients including avobenzone, oxybenzone, octisalate, octinoxate, homosalate, octocylene and zinc oxide. The Centers for Disease Control and Prevention ("CDC") states that the Department of Health and Human Services has determined that benzene causes cancer in humans.[2] The World Health Organization ("WHO") and the International Agency for Research on Cancer ("IARC") have classified benzene as a Group 1 compound thereby defining it as "carcinogenic to humans."[3] FDA currently recognizes the high danger of this compound and lists it as a "Class 1 solvent" that "should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity ... However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted" and benzene is restricted under such guidance to 2 parts per million ("ppm").[4] Because many of the sunscreen products Valisure tested did not contain detectable levels of benzene, it does not appear that benzene use is unavoidable for their manufacture, and considering the long history and widespread use of these products, it also does not appear that they currently constitute a

[1] Certain sunscreens may also be dually regulated as cosmetics under the FDCA, and the designations "drug" and "cosmetic" are not mutually exclusive.

[2] Centers for Disease Control and Prevention, *Facts About Benzene* (2018) (https://emergency.cdc.gov/agent/benzene/basics/facts.asp)

[3] International Agency for Research on Cancer and World Health Organization, *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* (https://monographs.iarc.who.int/list-of-classifications)

[4] Food and Drug Administration, *Q3C – Tables and List Guidance for Industry* (2017) (https://www.fda.gov/media/71737/download)

significant therapeutic advance; therefore, any significant detection of benzene should be deemed unacceptable. The National Institute for Occupational Safety and Health ("NIOSH") recommends protective equipment be worn by workers expecting to be exposed to benzene at concentrations of 0.1 ppm and defines "inhalation, skin absorption, ingestion, skin and/or eye contact" as exposure routes.[5, 6] Valisure found multiple sunscreen products that contain levels of benzene that significantly surpass the 2 ppm conditional FDA restriction. Furthermore, benzene is associated with certain blood cancers such as leukemia,[7] and recent studies by FDA researchers have shown that significant amounts of sunscreen ingredients absorb through the skin and are found in the blood; specifically, over 400 times the threshold for systemic carcinogenicity assessment for at least one sunscreen active ingredient.[8, 9]

The presence of this known human carcinogen in sunscreen products widely recommended for the prevention of skin cancer and regularly used by adults and children in large volumes makes this finding especially troubling.

Additionally, Valisure found multiple after-sun care products that contain benzene and some products with benzene contamination above 2 ppm. After-sun care products, which may also be labeled as "after-burn care" or other "skin care" references, are typically regulated by FDA as cosmetics under the FDCA and the Fair Packaging and Labeling Act ("FLPA") and may contain aloe and other ingredients that are marketed for topical use after exposure to the sun and are often sold in close proximity to sunscreen products.[10]

This Petition requests that the Commissioner take the following actions:

1) request a recall of identified batches of sunscreen products on the basis that, due to contamination with a known human carcinogen, these products are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352);

2) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer

[5] Centers for Disease Control and Prevention. *The National Institute for Occupational Safety and Health (NIOSH), Benzene* (October 30, 2019) (https://www.cdc.gov/niosh/npg/npgd0049.html)
[6] Centers for Disease Control and Prevention. *The National Institute for Occupational Safety and Health, BENZENE: Systemic Agent* (2011) (https://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750032.html)
[7] American Cancer Society. *Benzene and Cancer Risk* (January 5, 2016) (https://www.cancer.org/cancer/cancer-causes/benzene.html)
[8] Matta, MK; et. al. (2019). Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients A Randomized Clinical Trial. *Journal of the American Medical Association*. 2019;321(21):2082-2091 (https://jamanetwork.com/journals/jama/fullarticle/2733085)
[9] Matta, MK; et. al. (2020). Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients A Randomized Clinical Trial. *Journal of the American Medical Association*. 2020;323(3):256-267 (https://jamanetwork.com/journals/jama/fullarticle/2759002)
[10] Depending on the claims in the labeling, certain after-sun products may also be regulated as drugs under the FDCA.

submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)), and effect labeling revisions as needed;

3) provide information to the public regarding these products under Section 705(b) of the FDCA (21 U.S.C. § 375(b)), in particular, that safe sunscreen alternatives to contaminated products are available and that the use of unadulterated sunscreen is an important protection against cancers caused by exposure to harmful solar radiation;

4) consider promulgating rules or administrative orders, revising and reissuing, as necessary and appropriate, FDA's proposed sunscreen rule, published in 84 Federal Register 6,204 (Feb. 26, 2019), and including measures in the final sunscreen monograph, to help address the issues outlined in this Petition;

5) develop guidance documents for the analysis of benzene in sunscreen products;

6) review and update the current FDA guidance "Q3C – Tables and List, Guidance for Industry" to include guidance for the acceptable concentration of benzene for drug products, such as sunscreens, that do not require benzene for manufacturing and do not constitute a "significant therapeutic advance," or potentially expand the current statement that benzene "should not be employed in the manufacture of drug substances" to clarify that there is no acceptable level of benzene and define a reasonable limit of detection;

7) review and update the current FDA guidance "Q3C – Tables and List, Guidance for Industry" to include guidance on the permitted daily exposure of benzene for drug products that do not require benzene for manufacturing and do not constitute a "significant therapeutic advance" and separately for drug products that require benzene for manufacturing and constitute a "significant therapeutic advance";

8) develop guidance documents defining the mass of a standard daily total application of sunscreen, which may include multiple discrete applications, so that a daily exposure of benzene can be calculated for sunscreen products;

9) request a recall of identified batches of after-sun care cosmetic products on the basis that, due to contamination with a known human carcinogen, these products are adulterated under Section 601 of the FDCA (21 U.S.C. § 361) and misbranded under Section 602 (21 U.S.C. § 362);

10) review and update regulation and published guidance for cosmetic products to include limitations on various impurities that pose known risks to human health and include benzene in such updates;

11) consider working with the United States Environmental Protection Agency on a joint initiative to address benzene contamination and potentially enter into a formal agreement

committing to increase collaboration and coordination in areas of mutual interest relating to benzene contamination;

12) support the increasing number of independent drug quality testing programs in the United States by convening workshops, stakeholder meetings and providing other resources at FDA's disposal to further encourage and connect such programs; and

13) promulgate rules or administrative orders requiring robust independent chemical batch-level testing and verification of the chemical content of batches of drugs and other regulated consumer products and, while these are pending, issue guidance requesting such testing and verification.

Background on Petitioner

Valisure operates an analytical laboratory that is accredited to International Organization for Standardization ("ISO/IEC") 17025:2017 standards for chemical testing (PJLA Accreditation Number 94238). Valisure is registered with the Drug Enforcement Administration (License # RV0484814) and FDA (FEI #: 3012063246). Valisure's mission is to help ensure the safety, quality and consistency of medications and supplements in the market. In response to rising concerns about counterfeit medications, generics, and overseas manufacturing, Valisure developed proprietary analytical technologies that it uses in addition to FDA standard methods to test medications and consumer products distributed in the United States.

In an August 7, 2018, inspection of Valisure's facilities by FDA, it was determined that since Valisure's unique testing facility is not a part of the pharmaceutical manufacturing system and does not perform release testing, stability testing or any related services for pharmaceutical manufacturers, Valisure did not require FDA registration. However, Valisure has elected to maintain voluntary registration status with FDA. Valisure also received guidance that since it operates outside of the manufacturing industry using the appropriate ISO guidelines as opposed to GMPs, any product failures or concerns that Valisure identifies should be reported back to the pharmaceutical industry. Valisure has complied with this guidance and routinely provides reports to applicable parties in the pharmaceutical industry.

Given the high potential risk to public safety, Valisure seeks to utilize this Citizen Petition to bring these concerns directly to the attention of the Commissioner and FDA, and to request that they take prompt action.

B. Statement of Grounds

In addition to the information described above, which is incorporated by reference, Valisure provides the following as its statement of grounds. FDA currently recognizes the danger of benzene and, as a result, has claimed it should not be used in the manufacture of any component

of a drug product, and only if its use is "unavoidable" should a strict concentration limit of 2 ppm apply.[4]

There is a recent history of broad drug product recalls due to contamination with probable human carcinogens. Specifically, there have been a multitude of manufacturer recalls of medications, such as valsartan, irbesartan, losartan,[11] ranitidine, nizatidine,[12] and metformin,[13] due to the detection of the Group 2, "probable human carcinogen" N-Nitrosodimethylamine ("NDMA") in excess of FDA limits. FDA limits for NDMA are defined in both parts per million ("ppm") and permissible daily intake, which is held constant at a specified nanogram level ("ng") per day for all drug products.[14]

Having a constant permissible daily intake or exposure is critical when there is variability in product size and exposures per day; a situation particularly relevant to an individual's application of sunscreen and after-sun care products. Petitioner is not aware of any FDA guidance on a permissible daily exposure for benzene in any drug product, including sunscreen, or cosmetic product, including after-sun care products, and requests urgent action on behalf of FDA to issue guidance to fill this gap. Valisure's March 24, 2021 Citizen Petition on benzene contamination in hand sanitizer[15] and the recent recalls of certain hand sanitizer products due to the presence of benzene and other contaminants[16, 17] further underscores the necessity to better regulate benzene and its apparent broad prevalence in the drug and consumer product supply chains.

Although the dangers and carcinogenic potential of nitrosamines, like the aforementioned compound NDMA, have been well documented since the 1960s and there are important studies

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[11] Food and Drug Administration. *Search List of Recalled Angiotensin II Receptor Blockers (ARBs) Including Valsartan, Losartan and Irbesartan* (September 23, 2019) (https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

[12] Food and Drug Administration. *FDA Updates and Press Announcements on NDMA in Zantac (ranitidine)* (April 16, 2020) (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine)

[13] Food and Drug Administration. *FDA Updates and Press Announcements on NDMA in Metformin* (October 5, 2020) (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin)

[14] Food and Drug Administration. *FDA updates table of interim limits for nitrosamine impurities in ARBs* (February 28, 2019) (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan)

[15] Valisure's Citizen Petition on Hand Sanitizer Products Containing Benzene Contamination (filed March 24, 2021) (https://www.regulations.gov/document/FDA-2021-P-0338-0001).

[16] Food and Drug Administration. Scentsational Soaps & Candles, Inc. Issues Voluntary Nationwide Recall of Scented Hand Sanitizers Due to the Presence of Methanol (Wood Alcohol), Benzene and Acetaldehyde (April 28, 2021) (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/scentsational-soaps-candles-inc-issues-voluntary-nationwide-recall-scented-hand-sanitizers-due)

[17] Food and Drug Administration. Scentsational Soaps & Candles, Inc. Voluntarily Expands Nationwide Recall of Scented Hand Sanitizers Due to the Presence of Methanol (Wood Alcohol), Benzene and Acetaldehyde (May 13, 2021) (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/scentsational-soaps-candles-inc-voluntarily-expands-nationwide-recall-scented-hand-sanitizers-due#recall-announcement)

related to recent medication contamination findings,[18, 19] a direct link to cancer in humans has not yet been established. In contrast to nitrosamines, classified as "probable human carcinogens," benzene has long been directly associated with cancer in humans and classified as a "known human carcinogen" with persistent exposure as low as 0.8 ppm.[20] The hematotoxicity of benzene[21] has been described as early as 1897. A study from 1939 on benzene stated that "exposure over a long period of time to any concentration of benzene greater than zero is not safe," [22] which is a comment reiterated in a 2010 review of benzene research specifically stating, "There is probably no safe level of exposure to benzene, and all exposures constitute some risk in a linear, if not supralinear, and additive fashion." [23] According to the American Cancer Society:[24]

> IARC classifies benzene as "carcinogenic to humans," based on sufficient evidence that benzene causes acute myeloid leukemia (AML). IARC also notes that benzene exposure has been linked with acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma, and non-Hodgkin lymphoma.

Valisure engaged Boston Analytical, Inc., a GMP-compliant laboratory, to utilize the industry standard USP <467> Residual Solvents Procedure on a selected product using gas chromatography flame ionization detection ("GC-FID") instrumentation, the results of which are shown in Table 2. Although the industry standard USP method concluded benzene was present above the restricted limit, there was concern over the possibility that any impurities or other compounds in the products could have overlapping retention times. Therefore, Valisure elected to utilize gas chromatography and detection by mass spectrometry ("GC-MS") instrumentation that allows mass spectral separation and utilizing selected ion chromatograms. Gas

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[18] Braunstein LZ, Kantor ED, O'Connell K, Hudspeth AJ, Wu Q, Zenzola N, Light D. Analysis of Ranitidine-Associated N-Nitrosodimethylamine Production Under Simulated Physiologic Conditions. *Journal of the American Medical Association Network Open*. 2021;4(1):e2034766. doi:10.1001/jamanetworkopen.2020.34766 (https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2775727)

[19] White CM. Ranitidine's N-nitrosodimethylamine Problem May be Tip of the Iceberg. *Journal of the American Medical Association Network Open*. 2021;4(1):e2035158. doi:10.1001/jamanetworkopen.2020.35158 (https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2775725)

[20] Glass, Deborah et. al. (2003). Leukemia Risk Associated With Low-Level Benzene Exposure. *Epidemiology* (Cambridge, Mass.). 14. 569-77. 10.1097/01.ede.0000082001.05563.e0. (https://journals.lww.com/epidem/Fulltext/2003/09000/Leukemia_Risk_Associated_With_Low_Level_Benzene.11.aspx)

[21] Santesson GG. 1897. Uber chronische Vergiftungen mit steinkohlen Benzin. Vier todes falle. Arch. Hyg. 31: 336–76

[22] Hunter, F.T. (1939). Chronic Exposure to Benzene (Benzol). II. The Clinical Effects. *Journal of Industrial Hygiene and Toxicology.* 1939 Vol.21 pp.331-54 (https://www.cabdirect.org/cabdirect/abstract/19402700388)

[23] Smith, Martyn T. (2010). Advances in Understanding Benzene Health Effects and Susceptibility. *Annual Review of Public Health.* 2010 Vol. 31:133-148 (https://www.annualreviews.org/doi/full/10.1146/annurev.publhealth.012809.103646)

[24] American Cancer Society. *Benzene and Cancer Risk* (January 5, 2016) (https://www.cancer.org/cancer/cancer-causes/benzene.html)

chromatography conditions followed USP <467> with modifications to reduce run time that closely mirror those recommended by FDA in its August 24, 2020 guidance for impurities detection in hand sanitizer, which includes benzene analysis.[25] Valisure engaged the Chemical and Biophysical Instrumentation Center at Yale University to utilize GC-MS analysis on multiple selected sunscreen and after-sun care products, the results of which are shown in Tables 2 – 5.

Evaluating multiple methods had been useful in past drug product contaminations[26] and was performed here as well to help ensure validity of these highly concerning results. The use of high-resolution MS (GC-HRMS) for greater mass accuracy was employed for the identification and quantification of benzene in selected sunscreen products and confirmed both the identity and levels of contamination beyond 2 ppm.

As Valisure has noted in previous FDA Citizen Petitions, some GC-MS methodologies can lead ingredients to break down into a suspected analyte due to elevated GC oven temperatures during analysis breaking down an inherently unstable pharmaceutical ingredient. Valisure identified such a situation in its September 13, 2019 FDA Citizen Petition regarding the drug ranitidine, and Valisure therefore developed modifications to the existing methodologies to lower temperature and prevent degradation.[27] The GC-MS methodologies described in this petition utilized body temperature (37°C) for oven incubation. 40°C has been previously used for benzene analysis from liquid pharmaceuticals and beverages, and reduced false positive results compared with higher-temperature incubation.[28, 29]

Due to the presence of phenyl groups (similar chemical structures to benzene)[30] in the molecules of some sunscreen active ingredients, Valisure investigated the possibility of six sunscreen active ingredients (avobenzone, oxybenzone, octisalate, octinoxate, homosalate, and octocylene) forming benzene from degradation by the aforementioned GC-MS analytical method through analysis of pure reference standards at concentrations relevant to typical sunscreen products, and

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[25] Food and Drug Administration. FDA Guidance Document (August 24, 2020) *Direct Injection Gas Chromatography Mass Spectrometry (GC-MS) Method for the Detection of Listed Impurities in Hand Sanitizers* (https://www.fda.gov/media/141501/download)

[26] Wu, Qian; et. al. (2020): A Broadly Accessible Liquid Chromatography Method for Quantification of Six Nitrosamine Compounds and N,N-Dimethylformamide in Metformin Drug Products Using High Resolution Mass Spectrometry. ChemRxiv. Preprint. (https://doi.org/10.26434/chemrxiv.13202849.v1)

[27] Valisure FDA Citizen Petition Requesting to Recall Ranitidine (dated September 9, 2019) (https://www.regulations.gov/docket?D=FDA-2019-P-4281)

[28] Kyoung, H. et al. (2008). Evaluation of headspace-gas chromatography/mass spectrometry for the analysis of benzene in vitamin C drinks; pitfalls of headspace in benzene detection. Biomedical Chromatography, Vol. 22, p. 900-905 (https://analyticalscience.wiley.com/do/10.1002/sepspec.19271ezine/full/)

[29] Liu, H. et al. (2011) A general static-headspace gas chromatographic method for determination of residual benzene in oral liquid pharmaceutical products. J Pharm Biomed Anal. Vol. 54(2), p. 417-21. doi: 10.1016/j.jpba.2010.09.006. (https://www.sciencedirect.com/science/article/abs/pii/S0731708510005182?via%3Dihub)

[30] Nomenclature of Benzene Derivatives. (2019, June 5). *LibreTexts*. (https://chem.libretexts.org/@go/page/30650)

no substantive benzene was detected. Thus, the presence of benzene appears to be from contamination in the identified sunscreen products.

Valisure acquired sunscreen and after-sun care product samples from many retailers and in many different formulations. Sunscreen products are often available in dozens of formulations from numerous companies, and it is estimated by FDA that over 11,000 sunscreen products are on market in the United States.[31] After-sun care products are also diverse, though not broadly registered with FDA, since many do not contain a National Drug Code. Although Valisure has made a good faith effort to obtain samples reasonably representative of the general supply, many brands and formulations are not included in Valisure's analysis presented in this Petition. Even in this limited survey of certain available sunscreen and after-sun care products within the United States, multiple samples contained significantly detectable benzene and some batches contained up to 3.1 times the conditionally restricted limit. There was significant variability from batch to batch, even within a single brand, underscoring the importance of batch-level chemical analysis and the necessity of overall increased quality surveillance of these pharmaceutical and consumer products.

Valisure's results will be of significant concern to medical practitioners who endeavor to recommend safe sunscreens and to understand the implications of recent FDA findings showing sunscreen active ingredients are absorbed into the bloodstream even after single use.[32] Furthermore, a study by researchers at Health Canada's Bureau of Chemical Hazards has shown that the application of sunscreen specifically increases the absorption rate of benzene through the skin.[33] The clear evidence that benzene is associated with carcinogenic effects, specifically on blood-related tissues in humans, makes this especially concerning for the health impact of exposure to contaminated sunscreen products.

Beyond the significant concern for public health, there is also evidence that sunscreen products in general, and benzene itself, pose a serious risk to the environment, marine ecosystems, and United States waterways. FDA announced on May 12, 2021 a notice of intent to prepare an Environmental Impact Statement for certain sunscreen drug products due to their potential effects on coral and/or coral reefs.[34] The National Oceanic and Atmospheric Administration ("NOAA") has published reports and infographics intended to educate consumers regarding the

[31] Food and Drug Administration. *Technical Appendix to the Sunscreen Proposed Rule* (2019) (https://www.fda.gov/media/122883/download)
[32] Food and Drug Administration. *Shedding More Light on Sunscreen Absorption* (January 21, 2020) (https://www.fda.gov/news-events/fda-voices/shedding-more-light-sunscreen-absorption)
[33] J S Nakai 1, I Chu, A Li-Muller, R Aucoin. (1997). Effect of environmental conditions on the penetration of benzene through human skin. *Journal of Toxicology and Environmental Health.* 1997 Aug 8;51(5):447-62 (https://pubmed.ncbi.nlm.nih.gov/9233379/)
[34] Food and Drug Administration. *Environmental Impact Statement (EIS) for Certain Sunscreen Drug Products* (May 12, 2021) (https://www.fda.gov/drugs/guidance-compliance-regulatory-information/environmental-impact-statement-eis-certain-sunscreen-drug-products)

potential for sunscreen products to threaten corals and other marine life.[35] Additionally, scientific papers published by NOAA have shown that benzene can be rapidly absorbed by fish[36] and short-term exposure (48 hr) to concentrations of benzene at parts per billion levels can significantly reduce survival of certain fish eggs.[37] Furthermore, NOAA has proposed that the use of sunscreen followed by swimming or showering may cause sunscreen chemicals to wash off and enter waterways,[38] an area of significant concern to the Environmental Protection Agency ("EPA"), which extensively regulates benzene. Strict EPA regulations on benzene are detailed in a report authored by the Agency for Toxic Substances and Disease Registry ("ATSDR"),[39] which stated:

> EPA has set 5 ppb[40] [equivalent of 0.005 ppm] as the maximum permissible level of benzene in drinking water. EPA has set a goal of 0 ppb for benzene in drinking water and in water such as rivers and lakes because benzene can cause leukemia.
> …
> EPA recommends 200 ppb [equivalent of 0.2 ppm] as the maximum permissible level of benzene in water for short-term exposures (10 days) for children.

The depth of experience with benzene regulation at EPA and the concern over environmental impact of benzene contamination and sunscreen ingredients may offer a rational basis for collaboration between FDA and EPA to expeditiously address the current lack of much needed benzene regulation in sunscreen and other products. Such collaboration could efficiently result in regulations applicable for all FDA regulated drug and cosmetic products. Precedence for FDA formally working with EPA through the execution of an agreement committing to increase collaboration and coordination in areas of mutual interest is found in the October 18, 2019 announcement of a Memorandum of Understanding between FDA, EPA and the United States Department of Agriculture ("USDA") regarding food waste.[41, 42]

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[35] National Oceanic and Atmospheric Administration. *Skincare Chemicals and Coral Reefs* (February 26, 2021) (https://oceanservice.noaa.gov/news/sunscreen-corals.html)
[36] S Korn, N Hirsch, J W Struthsaker (1976). UPTAKE, DISTRIBUTION, AND DEPURATION OF 14C-BENZENE IN NORTHERN ANCHOVY, ENGRAULIS MORDAX, AND STRIPED BASS, MORONE SAXATILIS. *Fishery Bulletin*. 1976 March Vol 74, No. 3: 545-51 (https://spo.nmfs.noaa.gov/sites/default/files/pdf-content/1976/743/korn.pdf)
[37] J W Struthsaker (1977). EFFECTS OF BENZENE (A TOXIC COMPONENT OF PETROLEUM) ON SPAWNING PACIFIC HERRING, CLUPEA HARENGUS PALLASI. Fisher Bulletin. 1977 Vol 75, No. 1: 43-49 (https://spo.nmfs.noaa.gov/sites/default/files/pdf-content/1977/751/struhsaker.pdf)
[38] *Id*
[39] Agency for Toxic Substances and Disease Registry (August 2007). *Toxicological Profile for Benzene*. (https://www.atsdr.cdc.gov/toxprofiles/tp3.pdf)
[40] Parts per Billion ("ppb"), 1 ppb is equivalent to one thousandth (1/1000) of 1 ppm
[41] Food and Drug Administration (October 30, 2019). *MOU 225-19-033*. (https://www.fda.gov/about-fda/domestic-mous/mou-225-19-033)
[42] Environmental Protection Agency (May 27, 2020). *Winning on Reducing Food Waste Federal Interagency Strategy* (https://www.epa.gov/sustainable-management-food/winning-reducing-food-waste-federal-interagency-strategy)

Although sunscreen products are considered drug products by FDA and many potentially dangerous chemical impurities are specifically limited for drug products (with the notable exception of benzene), there is comparably a significant lack of similar regulation for cosmetic products despite significant concern for increased consumer protection and regulatory action.[43, 44, 45] As FDA has acknowledged, the FDCA prohibits the marketing of adulterated or misbranded cosmetics in interstate commerce and specifies a product as adulterated if "it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under conditions of use as are customary and usual." [46] However, specifically defined limits of "poisonous or deleterious" substances, such as benzene, are not defined and should be reviewed and addressed by FDA.

Petitioner urges the Commissioner and FDA to expeditiously request recalls on the affected batches of products and to take other such actions outlined in this Petition as deemed appropriate.

Analytical Methods

The method USP <467> Residual Solvents Procedure A was modified from flame ionization detection (FID) to mass spectrometry (MS) detection for benzene in sunscreen and after-sun care products. The sample preparation and headspace (HS) gas chromatography (GC) methods were also modified to fit different types of sunscreen and after-sun care product matrices (spray, lotion, and gel) and to allow shorter run time. Identification of benzene is based on the retention time matching to certified reference standards and mass spectral matching to benzene. Quantification of benzene is performed by comparing peak area of benzene in a sample to a validated 10-point calibration curve. Results in parts per million is determined by dividing the micrograms of benzene detected per sample by the grams of material used for each sample.

Materials and Methods

Agilent 7890B GC equipped with 7697A headspace autosampler coupled with 5977B MS was utilized for sample analysis, and a DB-Select 624 UI, 60m × 0.32mm × 1.8µm GC column (Agilent Technology, Santa Clara, CA) was used to separate benzene from other compounds. Dimethyl sulfoxide (DMSO, GC Grade) was used for sample preparation (Thermo Fisher Scientific, Waltham, MA). Standard of benzene (99.8 % purity) and isotopic labeled benzene

[43] A Kaufman, B Rauenzahn, J Chung (May 1, 2021). Does Cosmetics Regulation Need a Makeover? *The Regulatory Review*. (https://www.theregreview.org/2021/05/01/saturday-seminar-does-cosmetic-regulation-need-makeover/)

[44] W F Watt (July 17, 2015). Time for a Makeover: Newly Proposed Cosmetic Safety Legislation. *American Bar Association* (https://www.americanbar.org/groups/litigation/committees/products-liability/practice/2015/time-for-makeover-newly-proposed-cosmetic-safety-legislation/)

[45] A McDougall (March 27, 2012). Cosmetics regulation needs a makeover, industry urges Congress. *Cosmetics Design* (https://www.cosmeticsdesign.com/Article/2012/03/28/Cosmetics-regulation-needs-a-makeover-industry-urges-Congress)

[46] Food and Drug Administration (March 8, 2021). *FDA Authority Over Cosmetics: How Cosmetics Are Not FDA-Approved, but Are FDA-Regulated* (https://www.fda.gov/cosmetics/cosmetics-laws-regulations/fda-authority-over-cosmetics-how-cosmetics-are-not-fda-approved-are-fda-regulated)

standard (d_3-, 99.8% purity) was used for calibration, continuing calibration verification, retention time verification, and recovery determination (Sigma-Aldrich, St. Louis, MO). USP Class 1 residual solvents mixture was used for calibration confirmation (USP, Rockville, MD). All volumetric glassware used are Class A certified.

Standard and Sample Preparation

Benzene standard was diluted in DMSO. Calibration standards were prepared in 20-mL GC headspace vials to a total of 5 mL volume. Sunscreen and after-sun care product samples were dispensed into the GC headspace vials at approximately 500 mg and weighed, followed by adding 4.5 mL of DMSO to make up the final volume to approximately 5 mL and gently vortexing to mix. Five (5) mL of DMSO was used as blank samples.

Instrumental Analysis

Table 1 summarizes the major instrumental parameters used for analysis of benzene in the sunscreen samples.

Table 1. Instrumental parameters optimized for benzene detection in sunscreen samples.

HS Autosampler		GC		MS	
Oven temperature (Temp)	37 °C	Carrier gas	Helium	Source Temp	230 °C
Loop Temp	55 °C	Inlet Temp	220 °C	Quad Temp	150 °C
Transfer line Temp	175 °C	Column flow	2 mL/min	Acquisition type	SIM
Vial equilibration	20 minutes (min)	Split ratio	5:1	Gain factor	1
Injection time	1 min	Oven Temp Gradient	60 °C (12 min) > 240 °C at 40 °C/min	Solvent delay	3 min
Vial shaking	71 shakes/min	GC run time	18.5 min		
Fill pressure	15 psi				

Quality Assurance and Quality Control

In some cases, trace levels of benzene were detected in blank samples and the peak area was subtracted from all standards and samples. Linear non-forcing through zero calibration curve was generated from the peak areas of the 10-point calibration standards. Calibration curve was accepted when the coefficient of determination R^2 was equal or greater than 0.995. Lower limit of detection (LLOD) and lower limit of quantification (LLOQ) were determined by spiking known amount of benzene into sunscreen samples that were pre-screened to be not detected for benzene or lower than the concentration of the lowest calibration standard. LLOD was 0.01 µg (equivalent to 0.02 ppm in sunscreen products) and LLOQ was 0.025 µg (equivalent to 0.05 ppm in sunscreen products). The measurement uncertainty was determined to be 25%. USP Class 1 residual solvent mixture was analyzed against the calibration and result of benzene agreed with certified concentration. All sunscreen and after-sun care samples with benzene concentration above LLOQ were analyzed in triplicates and reported herein. Values are given for quantification of 2-fold over LLOQ or 0.1 ppm. Therefore, for the data presented in this petition, Valisure is using the nomenclature that any benzene detection of 0.10 ppm or above is "significantly detected," and any detection below this value is described as "< 0.10 ppm" and warrants further investigation but is likely of less concern than products with a defined value of 0.10 ppm or higher.

Analytical Findings

Using the GC-MS method described above for the determination of benzene, Valisure analyzed 294 unique batches from 69 brands of sunscreen and after-sun care products with the results detailed below. In summary, 78 product batches had detectable levels of benzene, 26 contained benzene in concentrations between 0.1 ppm and 2.0 ppm and 14 contained over 2 ppm. In Tables 2 – 5, an asterisk "*" denotes data generated by the Chemical and Biophysical Instrumentation Center at Yale University from a sample from the same lot and specific product package. Two asterisks "**" denotes data generated by Boston Analytical from a sample of the same lot and specific product package. For samples where benzene was detected, at least three samples from each batch were tested individually and the amount of benzene detected is reported as an average followed by the percent standard deviation of the results from replicate measurements.

Table 2. Product description and results of benzene analysis on various batches of sunscreen and after-sun care products in which benzene was detected at 2 ppm or higher.

Brand Name	Type	Description	SPF	UPC	Lot	Exp.	Active Pharmaceutical Ingredient(s)	Benzene Avg ppm	% St Dev
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 100+	100+	086800100416	04820E04	2022-01	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	6.26 6.77*	7%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 70	70	086800100409	07020E01	2023-02	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	5.96	7%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 70	70	086800100409	06920E01	2023-02	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	5.76	5%
Sun Bum	Gel	Cool Down Gel	N/A	871760002005	S0082C	--	N/A (Cosmetic Product)	5.33 5.49*	3%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 70	70	086800100409	02320E01	2022-12	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	5.30	2%
Neutrogena	Spray	Beach Defense Oil-Free Body Sunscreen Spray - SPF 100	100	086800101444	04721E02	2023-01	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	5.20 5.59*	5%
CVS Health	Spray	After-sun Aloe Vera Soothing Spray	N/A	050428390832	8140449A	--	N/A (Cosmetic Product)	4.71 4.55*	1%
Neutrogena	Spray	Invisible Daily Defense Body Sunscreen Broad Spectrum SPF 60+	60+	086800111542	04921E01	2024-01	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%	4.65 5.27*	4%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 100+	100+	086800100416	03120E02	2021-12	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	4.11 6.00**	15%
Neutrogena	Spray	Beach Defense Oil-Free Body Sunscreen Spray - SPF 100	100	086800101444	28020E01	2022-09	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	4.01 4.00*	4%
CVS Health	Spray	After-sun Aloe Vera Soothing Spray	N/A	050428390832	4111849A	--	N/A (Cosmetic Product)	3.58 3.93*	4%
Neutrogena	Spray	Beach Defense Spray Body Sunscreen SPF 50	50	086800112549	25520E01	2023-08	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%	3.52 3.71*	3%
Neutrogena	Spray	Beach Defense Oil-Free Body Sunscreen Spray - SPF 100	100	086800101444	31420E04	2022-10	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	3.08 2.64*	2%
Fruit of the Earth	Gel	Aloe Vera Gel	N/A	071661001200	6612940A	--	N/A (Cosmetic Product)	2.78 2.94*	6%

Table 3. Product description and results of benzene analysis on various batches of sunscreen and after-sun care products in which benzene was detected at 0.1 ppm to 2 ppm.

Brand Name	Type	Description	SPF	UPC	Lot	Exp.	Active Pharmacutical Ingredient(s)	Benzene Avg ppm	% St Dev
Neutrogena	Spray	Invisible Daily Defense Body Sunscreen Broad Spectrum SPF 60+	60+	086800111542	17820E01	2023-05	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%	1.99 1.66*	8%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 100+	100+	086800100416	06420E05	2022-02	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	1.44 1.06*	6%
Raw Elements	Lotion	Eco Formula Sunscreen Lotion SPF 30	30	858855002003	58J19	2021-07	Zinc Oxide 23%	1.35 1.31*	9%
CVS Health	Spray	After-sun Aloe Vera Soothing Spray	N/A	050428390832	1101990A	--	N/A (Cosmetic Product)	0.90 1.04*	3%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 70	70	086800100409	26119E01	2022-08	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	0.87	9%
CVS Health	Gel	After-sun Aloe Vera Moisturizing Gel	N/A	050428324837	4500231A	--	N/A (Cosmetic Product)	0.81 0.98*	2%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 100+	100+	086800100416	08119F36	2022-02	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	0.77	4%
SunBurnt	Gel	Advanced After-Sun Gel	N/A	324330210060	62R20	2022-12	N/A (Cosmetic Product)	0.75 0.87*	2%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 100+	100+	086800100416	32619E06	2021-10	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	0.73	9%
Goodsense	Lotion	Sunscreen Lotion SPF 30	30	846036001143	070606920	2022-07	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%	0.71	4%
Neutrogena	Spray	CoolDry Sport Water-Resistant Sunscreen Spray SPF 70	70	086800100379	33719E01	2022-10	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	0.66	5%
Neutrogena	Spray	Ultra Sheer Body Mist Sunscreen Broad Spectrum SPF 30 Spray	30	086800100386	28219E02	2021-09	Avobenzone 3%, Homosalate 8%, Octisalate 5%, Octocrylene 8%	0.49	18%
Banana Boat	Spray	Kids Max Protect & Play Sunscreen C-Spray SPF 100	100	079656050820	200910346	2023-02	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	0.41 0.43*	7%
Neutrogena	Spray	Beach Defense Oil-Free Body Sunscreen Spray - SPF 100	100	086800101444	35219E05	2021-11	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	0.41	8%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 100+	100+	086800100416	29519E02	2021-09	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	0.37 0.38*	2%
Banana Boat	Spray	UltraMist Deep Tanning Dry Oil Continuous Clear Spray SPF 4	4	79656046632	200944022	2023-03	Homosalate 3.0%, Octocrylene 1.0%	0.36	18%
Banana Boat	Spray	Kids Max Protect & Play Sunscreen C-Spray SPF 100	100	079656050820	200273634	2022-12	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	0.19	11%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 70	70	086800100409	13019F84	2022-04	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	0.18	10%
Neutrogena	Spray	Ultra Sheer Body Mist Sunscreen Broad Spectrum SPF 45	45	086800100393	15719F83	2022-05	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 2.35%, Oxybenzone 6%	0.15	12%
Banana Boat	Spray	Ultra Sport Clear Sunscreen Spray SPF 100	100	79656050806	201060792	2023-03	Avobenzone 3.0%, Homosalate 10.0%, Octisalate 5.0%, Octocrylene 10.0%, Oxybenzone 6.0%	0.15	4%
Neutrogena	Lotion	Ultra Sheer Dry-Touch Water Resistant Sunscreen SPF 70	70	86800687702	0090L0069	2022-06	Avobenzone 3.0%, Homosalate 15.0%, Octisalate 5.0%, Octocrylene 2.8%, Oxybenzone 6.0%	0.13	73%
Neutrogena	Spray	CoolDry Sport Water-Resistant Sunscreen Spray SPF 50	50	086800100362	15619F25	2022-05	Avobenzone 2.7%, Homosalate 9%, Octisalate 4.5%, Octocrylene 6%, Oxybenzone 4.5%	0.13	4%
TopCare Everyday	Lotion	Ultimate Sheer Sunscreen Lotion SPF 70	70	036800459007	9533119A	2021-11	Avobenzone 3%, Homosalate 10%, Octisalate 3%, Octocrylene 7%, Oxybenzone 6%	0.12 0.16*	6%
EltaMD	Spray	UV Aero Broad-Spectrum Full-Body Sunscreen Spray, SPF 45	45	390205025879	67155I	2022-11	Zinc Oxide 9.3%, Octinoxate 7.5%	0.11 0.17*	18%
EltaMD	Spray	UV Aero Broad-Spectrum Full-Body Sunscreen Spray, SPF 45	45	390205025879	67155H	2022-11	Zinc Oxide 9.3%, Octinoxate 7.5%	0.11	9%
Banana Boat	Spray	Kids Max Protect & Play Sunscreen C-Spray SPF 100	100	079656050820	200243635	2022-12	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	0.11	19%

Table 4. Product description and results of benzene analysis on various batches of sunscreen and after-sun care products in which benzene was detected at below LLOQ.

Brand Name	Type	Description	SPF	UPC	Lot	Exp.	Active Pharmaceutical Ingredient(s)	Benzene Avg ppm	% St Dev
Live Better by CVS Health	Spray	Body Mineral Spray Sunscreen SPF 50	50	050428538913	4270950B	2022-03	Titanium Dioxide 3.5%, Zinc Oxide 7.25%	< 0.1	5%
CVS Health	Lotion	Ultra Sheer Broad Spectrum Sunscreen Lotion SPF 100 (050428415528)	100	050428616062	5881760A	2022-06	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	< 0.1	1%
Ethical Zinc	Lotion	Natural Clear Zinc Sunscreen SPF 50+	50+	9354028000025	A0747	2022-09	Zinc Oxide 22.0%	< 0.1	25%
Banana Boat	Spray	Protective Dry Oil Clear Sunscreen Spray with Coconut Oil SPF 15	15	79656044836	202023826	2023-06	Avobenzone 1.5%, Homosalate 5.0%, Octocrylene 3.5%	< 0.1	11%
Babyganics	Spray	Kid's Sunscreen Continuous Spray - SPF 50	50+	813277017554	3713449A	2021-12	Octisalate 5%, Zinc Oxide 15%	< 0.1	24%
Walgreens	Lotion	Sport Lotion Sunscreen SPF 50	50	049022977464	2142499A	2021-09	Avobenzone 3%, Homosalate 10%, Octisalate 4.5%, Octocrylene 8%	< 0.1	12%
Banana Boat	Spray	Ultra Defense Ultra Mist Clear Sunscreen Spray SPF 100	100	079656050813	191932590	2022-06	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	< 0.1	11%
CVS Health	Lotion	Ultra Sheer Lotion Broad Spectrum Sunscreen SPF 45	45	050428620083	6060370C	2022-02	Avobenzone 3.0%, Homosalate 10.0%, Octisalate 5.0%, Octocrylene 2.8%	< 0.1	3%
Raw Elements	Lotion	Eco Formula Sunscreen Lotion Tin SPF 30	30	858855002065	21J19	2021-07	Zinc Oxide 23%	< 0.1	11%
Coppertone	Spray	Whipped Sunscreen Lotion Spray SPF 50	50	041100007094	9J03CS	2021-08	Avobenzone 3%, Homosalate 9%, Octisalate 4.5%, Octocrylene 9%	< 0.1	10%
CVS Health	Lotion	Ultra Sheer Broad Spectrum Sunscreen Lotion SPF 100 (050428415528)	100	050428616062	7470720B	2022-03	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	< 0.1	7%
CVS Health	Lotion	70 Beach Guard Sun Sunscreen SPF 70	70	050428402528	5980339C	2022-01	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 4.5%, Oxybenzone 4%	< 0.1	70%
Max Block	Lotion	Sunscreen Lotion 4 Fl Oz Broad Spectrum Water Resistant SPF 30	30	639277292865	91047	2022-01	Avobenzone 3%, Homosalate 7.5%, Octisalate 5%, Octocrylene 5%	< 0.1	70%
Walgreens	Lotion	Broad Spectrum Sport SPF 50 Sunscreen	50	049022977471	4440660B	2022-03	Avobenzone 3%, Homosalate 10%, Octisalate 4.5%, Octocrylene 8%	< 0.1	10%
CVS Health	Lotion	Ultra Sheer Broad Spectrum Sunscreen Lotion SPF 100 (050428415528)	100	050428616062	1362040A	2022-07	Avobenzone 3.0%, Homosalate 15.0%, Octisalate 5.0%, Octocrylene 10.0%, Oxybenzone 6.0%	< 0.1	4%
TopCare Everyday	Lotion	Sport Sunscreen Lotion SPF 70	70	036800456303	0440090A	2023-01	Avobenzone 3%, Homosalate 10%, Octisalate 3%, Octocrylene 7%, Oxybenzone 6%	< 0.1	27%
Max Block	Lotion	Sport Sunscreen Lotion Water Resistance Blue 30 SPF	30	639277292063	00189	2022-03	Avobenzone 3%, Homosalate 7.5%, Octisalate 5%, Octocrylene 5%	< 0.1	7%
Walgreens	Lotion	Sunscreen Sport SPF 50	50	049022977457	3232629A	2021-09	Avobenzone 3%, Homosalate 10%, Octisalate 4.5%, Octocrylene 8%	< 0.1	10%
Max Block	Lotion	Sunscreen Lotion 4 Fl Oz Broad Spectrum Water Resistant SPF 30	30	639277292865	91188	2021-12	Avobenzone 3%, Homosalate 7.5%, Octisalate 5%, Octocrylene 5%	< 0.1	51%
Max Block	Lotion	Sunscreen Lotion 4 Fl Oz Broad Spectrum Water Resistant SPF 30	30	639277292865	91188B	2021-12	Avobenzone 3%, Homosalate 7.5%, Octisalate 5%, Octocrylene 5%	< 0.1	7%
Banana Boat	Spray	Kids Sport Sunscreen Lotion Spray SPF 50	50	079656020526	192546543	2022-08	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 6%	< 0.1	19%
TopCare Everyday	Lotion	Ultimate Sheer Sun Lotion Sunscreen SPF 55	55	036800456242	9543129A	2021-11	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 7%	< 0.1	9%

Solimo	Lotion	Sheer Face Sunscreen Lotion SPF 55 (842379152474 UPC Description)	55	842379167430	0495376	2022-07	Avobenzone 3%, Homosalate 12%, Octisalate 5%, Octocrylene 10%	< 0.1	6%
Max Block	Lotion	Sport Sunscreen Lotion Water Resistance Blue 30 SPF	30	639277292063	91051	2022-02	Avobenzone 3%, Homosalate 7.5%, Octisalate 5%, Octocrylene 5%	< 0.1	39%
Walgreens	Lotion	Sunscreen Sport SPF 50	50	049022977457	3222629B	2021-09	Avobenzone 3%, Homosalate 10%, Octisalate 4.5%, Octocrylene 8%	< 0.1	10%
Neutrogena	Lotion	Sheer Zinc Dry-Touch Face Sunscreen SPF 50	50	086800110811	2979L1236	2022-03	Zinc Oxide 21.6%	< 0.1	8%
CVS Health	Spray	Sport Clear Spray Sunscreen SPF 100+	100+	050428618868	7062049B	2021-07	Avobenzone 3%, Homosalate 15%, Octinoxate 2%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%	< 0.1	39%
La Roche-Posay	Spray	Anthelios Sunscreen Lotion Spray SPF 60	60	883140500841	201401230	2022-02	Avobenzone 2.68%, Homosalate 9.60%, Octisalate 2.88%, Octocrylene 5.38%, Oxybenzone 3.46%	< 0.1	79%
Banana Boat	Spray	Simply Protect Kids Sunscreen Spray SPF 50+	50	079656024500	193639916	2022-11	Avobenzone 3%, Homosalate 9%, Octisalate 4.5%, Octocrylene 6%	< 0.1	7%
Equate	Lotion	Kids Broad Spectrum Sunscreen Lotion, SPF 50	50	681131002462	3941300A	2023-05	Titanium Dioxide 3.1%, Zinc Oxide 4.0%	< 0.1	13%
CVS Health	Spray	Sheer Mist Spray Broad Spectrum Uva/Uvb Cont. Spray Sunscreen SPF 70	70	050428449240	2700189A	2022-01	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	< 0.1	15%
Max Block	Lotion	Sport Sunscreen Lotion Water Resistance Blue 30 SPF	30	639277292063	91186	2021-12	Avobenzone 3%, Homosalate 7.5%, Octisalate 5%, Octocrylene 5%	< 0.1	5%
Neutrogena	Spray	Ultra Sheer Weightless Sunscreen Spray, SPF 70	70	086800100409	32318F63	2021-10	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%	< 0.1	9%
Sun Bum	Lotion	Oxy Free Zinc Oxide Sunscreen Lotion - SPF 50	50	871760003903	S9351AN	2021-12	Homosalate 10%, Octisalate 5%, Octocrylene 10%, Zinc Oxide 7%	< 0.1	24%
Aveeno	Lotion	Baby Continuous Protection Sensitive Skin Sunscreen Lotion Broad Spectrum SPF 50	50	381371164509	2419L1022	2022-02	Zinc Oxide 21.6%	< 0.1	58%
Sun Bum	Spray	After Sun Cool Down Aloe Vera Spray	N/A	871760003187	S1039D	--	N/A (Cosmetic Product)	< 0.1	6%
Walgreens	Gel	After Sun Gel	N/A	049022507326	0701970A	--	N/A (Cosmetic Product)	< 0.1	2%
Up & Up	Gel	Clear Aloe Vera Gel	N/A	371661826163	9701930A	--	N/A (Cosmetic Product)	< 0.1	16%

Table 5. Product description of various batches of sunscreen for which benzene was not detected through initial analysis of at least one sample from each batch. Due to length of this table, it is contained in Attachment A to this Petition.

Recall Request and Other Actions

This Petition seeks to have the Commissioner and FDA request recalls for the identified batches of sunscreen products, consistent with FDA's mandate to ensure the safety of the drug supply in America. The 40 batches in Table 2 and Table 3 have significantly detected benzene and should be recalled.

Such recalls are important for public safety. As indicated in Tables 2 - 5, there is significant batch-to-batch variation in benzene content, but many batches of sunscreen contain no detectable

benzene and thus recalls should not overly burden the distribution chain or impact the availability of sunscreen for use by the public.

Petitioner further requests updates and revisions to the current "Q3C – Tables and List, Guidance for Industry" that consider drug products, such as sunscreens, whose manufacture does not require benzene and that do not constitute a significant therapeutic advance, and where the common exposure per individual can vary widely. Regarding the conditional restriction limit on benzene, a substantially lower limit than 2 ppm should be set for such products where, according to current FDA guidance, benzene should not be used at any point in manufacturing, or FDA should potentially expand the current statement that benzene "should not be employed in the manufacture of drug substances" to clarify that there is no acceptable level of benzene and define a reasonable limit of detection. Regarding the highly variable exposure of an individual to sunscreen products, which can relate to variations in application amount per individual and number of applications per day, FDA should update current guidance with a daily permissible exposure limit, as is the case with nitrosamine impurities. To properly quantify daily exposure, FDA should provide further guidance on the amount of sunscreen product and number of applications that a daily permissible exposure limit should apply to.

Petitioner notes that recent studies authored by FDA personnel where sunscreen application was studied,[8, 9] defined the mass of an application of sunscreen by mass per surface area and the number of applications as four per day. With respect to mass, the referenced studies stated, "Sunscreen product was applied at 2 mg/cm^2 to 75% of body surface area (area outside of normal swim wear)" and most bodies measured approximately 1.85 m^2. This equates to approximately 28.5 g per sunscreen application. At the FDA conditional restriction limit of 2 ppm for benzene, 28.5 g of sunscreen would contain 57,000 ng of benzene in a single application which may reasonably be used 4 times per day, therefore amounting to 228,000 ng of benzene exposure per day. As aforementioned, the probable human carcinogen NDMA is restricted in drug products at concentrations similar to benzene, specifically 0.3 – 3.0 ppm in -sartan medication, and has a corresponding permissible daily intake of 96 ng. Using NDMA as a comparable benchmark, sunscreen products applied according to amounts consistent with FDA researchers' studies and contaminated at 2 ppm benzene, will expose an individual to 2,375 times the acceptable daily limit. In Valisure's limited evaluation of sunscreen products in the United States and utilizing the aforementioned benchmark, the highest benzene detection of 6.26 ppm equates to approximately 695,800 ng of benzene in one day or 7,248 times the NDMA limit. Sunscreen products are typically used in many times higher volume than standard drug products like tablets or capsules, so even a relatively low concentration limit can result in very high total exposure. As a recent study by FDA researchers states, "Understanding the extent of systemic exposure of [sunscreen] products is important, as even a low percentage of systemic absorption could represent a significant systemic exposure." [8] This strongly underscores the need for a daily limit in addition to a concentration limit.

Many professionals have been concerned with the safety thresholds of sunscreen systemic exposure.[47] One researcher and clinician from Yale University commented to Valisure:

> "Considering that human skin has a large total surface area (~1.85 m^2), and that ~28.5 g of sunscreen is needed per application to properly cover that skin surface, it follows then that there is not a safe level of benzene that can exist in sunscreen products. The total mass of sunscreen required to cover and protect the human body, in single daily application or repeated applications daily, means that even benzene at 0.1 ppm in a sunscreen could expose people to excessively high nanogram amounts of benzene." [48]

In addition, for the reasons stated above, Valisure requests that FDA conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a)of the FDCA (21 U.S.C. § 374(a)), and effect labeling revisions as needed. Further, FDA should provide information to the public regarding these drug products under Section 705(b) of the FDCA (21 U.S.C. § 375(b)). Given the significant health benefit of using sunscreen to protect against harmful solar radiation and the potential that the alarming nature of this Petition's findings could deter individuals from using any sunscreen, Valisure would maintain that it is important for information provided to the public to clarify and underscore that this contamination has not been detected in all sunscreen products and that unadulterated sunscreen products are available and should continue to be utilized.

With regard to after-sun care products, this Petition urges FDA to request a recall of identified batches of after-sun care products on the basis that they contain benzene, a known human carcinogen and, as such, a deleterious substance which may render the affected products injurious to users under the conditions of use in the labeling, or under customary and usual conditions. For this reason, FDA should find that these products are adulterated under Section 601 of the FDCA (21 U.S.C. § 361) and misbranded under Section 602 (21 U.S.C. § 362).

Independent, Batch-level Testing and Certification of Drug Products in the United States

Petitioner is also requesting that FDA promulgate rules or issue administrative orders requiring robust independent chemical batch-level testing and verification of sunscreen products that are regulated as drugs by FDA, or revise and reissue, as necessary and appropriate, FDA's proposed sunscreen rule, published in 84 Federal Register 6,204 (Feb. 26, 2019), and include measures in the final sunscreen monograph to help address these issues. In the interim, while these are pending, FDA should issue formal guidance recommending such testing and verification.

[47] Wang, J. and Ganley, C.J. (2019), *Safety Threshold Considerations for Sunscreen Systemic Exposure: A Simulation Study*. Clin. Pharmacol. Ther., 105: 161-167. (https://doi.org/10.1002/cpt.1178)
[48] Email from Dr. Christopher Bunick, MD, PhD, Associate Professor of Dermatology at Yale University, New Haven, CT.

This is necessary in order to serve public health and help protect Americans from adulterated drug products, an issue of growing concern. Grounds for this request are also rooted in strong support from the medical community, as evidenced by a 2019 resolution from the American College of Cardiology ("ACC"), calling for the American Medical Association to advocate for legislation requiring independent testing and verification of the chemical content of batches of pharmaceuticals. The resolution is at Attachment B.

Particularly with quality issues that broadly affect a subset of brands and specific batches of consumer products, independent batch-level testing should be made known to an individual or any purchaser though visible certification on product labels. Independent certification of products can help prevent adulterated products from entering the market and can help ensure consumers, patients, and practitioners continue to feel safe using and recommending or prescribing certified drug and cosmetic brands of products, which are important for public health, such as sunscreens.

In addition, Petitioner requests that FDA support the expanding number of independent drug quality analysis programs, including that recently announced at The University of Kentucky,[49] through various means available to it. This may include convening new focused meetings, seminars, symposiums, and similar gatherings to connect programs and healthcare stakeholders that could benefit by learning from and augmenting such programs. It may also include adding such a topic to existing meetings, seminars, symposiums, and similar gatherings when appropriate.

As Valisure's results indicate, relying on industry self-reporting of analytical results is not sufficient protection from potentially dangerous contamination. A proactive drive for broad, independent testing should be combined with decisive action on the part of regulators to quickly request recalls and take other actions as appropriate.

C. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.30, and believes that this Petition qualifies for a categorical exclusion from the requirement to submit an environmental assessment or environmental impact statement. To Petitioner's knowledge, no extraordinary circumstances exist.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information will be submitted by the Petitioner only upon request of the Commissioner following review of this Petition.

[49] Chapin, Elizabeth; Willett, Kristi. (October 1, 2020) UK Drug Quality Testing Leads to Petition to Recall Injectable Drug. *University of Kentucky* (http://uknow.uky.edu/research/uk-drug-quality-testing-leads-petition-recall-injectable-drug)

E. Certification

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

Respectfully submitted,

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