



March 5, 2024

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

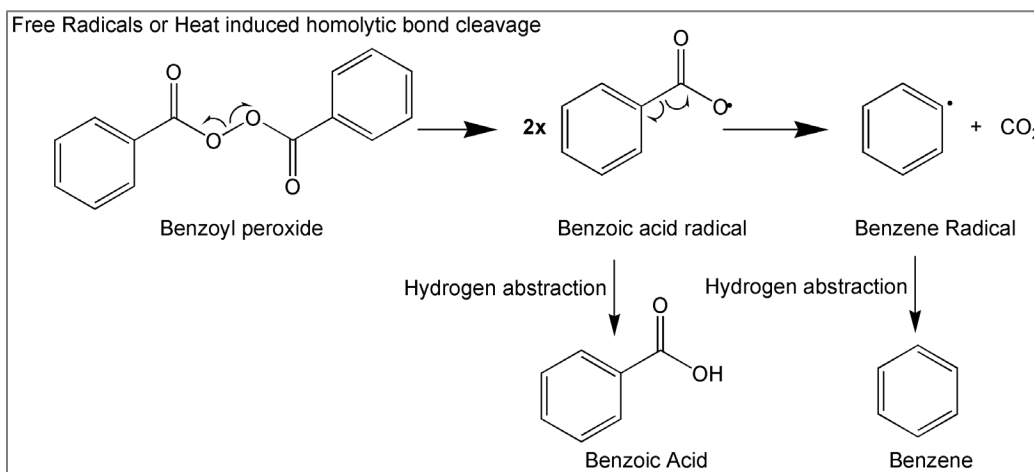
Re: Valisure Citizen Petition on Benzene in Benzoyl Peroxide Drug Products

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), 502 (21 U.S.C. § 352), 505 (21 U.S.C. § 355), 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, revise industry guidance, and request a recall and suspend sales of benzoyl peroxide from the US market and take such other actions set forth below.

A. Action Requested

The drug benzoyl peroxide (“BPO”) is a diacyl peroxide with bactericidal activity and is widely used standalone or in combination with other drugs for the treatment of *acne vulgaris* (“acne”) in children, teens, and adults by prescription and over-the-counter (“OTC”). Valisure has tested and detected high levels of benzene, a known human carcinogen, in many specific batches of BPO products, and the current evidence suggests that on-market BPO products could produce substantial amounts of benzene when stored at above-ambient temperatures, specifically 37°C (98.6°F), 50°C (122°F) and 70°C (158°F). BPO is well known to decompose into benzene according to the mechanism below:¹



¹ Shang-Hao Liu, Hung-Yi Hou, Chi-Min Shu, Thermal hazard evaluation of the autocatalytic reaction of benzoyl peroxide using DSC and TAM III, *Thermochimica Acta*, Volume 605, 2015, Pages 68-76, ISSN 0040-6031, (<https://www.sciencedirect.com/science/article/pii/S004060311500057X>)

Figure 1. The disposition of benzoyl peroxide to form benzene.

Benzoyl peroxide is known to thermally decompose to form two molecules of benzoic acid radicals that can further decompose to benzene radicals with liberation of carbon dioxide. The benzene radicals can then produce benzene.

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 The Food and Drug Administration (“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 Considering the long history and widespread use of BPO products, it does not appear that they currently constitute a significant therapeutic advance; therefore, any significant detection of benzene should be deemed unacceptable. FDA has also recognized the need to reformulate drug products that could be at risk of containing benzene with the recently posted guidance on “Reformulating Drug Products That Contain Carbomers Manufactured With Benzene.”⁵

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.⁶ ⁷ The Environmental Protection Agency (“EPA”) has estimated that lifetime exposure to benzene at 0.4 parts per billion (“ppb”), or 0.0004 ppm, will increase the risk of developing cancer in humans at the same 1 in 100,000 exposed persons rate as FDA uses to set regulatory limits on other trace impurities like N-nitrosamines.^{8, 9} It is important to note that Valisure has detected the formation of benzene not only inside benzoyl peroxide products, but also the substantial

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>)

⁵ Food and Drug Administration. *Reformulating Drug Products That Contain Carbomers Manufactured With Benzene* (December 27, 2023) (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reformulating-drug-products-contain-carbomers-manufactured-benzene>)

⁶ 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>)

⁷ Centers for Disease Control and Prevention. *The National Institute for Occupational Safety and Health, BENZENE: Systemic Agent* (2011) (https://www.cdc.gov/niosh/ershdb/emergencypresponsecard_29750032.html)

⁸ Environmental Protection Agency. *Benzene; CASRN 71-43-2*. (https://iris.epa.gov/static/pdfs/0276_summary.pdf)

⁹ Food and Drug Administration (February 2021). *Control of Nitrosamine Impurities in Human Drugs*. (<https://www.fda.gov/media/141720/download>)

production of benzene emanating externally into the air surrounding an unopened benzoyl peroxide product, implicating significant concern over inhalation exposure to benzene and that levels detected within a product may only be a fraction of the total production of benzene and potential exposure to a patient.

In response to Valisure’s 2019 Citizen Petition on the inherent instability of ranitidine (Zantac)¹⁰ and its formation of the probable human carcinogen N-nitrosodimethylamine (“NDMA”), FDA requested that manufacturers withdraw all ranitidine drug products from the market due to FDA’s finding that “NDMA has been found to increase significantly in samples stored at higher temperatures, including temperatures the product may be exposed to during distribution and handling by consumers.”¹¹ Valisure presents substantial evidence that BPO products are similarly unstable and, at such temperatures of distribution and consumer handling, can form hundreds of times any FDA regulatory guidance for benzene levels.

Furthermore, FDA began reevaluating BPO in 1991 due to new data available that raised concern over carcinogenicity.¹² By 2011, FDA determined “that benzoyl peroxide [2.5% to 10%] can be adequately labeled to minimize risks while delivering effective acne treatment.” This rule was based on review of: “...studies on genotoxicity, tumor promotion with chemical/ultraviolet initiation, animal carcinogenicity, and photocarcinogenicity, as well as the related epidemiological data.”¹³ The new labelling guidance only applies to OTC products. Prescription benzoyl peroxide products still contain warnings as exemplified below.¹⁴

“The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.”

This background on benzoyl peroxide in combination with the new data presented in this Petition raise serious concern over the safety of drug products formulated with BPO.

This Petition requests that the Commissioner take the following actions:

¹⁰ Valisure FDA Citizen Petition Requesting to Recall Ranitidine (dated September 9, 2019) (<https://www.regulations.gov/docket?D=FDA-2019-P-4281>)

¹¹ Food and Drug Administration. *FDA Requests Removal of All Ranitidine Products (Zantac) from the Market* (April 1, 2020) (<https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market>)

¹² Food and Drug Administration, 21 CFR Part 201, Topical Drug Products Containing Benzoyl Peroxide; Required Labeling; Proposed Rule. Federal Register / Vol. 60, No. 33 (February 1995) (<https://www.govinfo.gov/content/pkg/FR-1995-02-17/html/95-4007.htm>)

¹³ Food and Drug Administration, Guidance for Industry, Topical Acne Drug Products for Over-the-Counter Human Use — Revision of Labeling and Classification of Benzoyl Peroxide as Safe and Effective (June 2011) (<https://www.fda.gov/files/drugs/published/Topical-Acne-Drug-Products-for-Over-the-Counter-Human-Use--Revision-of-Labeling-and-Classification-of-Benzoyl-Peroxide-as-Safe-and-Effective.pdf>)

¹⁴ Epsolay [Generic name: benzoyl peroxide] Prescribing Information, Drugs.com (accessed February 2024) (<https://www.drugs.com/pro/epsolay.html>)

- 1) request a recall and suspension of sale of products containing benzoyl peroxide. Given the drug's propensity to form the known human carcinogen benzene, the drug is 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 submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a));
- 3) provide information to the public regarding these products under Section 705(b) of the FDCA (21 U.S.C. § 375(b));
- 4) develop guidance documents for the analysis of benzene in benzoyl peroxide products;
- 5) 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 BPO containing products, that likely 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;
- 6) 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";
- 7) 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;
- 8) support the increasing number of independent drug quality testing programs in the United States, including by the United States Department of Defense,¹⁵ by convening workshops, stakeholder meetings and providing other resources at FDA's disposal to further encourage and connect such programs; and
- 9) promulgate regulations requiring robust independent chemical testing and verification of pharmaceuticals and, while these regulations are pending, issue guidance requesting such testing and verification.

¹⁵ Anna Edney and Riley Griffin. *Tainted Medication Fears Spur US Defense Department to Seek Outside Testing* (August 8, 2023) (<https://www.bloomberg.com/news/articles/2023-08-08/tainted-medication-fears-spur-us-defense-department-to-seek-outside-testing>)

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). Valisure’s mission is to help ensure the safety, quality, and consistency of medications and supplements in the market and create actionable transparency to quality for large purchasers of drug products such as the Military Health System.¹⁶ In response to rising concerns about drug shortages, generics, and overseas manufacturing, Valisure developed and validated methods to test medications and consumer products distributed in the United States.

Valisure’s test methods largely mirror those utilized by FDA’s own “Drug Quality Sampling and Testing” (“DQST”) Program. As stated during FDA’s November 1, 2023 Pharmaceutical Quality Symposium, FDA’s DQST test methods selection are first selected “from USP-NF monographs and/or USP general chapters” and not based on Current Good Manufacturing Practice (“CGMP”) methodologies.¹⁷ Only “In the absence of the USP monographs the firm’s test methods [CGMP methods] are selected or a validated test method is used. FDA also can conduct more specialized testing if needed.” Valisure likewise prioritizes the selection of a USP monograph or general chapter when it is available, and multiple USP methods are specifically cited in Valisure’s ISO/IEC 17025:2017 accreditation.¹⁸ When applicable USP methods are not available, Valisure rarely has access to a firm’s methods as they are typically proprietary, and so will validate separate tests or conduct more specialized testing, which Valisure also validates.

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 regulatory purpose, Valisure did not require FDA registration. 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 industry. Valisure has complied with this guidance and routinely provides reports to applicable parties in the industry.

Given the 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.

¹⁶ Anna Edney and Riley Griffin. *The Pentagon is Skeptical of Cheap Generics Drugs Approved by the FDA* (December 4, 2023) (<https://www.bloomberg.com/news/features/2023-12-05/pentagon-is-skeptical-of-cheap-generic-drugs-approved-by-the-fda>)

¹⁷ Stephen Cahill. *Overview of the OQS Drug Quality Sampling and Testing (DQST) Program*. (November 1, 2023). Office of Quality Surveillance, Food and Drug Administration. Presented at Pharmaceutical Quality Symposium 2023.

¹⁸ Perry Johnson Laboratory Accreditation, Inc. Certificate of Accreditation, Valisure, LLC, ISO/IEC 17025:2017. (May 23, 2023). (<https://www.pjview.com/clients/pjl/viewcert.cfm?certnumber=24499>)

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.

Background

Benzene known to cause cancer in humans

Benzene has long been directly associated with cancer in humans by epidemiological studies with persistent exposure as low as 0.8 ppm.¹⁹ The hematotoxicity of benzene²⁰ 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,”²¹ 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.”²² In an October 15, 2021 recall of sunscreen products due to the presence of benzene, Canadian health regulator Health Canada stated “there is no safe level of benzene.”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.

FDA and EPA limits on benzene

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.²⁵ Valisure has detected benzene in many drug and consumer products in excess of this limit since 2021, including: Valisure’s March 24, 2021

¹⁹ 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)

²⁰ Santesson GG. 1897. Uber chronische Vergiftungen mit steinkohlen Benzin. Vier todes falle. Arch. Hyg. 31: 336–76

²¹ 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>)

²² 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>)

²³ Health Canada (October 15, 2021). *Ombrelle Garnier Complete Dry Mist Spray sunscreen recalled due to elevated benzene levels* (<https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/76663a-eng.php>)

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

²⁵ Food and Drug Administration, *Q3C – Tables and List Guidance for Industry* (2017) (<https://www.fda.gov/media/71737/download>)

Citizen Petition on benzene contamination in hand sanitizer,²⁶ Valisure's May 24, 2021 Citizen Petition on benzene contamination in sun care products,²⁷ Valisure's November 3, 2021 Citizen Petition on benzene contamination in body spray products,²⁸ and Valisure's October 31, 2022 Citizen Petition on benzene contamination in dry shampoo products.²⁹ These petitions, and the multiple recalls, some as recent as December 2023, of certain hand sanitizers,^{30, 31} sunscreens,^{32,}

²⁶ 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>).

²⁷ Valisure's Citizen Petition on Benzene in Sunscreen and After-sun Care Products (filed May 24, 2021) (<https://www.regulations.gov/document/FDA-2021-P-0497-0001>)

²⁸ Valisure's Citizen Petition on Benzene in Body Spray Products (filed November 3, 2021) (<https://www.regulations.gov/document/FDA-2021-P-1193-0001>)

²⁹ Valisure's Citizen Petition on Benzene in Dry Shampoo Products (filed October 31, 2022) (<https://www.regulations.gov/document/FDA-2022-P-2707-0001>)

³⁰ 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>)

³¹ Food and Drug Administration. *Best Brand Consumers Products, Inc. Issues Voluntary Recall of Mickey Mouse Hand Sanitizer Ethyl Alcohol 68% Due to Presence of Methanol and the Mandalorian Hand Sanitizer Ethyl Alcohol 68% Due to the Presence of Benzene* (April 1, 2022) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/best-brand-consumers-products-inc-issues-voluntary-recall-mickey-mouse-hand-sanitizer-ethyl-alcohol>)

³² Food and Drug Administration. *Johnson & Johnson Consumer Inc. Issues Voluntary Recall of Specific NEUTROGENA® and AVEENO® Aerosol Sunscreen Products Due to the Presence of Benzene* (July 14, 2021) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/johnson-johnson-consumer-inc-issues-voluntary-recall-specific-neutrogenar-and-aveenor-aerosol>)

³³ anti-fungal sprays,^{34, 35} antiperspirants,^{36, 37} dry shampoos,^{38, 39} and antiseptics⁴⁰ due to the presence of benzene, further underscores the necessity to better regulate benzene and its apparent broad and persistent prevalence in consumer product supply chains. FDA has made notable progress in addressing benzene contamination concerns by issuing guidance to reformulate drug products⁴¹ that contain a specific gelling agent ingredient, carbomer, that could be a substantial source of benzene in drug products such as hand sanitizers.⁴² However, carbomers are only one potential source of benzene, which likely does not account for the broad benzene contamination issues aforementioned which have been ongoing for nearly 3 years. **Furthermore, it is important to note that the specific problem with benzene in benzoyl peroxide products does not appear to be a contamination issue from a specific ingredient, but instead the inherent instability of the benzoyl peroxide molecule that breaks down and forms benzene.**

³³ Food and Drug Administration. *Coppertone® Issues Voluntary Nationwide Recall of Specific Lots of Pure & Simple SPF 50 Spray (2021 Launch), Sport Mineral SPF 50 Spray (2021 Launch), and Travel-Size Coppertone® Sport Spray SPF 50 (1.6OZ) Aerosols Sunscreen Sprays Due to the Presence of Benzene.* (September 30, 2021) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/coppertone-issues-voluntary-nationwide-recall-specific-lots-pure-simple-spf-50-spray-2021-launch>)

³⁴ Food and Drug Administration. *Odor-Eaters® Issues Voluntary Nationwide Recall of Specific Lots of Odor-Eaters® Spray Powder and Odor-Eaters® Stink Stoppers® Spray Due to Benzene Contamination* (November 17, 2021) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/odor-eaters-issues-voluntary-nationwide-recall-specific-lots-odor-eaters-spray-powder-and-odor>)

³⁵ Food and Drug Administration. *Bayer Issues Voluntary Recall of Specific Lotrimin® and Tinactin® Spray Products Due to the Presence of Benzene* (October 1, 2021) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/bayer-issues-voluntary-recall-specific-lotrimin-and-tinactin-spray-products-due-presence-benzene>)

³⁶ Food and Drug Administration. *TCP HOT Acquisition LLC dba HRB Brands Issues Voluntary Nationwide Recall of Sure and Brut Aerosol Sprays Due to the Presence of Benzene* (February 16, 2022) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/tcp-hot-acquisition-llc-dba-hrb-brands-issues-voluntary-nationwide-recall-sure-and-brut-aerosol>)

³⁷ Food and Drug Administration. *Unilever Issues Voluntary Nationwide Recall of Suave 24-Hour Protection Aerosol Antiperspirant Powder and Suave 24-Hour Protection Aerosol Antiperspirant Fresh Due to Presence of Slightly Elevated Levels of Benzene* (March 30, 2022) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/unilever-issues-voluntary-nationwide-recall-suave-24-hour-protection-aerosol-antiperspirant-powder>)

³⁸ Food and Drug Administration. *P&G Issues Voluntary Recall of Aerosol Dry Conditioner Spray Products and Aerosol Dry Shampoo Spray Products* (December 17, 2021) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/pg-issues-voluntary-recall-aerosol-dry-conditioner-spray-products-and-aerosol-dry-shampoo-spray>)

³⁹ Food and Drug Administration. *Unilever Issues Voluntary U.S. Recall of Select Dry Shampoos Due to Potential Presence of Benzene* (October 21, 2022) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/unilever-issues-voluntary-us-recall-select-dry-shampoos-due-potential-presence-benzene>)

⁴⁰ Food and Drug Administration. *Insight Pharmaceuticals Issues Voluntary Nationwide Recall of Americaine® 20% Benzocaine Topical Anesthetic Spray Due to the Presence of Benzene* (December 22, 2023) (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/insight-pharmaceuticals-issues-voluntary-nationwide-recall-americainer-20-benzocaine-topical>)

⁴¹ Food and Drug Administration. *Reformulating Drug Products That Contain Carbomers Manufactured With Benzene* (December 27, 2023) (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reformulating-drug-products-contain-carbomers-manufactured-benzene>)

⁴² 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>).

Although there have been actions taken regarding products with unacceptably high concentrations of benzene, Petitioner is not aware of any FDA guidance on a total amount, or permissible daily exposure limit, for benzene in any drug or cosmetic product, including benzoyl peroxide products, and requests urgent action on behalf of FDA to issue guidance to fill this gap. 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 benzoyl peroxide products.

Other carcinogenic contaminants found in drug products have been regulated by FDA using both a concentration limit and a total amount, or permissible daily exposure limit. For example, there have been a multitude of manufacturer recalls of medications, such as valsartan, irbesartan, losartan,⁴³ ranitidine, nizatidine,⁴⁴ and metformin,⁴⁵ 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 ppm and permissible daily intake, which is held constant at a specified nanogram level ("ng") per day for all drug products.⁴⁶ Petitioner requests a similar approach be taken for benzene in drug products.

Strict Environmental Protection Agency ("EPA") regulations on benzene are detailed in a report authored by the Agency for Toxic Substances and Disease Registry ("ATSDR"),⁴⁷ which stated:

EPA has set 5 ppb [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.

Furthermore, the long-established epidemiological data in humans is utilized by EPA to determine that a lifetime exposure of 0.4 ppb, or 0.0004 ppm, of benzene in air can lead to one additional cancer case in 100,000 exposed persons.⁴⁸

⁴³ 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-irbesartan>).

⁴⁴ 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>).

⁴⁵ 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>).

⁴⁶ 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>).

⁴⁷ Agency for Toxic Substances and Disease Registry (August 2007). *Toxicological Profile for Benzene*. (<https://www.atsdr.cdc.gov/toxprofiles/tp3.pdf>)

⁴⁸ Environmental Protection Agency. Benzene; CASRN 71-43-2. Integrated Risk Information System (IRIS) (https://iris.epa.gov/static/pdfs/0276_summary.pdf)

The depth of experience with benzene regulation at EPA and the concern over environmental impact of benzene contamination may offer a rational basis for collaboration between FDA and EPA to expeditiously address the current lack of much needed benzene regulation in drug and consumer 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.^{49, 50}

Methodology summary

For the majority of measurements in this Petition, Valisure elected to utilize industry standard Gas Chromatography-Mass Spectrometry (“GC-MS”) instrumentation that allows mass spectral separation and utilizing selected ion chromatograms, along with Selected Ion Flow Tube-Mass Spectrometry (“SIFT-MS”) for detection of benzene released into the air around certain benzoyl peroxide products, and other orthogonal approaches for confirmation of a few select products. Gas 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 sanitizers, which includes benzene analysis.⁵¹

Evaluating multiple methods had been useful in past drug product contaminations⁵² and was performed here as well to help ensure validity of these highly concerning results. GC-HRMS, HPLC and SIFT-MS were employed for the identification and quantification of benzene in selected benzoyl peroxide 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. 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 minimize any degradation during detection.⁵³ The GC-MS methodologies described in this petition utilized body temperature (37°C) for oven incubation. 40°C has been

⁴⁹ Food and Drug Administration (October 30, 2019). *MOU 225-19-033*. (<https://www.fda.gov/about-fda/domestic-mous/mou-225-19-033>)

⁵⁰ 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>)

⁵¹ 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>)

⁵² 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>)

⁵³ Valisure FDA Citizen Petition Requesting to Recall Ranitidine (dated September 9, 2019) (<https://www.regulations.gov/docket?D=FDA-2019-P-4281>)

previously used for benzene analysis from liquid pharmaceuticals and beverages, and reduced false positive results compared with higher-temperature incubation.^{54, 55}

Valisure acquired benzoyl peroxide product samples from many retailers and distributors, and in many different formulations. 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 acne treatment products within the United States, multiple samples contained significantly detectable benzene and benzoyl peroxide containing products that were stability tested at elevated temperatures appeared to broadly exhibit a propensity to form substantial amounts of benzene. This indicates a fundamental instability of the benzoyl peroxide molecule and a need to take broad action for drug products containing BPO.

Detailed Analytical Methods

GC-MS

The method USP <467> Residual Solvents Procedure A was modified from flame ionization detection (FID) to mass spectrometry (MS) detection for benzene in acne treatment products. The sample preparation and headspace (HS) gas chromatography (GC) methods were also modified to fit product matrices 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 in micrograms is performed by comparing peak area of benzene in a sample to a validated 11-point calibration curve of native benzene and ¹³C₆ isotopically labeled benzene and adjusting for the ratio of peak area for a known amount of ¹³C₆ benzene spiked into the sample to that of ¹³C₆ in the calibration curve. Results in ppm are determined by dividing the micrograms of benzene detected per sample by the grams of material used for each sample during preparation.

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 standard (¹³C₆ -, 99 % purity) was used for retention time verification (Sigma-Aldrich, St. Louis, MO). USP Class 1 residual solvents mixture and isotopic labeled benzene standard (¹³C₆-, 99 % purity) was used for calibration confirmation (USP, Rockville, MD). All volumetric glassware

⁵⁴ 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/>)

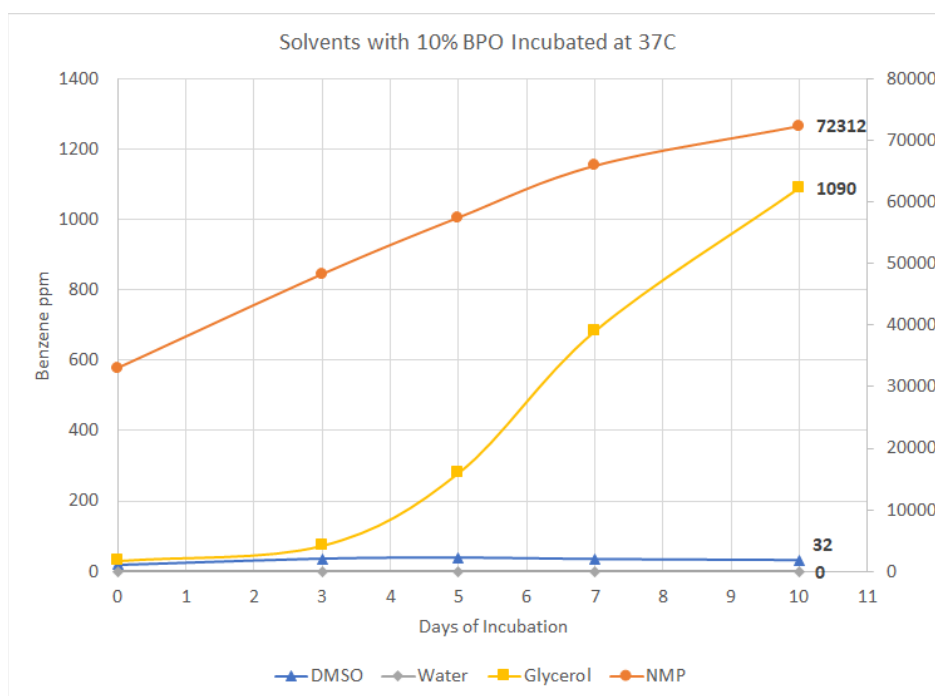
⁵⁵ Liu, H. et al. (2011) A general static-headspace gas chromatographic method for determination of residual benzene in oral liquid pharmaceutical products. J Pharm Biomed Anal. Vol. 54(2), p. 417-21. doi: 10.1016/j.jpba.2010.09.006. (<https://www.sciencedirect.com/science/article/abs/pii/S0731708510005182?via%3Dihub>)

used are Class A certified. Stability testing was performed in a laboratory oven (Precision Freas Mechanical Convection Oven 605, Thermo Electron Corporation).

Standard and Sample Preparation

Initial experiments on benzene formation in simple solutions (water, N-Methyl-2-pyrrolidone, glycerol, and DMSO) resulted in DMSO being chosen as a carrier and calibration solvent for GC-MS studies due to the apparent stability of 10% BPO when incubated up to ten days at 37°C. Product samples prepared in DMSO and incubated at 37°C for 20 minutes in the GC-MS procedure are not expected to meaningfully form benzene from sample preparation. Neither BPO nor its primary decomposition product of benzoic acid are volatile so formation of benzene from decomposition of BPO or intermediates in the higher heat GC-MS transfer loop, transfer line, or column are not expected to significantly impact analysis of benzene. Benzoic acid was empirically tested for the potential of forming benzene in this study's analytical conditions by analyzing it in DMSO and by adding it to a sample of BPO product prepared in DMSO, and in no instance was benzene or additional benzene detected. All samples were prepared and treated uniformly.

Figure 2. Incubation up to ten days at 37°C showed that BPO is stable as a 10% solution in Dimethyl Sulfoxide (DMSO) and water compared to Glycerol (also called Glycerin) and N-Methyl-2-pyrrolidone (NMP).



Native benzene standard was diluted in DMSO to a volume of 0.5 mL and added to 4.5 mL of DMSO containing 0.25 µg/mL of ¹³C₆ benzene standard. Calibration standards were prepared in 20-mL GC headspace vials with a total of 5 mL volume.

Acne treatment products were sampled and placed into the GC headspace vials at approximately 500 mg and weighed, followed by adding 4.5 mL of DMSO containing 0.25 µg/mL of ¹³C₆ benzene standard to make up the final volume to approximately 5 mL and vortexing to mix. In instances where different isotopic standard than ¹³C₆ was used, subsequent reanalysis of the same product utilizing ¹³C₆ would be conducted and calculated recovery ratios used to adjust final benzene concentrations. Heated products were brought to room temperature prior to sampling and returned to incubator after sampling. Notably, products incubated at elevated temperatures often changed consistency over time and gentle shaking helped to ensure homogenous sample collection and minimize variability. Five (5) mL of DMSO containing 0.25 µg/mL of ¹³C₆ benzene standard was used as blank samples.

Instrumental Analysis

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

Table 1. Instrumental parameters optimized for benzene detection in acne treatment 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	1.2
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

Linear non-forcing through zero calibration curve was generated from the peak areas of the 11-point calibration standards ranging from 10 ng/vial to 100 µg/vial. Calibration curve was accepted when the coefficient of determination R² was equal or greater than 0.995. Lower limit of detection (LLOD) and lower limit of quantification (LLOQ) were determined from linear regression and reference standard control samples prepared at the concentration of the lowest calibration standard that were ran with each experiment. LLOD was 20 ng (equivalent to 0.04 ppm in products) and LLOQ was 40 ng (equivalent to 0.08 ppm in products). The measurement variability, as calculated by the standard deviation of replicate standard samples, is concentration dependent and determined to be 34% near 0.1 ppm and 2% near 2 ppm. USP Class 1 residual solvent mixture was analyzed against the calibration and result of benzene agreed with certified concentration.

SIFT-MS

A Syft Technologies *Voice200ultra* mass spectrometer equipped with a high-performance inlet was utilized for measurement of benzene in real time. The inlet was connected via capillary tubing to an environmental chamber of approximately 528 liters of air volume. This environmental chamber had approximate dimensions of 45L x 24W x 44H inches, was constructed from polypropylene material and could be opened by separating its two halves that

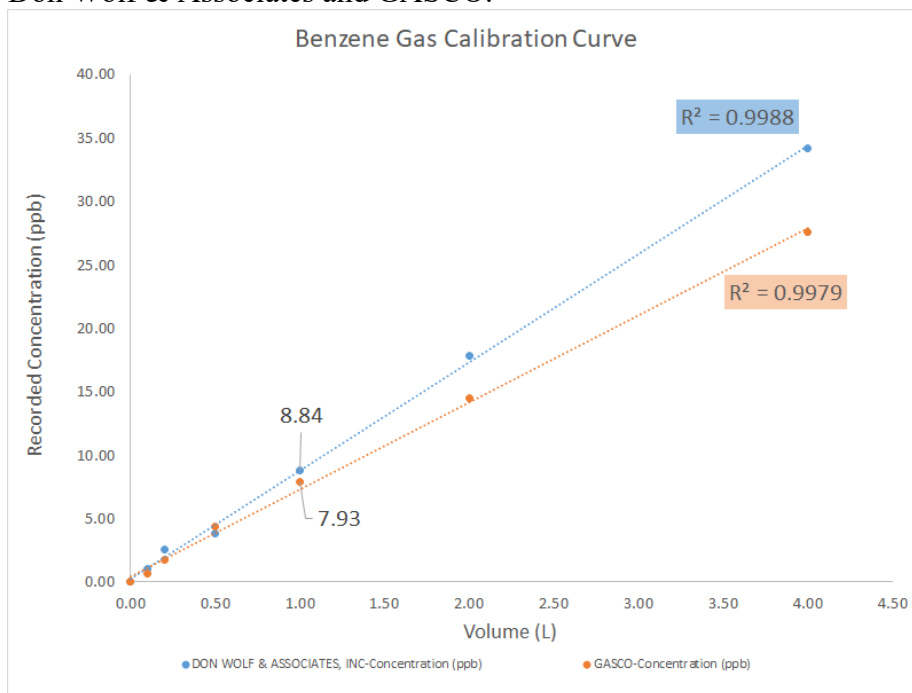
were connected by metallic hinges. Four USB-powered PC-fans were affixed to the top (2) and bottom (2) of the chamber and were all powered on during incubation to ensure rapid homogenization of the air in the chamber. Two common OTC BPO products were separately incubated at 70°C for 16.7 hours utilizing a 2L DuoBath from Benchmark Scientific that was placed in the chamber and filled with metallic Lab Armor® Beads. BPO products were removed from external cardboard packaging, if present, but otherwise not modified in any manner. Notably, caps on the BPO product tubes were not removed, so all products were analyzed as factory-sealed products.

Analytical Methods

The two product ions, $C_6H_6 \cdot NO^+$ and $C_6H_6^+$, with masses 108 and 78 respectively, were used to measure the concentration of benzene before and during the incubation of BPO products in the environmental chamber and were generated from reagent ions NO^+ and O_2^+ respectively.

Benzene concentrations in ppb were plotted in real time for each of the BPO samples using LabSyft analysis software, and each measurement cycle was three seconds. LLOD and LLOQ of benzene was calculated from the two separate reference gas calibration curves and resulted in Don Wolf & Associates LLOD of 1.55 ppb and LLOQ of 4.70 ppb, and GASCO LLOD of 1.64 ppb and LLOQ of 4.97 ppb.

Figure 3. SIFT-MS gas calibration with 5 ppm benzene reference gas standards from Don Wolf & Associates and GASCO.



Standards and Sample Preparation Methods

LabSyft analysis software automatically calculates benzene in air concentrations based on known product ion ratios from the reaction of benzene with the SIFT-MS reagent ions. Additionally, the

environmental chamber and SIFT-MS was validated with injection of two separate reference gasses (Don Wolf & Associates and GASCO) where benzene was contained at a known concentration of 5 ppm. The gasses were injected at known volumes into the chamber generating a 7-point curve with R² values greater than 0.995 and absolute concentrations within the expected variability of the reference standards.

Results – GC-MS

Initial GC-MS analysis was performed on 175 acne treatment products. 99 products contained BPO as at least one of the active ingredients, 58 products contained active ingredients either individually or in combination of salicylic acid (46 of 58 products), sulfur, adapalene, azelaic acid, niacinamide and zinc, and 18 products contained no drug ingredient. 83 of the BPO products were OTC and purchased from major retailers and 16 were prescription products purchased from licensed wholesalers. All non-BPO products were OTC products purchased from major retailers.

GC-MS analysis for benzene was performed on all 175 acne treatment products to investigate if any native benzene was present in the products. 70 of the 76 non-BPO products had no detectable benzene or values below 0.1 ppm. 6 non-BPO products contained traces of benzene below 2 ppm, which could be due to various inactive ingredients used in consumer products that have been theorized to contain trace benzene.⁵⁶ No further analyses of non-BPO products were performed.

GC-MS analysis for native benzene was performed on 99 BPO containing acne medication products, and resulted in the detection of benzene in 94 products, often with values well above 2 ppm in an initial analysis. This high prevalence of benzene in specifically BPO acne treatment products and discovering research in the academic literature as early as 1936 that concluded BPO can directly degrade into benzene,⁵⁷ led Valisure to conduct a stability study at elevated temperatures on a diverse market sweep of BPO products and formulations.

An initial stability study of 5 products using 37°C, 50°C and 70°C revealed that dozens of ppm of benzene can form in just a few weeks at 37°C, hundreds of ppm at 50°C, and 70°C often would lead BPO product packaging to burst. Therefore, 50°C was chosen as a stability temperature for a broader study of 66 BPO products detailed below.

50°C Incubation for 18 Days

66 different BPO containing drug products, both prescription and OTC, were acquired by Valisure and incubated at 50°C for 18 days, with samples measured for benzene at Day 0, 4, 10, 14 and 18. These products represented creams, lotions, gels, washes, liquids and bars. Results are

⁵⁶ A. Hudspeth, et. al. (2022) Independent Sun Care Product Screening for Benzene Contamination. *J Environmental Health Perspectives*. 037701.130-3. doi:10.1289/EHP10386 (<https://ehp.niehs.nih.gov/doi/full/10.1289/EHP10386>)

⁵⁷ Erlenmeyer, H. and Schoenauer, W. (1936), Über die thermische Zersetzung von Di-acyl-peroxyden. *HCA*, 19: 338-342. <https://doi.org/10.1002/hlca.19360190153> (<https://onlinelibrary.wiley.com/doi/10.1002/hlca.19360190153>)

shown below in Figure 4. Note that each graph utilizes a different y-axis scale for display purposes.

Figure 4(A – I). Benzene detection in ppm of 66 BPO containing acne treatment products incubated at 50°C for 18 days. Each graph utilizes a different y-axis scale ranging from a maximum of 2,000 ppm to 1.8 ppm in order to most effectively display the levels of benzene detected in different products at the different time points. Products are labeled by the BPO percentage they contained, the brand name, the product type and the Universal Product Code (“UPC”) number.

Figure 4A

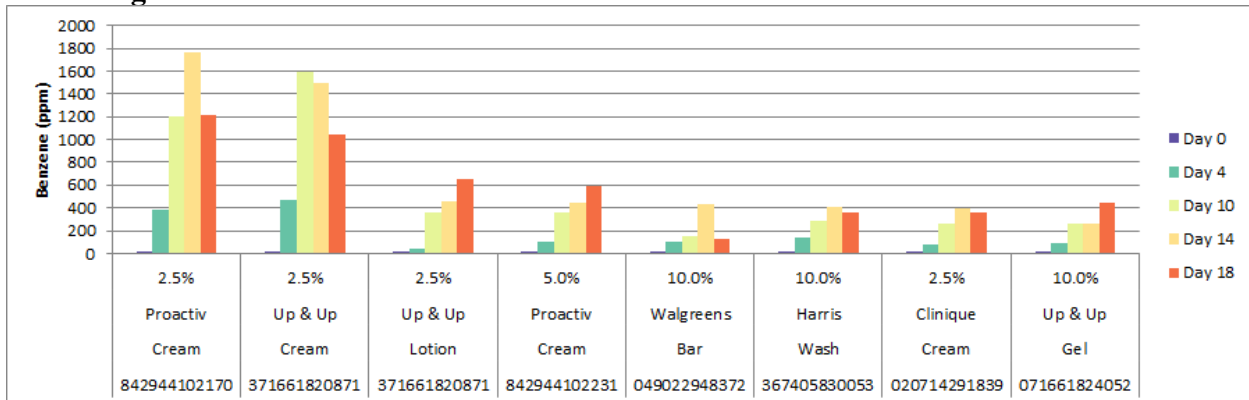


Figure 4B

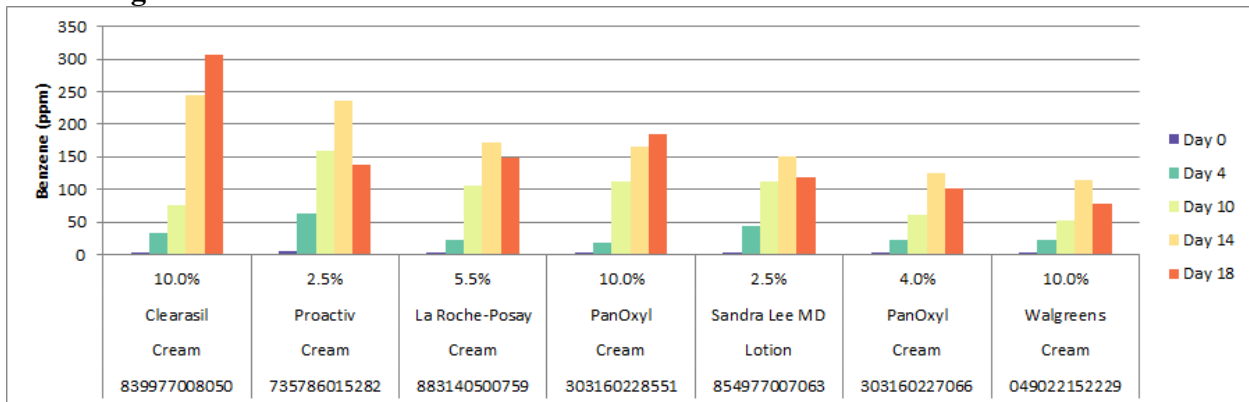


Figure 4C

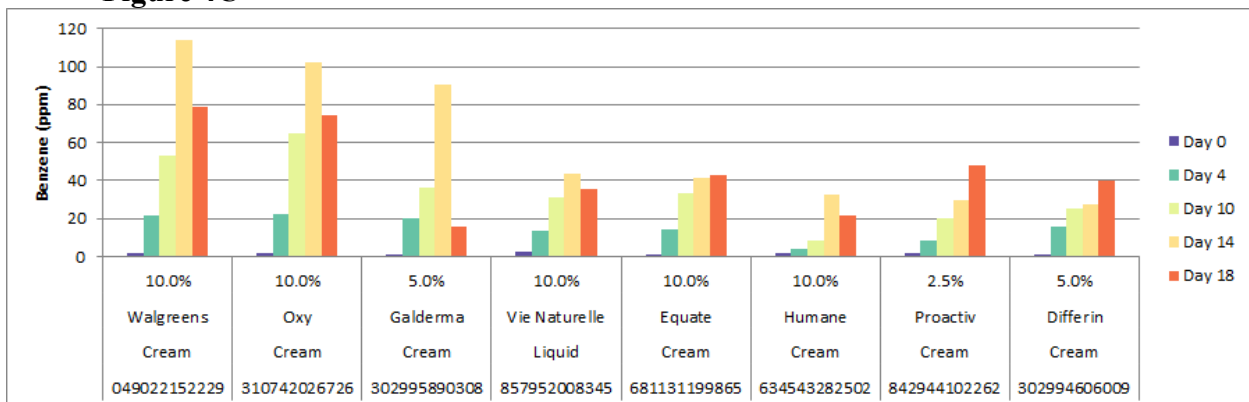


Figure 4D

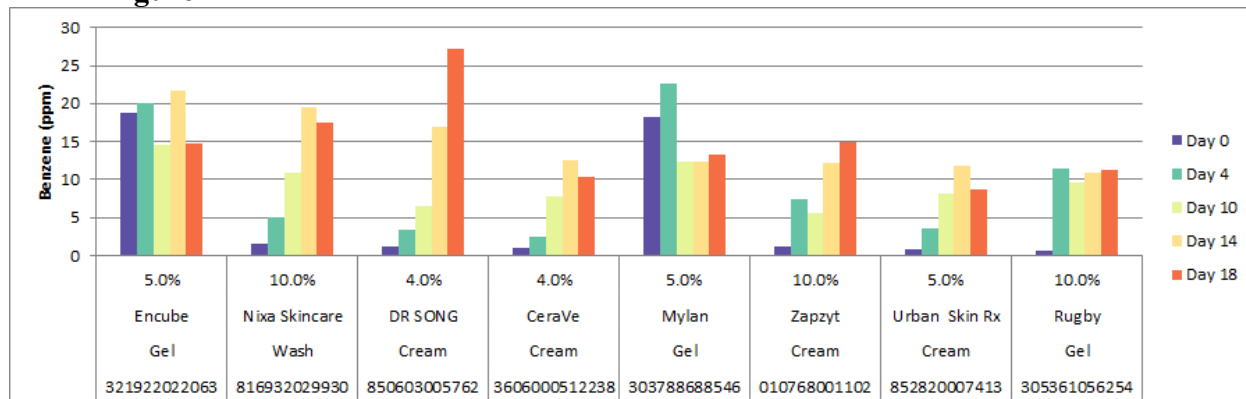


Figure 4E

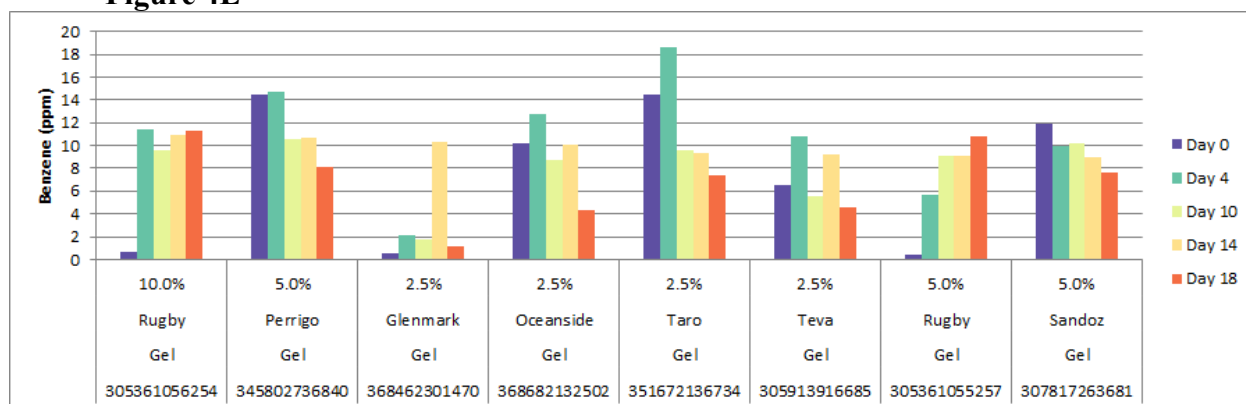


Figure 4F

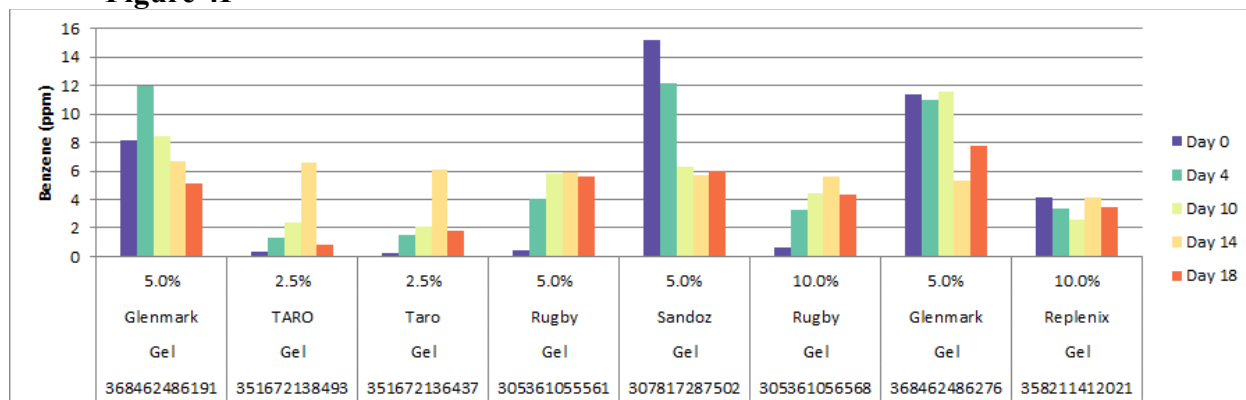


Figure 4G

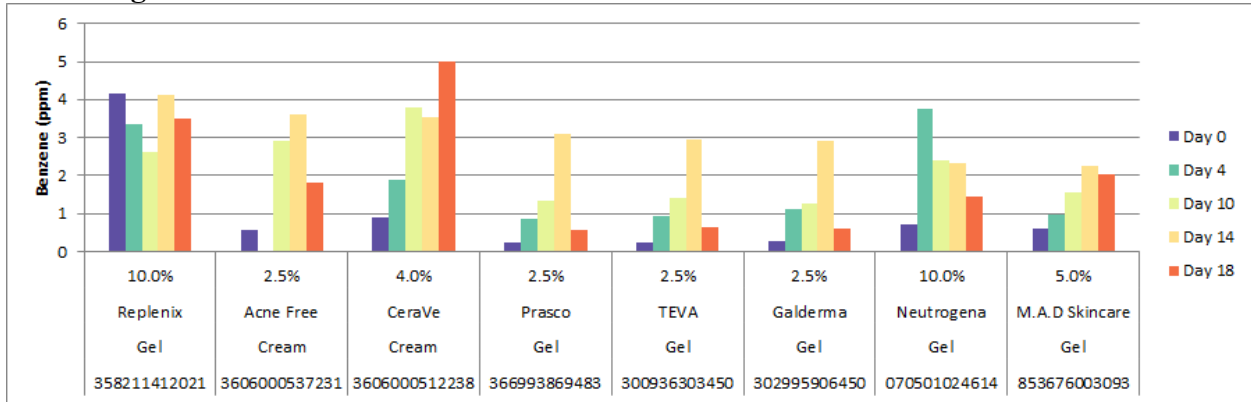


Figure 4H

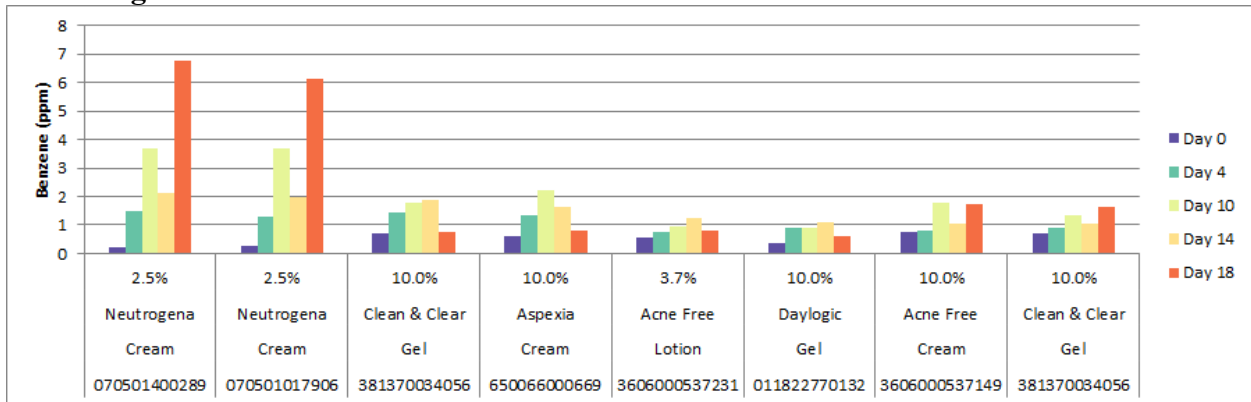
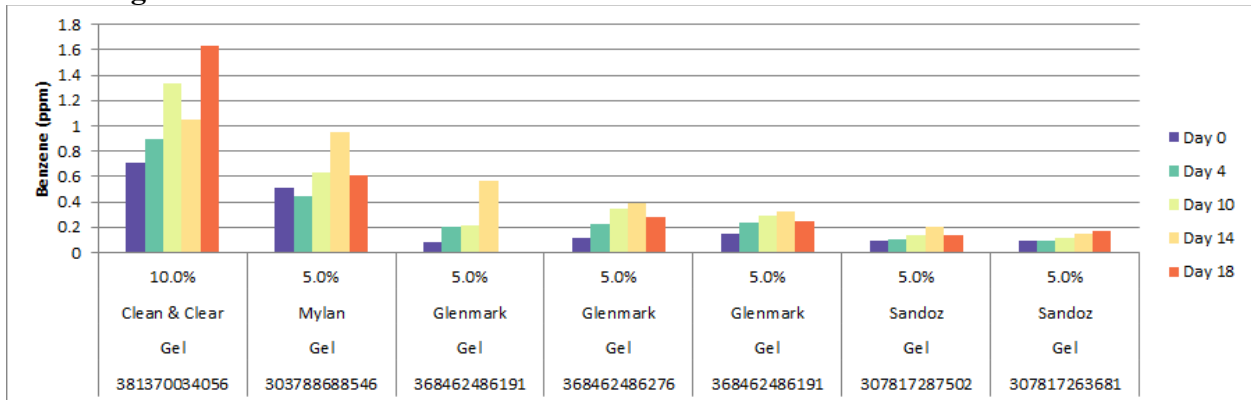


Figure 4I



Results from this 50°C stability study showed substantial instability of BPO and its propensity to form concerningly high levels of benzene in only 18 days. Petitioner notes that 50°C (122°F) is not only a reasonable temperature that “the product may be exposed to during distribution and

handling by consumers”⁵⁸ but is an accepted incubation temperature used by the pharmaceutical industry for performing accelerated stability studies with a duration of at least 3 months.⁵⁹

Incubated BPO products typically displayed an increase in benzene concentration over time; however, some products displayed patterns that were either erratic, relatively stable or potentially diminishing over time. This led to a hypothesis that product packaging could potentially be enabling benzene to “leak” into the surrounding environment, especially considering the volatile nature of benzene and that this volatility increases at the higher temperatures of the stability study. Therefore, the detection of benzene concentration in the BPO product could be a function of both how quickly it forms in the product, and how quickly the packaging allows it to evaporate externally. Valisure investigated this hypothesis utilizing SIFT-MS, as is subsequently presented in this Petition.

70°C for 18 days on more stable formulations

A selection of BPO formulations displaying relatively high stability compared to other BPO containing products and that formed less than 2 ppm in 50°C for 18 days, were subsequently placed in 70°C (158°F) incubation for 18 days. Samples from the incubated products were taken and analyzed for benzene on Day 2, 4, 7, 10, and 18 (Day 0 is the value taken from Day 18 of the 50°C incubation), though not all products contained sufficient material to be sampled on each day. Notably the 25 g packages of Glenmark and Sandoz products only had enough remaining material to be sampled and analyzed on Day 2 and 7. New containers of the 25 mg Glenmark and Sandoz products were acquired and another 70°C incubation was run for 14 days with samples taken and analyzed on Day 0, 10 and 14. Results shown in Figure 5 below.

⁵⁸ Food and Drug Administration. *FDA Requests Removal of All Ranitidine Products (Zantac) from the Market* (April 1, 2020) (<https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market>)

⁵⁹ Ghimire, Prakash & Shrestha, Abinash & Pandey, Sandhya. (2020). Guidelines on Stability Studies of Pharmaceutical Products and Shelf Life Estimation. *International Journal of Advances in Pharmacy and Biotechnology*. 06. 15-23. 10.38111/ijapb.20200601004.

Figure 5(A – B). Benzene detection in ppm of 7 BPO containing acne treatment products incubated at 70°C. Products are labeled by the BPO percentage they contained, the brand name, the product type and the UPC number.

Figure 5A

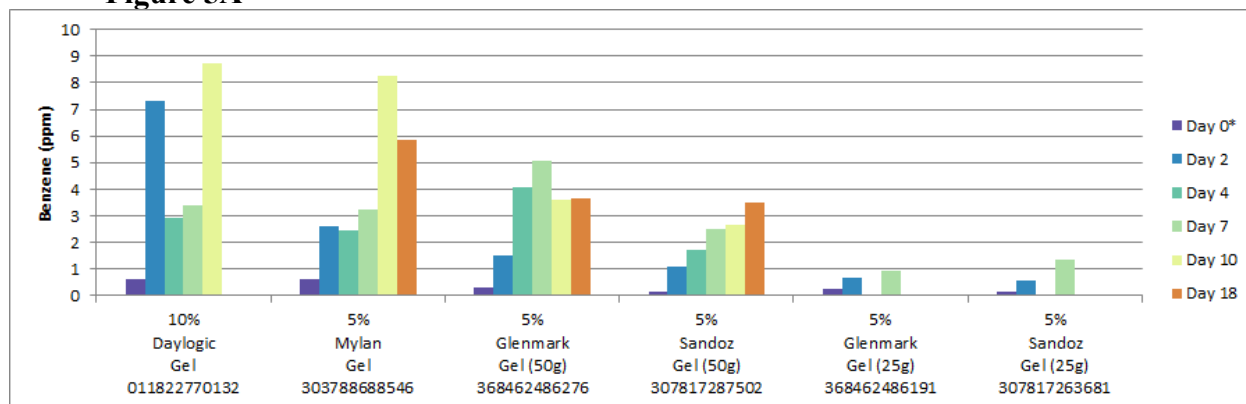
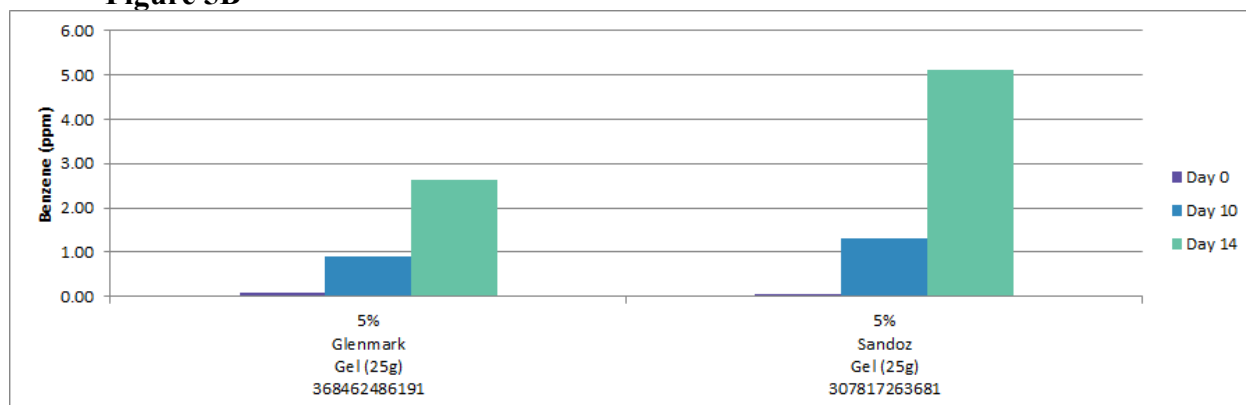


Figure 5B



The results show that even the most stable of the 66 formulations Valisure tested still produce over 2 ppm of benzene when incubated at 70°C for 14 or 18 days. The differences in results from the 50 g and 25 g of the same Glenmark and Sandoz formulations also again suggest a substantive effect of packaging on the amount of benzene remaining in an incubated sample and the likelihood that a meaningful volume of benzene could be escaping from the product container.

Petitioner notes that 70°C (158°F) is not only a reasonable temperature that “the product may be exposed to during distribution and handling by consumers”⁶⁰ and that it is within the reported temperature range of a hot car⁶¹ where many consumers may store or transport an acne treatment

⁶⁰ Food and Drug Administration. *FDA Requests Removal of All Ranitidine Products (Zantac) from the Market* (April 1, 2020) (<https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market>)

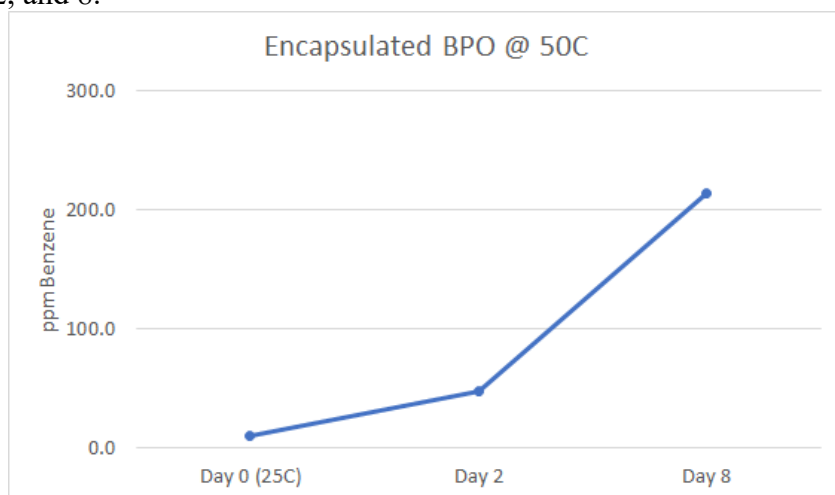
⁶¹ Grundstein A, Meentemeyer V, Dowd J. Maximum vehicle cabin temperatures under different meteorological conditions. *Int J Biometeorol.* 2009 May;53(3):255-61. doi: 10.1007/s00484-009-0211-x. Epub 2009 Feb 21. PMID: 19234721.

product, but it is also calculated to be the 3-year accelerated stability equivalent of 43 days.⁶² This means that to achieve the expected minimum shelf life of 3 years for a standard pharmaceutical product, the product should exhibit stability for at least 43 days of 70°C incubation. Valisure’s results at only 14 and 18 days of 70°C incubation already show unacceptably high levels of benzene detected within the product and would expect substantially more benzene to have been produced by Day 43.

Testing of BPO Formulations with Stabilization Technologies

Due to the known instability of benzoyl peroxide, several manufacturers of BPO products have developed specialized “stable delivery systems” of benzoyl peroxide for the treatment of acne.⁶³ Valisure acquired a sample of BPO product where the benzoyl peroxide had been encapsulated in sub-micron sized particles using SalSphere® technology that claims to enable “superior stability.” Testing of this product for benzene before incubation showed benzene levels well above 2 ppm and 8 days of incubation at 50°C resulted in benzene concentration over 100 ppm.

Figure 6. Salvona SalSphere® encapsulated BPO product tested for benzene at Day 0, 2, and 8.



At the time of submission of this Petition, Valisure had recently acquired additional prescription formulations of BPO that were thought to also contain potential stabilization technologies, such as polymeric mesh.⁶⁴ These products were: Cabtreo (UPC 301870006254, NDC 0187-0006-25) and the authorized generic (“AG”) of Onexton (UPC 368682133509 NDC 68682-0133-50), both packaged in a pump dispenser. Initial results of incubation at 50°C for up to 10 days detected

⁶² Packaging Compliance Labs. *Accelerated Aging Calculator*. (Accessed January 4, 2024) (<https://pkgcompliance.com/resource/accelerated-aging-calculator/>)

⁶³ Salvona, LLC. *SalSphere® BPO, A stable and targeted delivery system of benzoyl peroxide for the treatment of acne*. (Accessed January 4, 2024) (<https://www.salvona.com/product/salsphere-benzoyl-peroxide/>)

⁶⁴ Draelos, Zoe & Tanghetti, Emil & Gold, Linda & Kircik, Leon & Bhatia, Neal & Zeichner, Joshua & Sugarman, Jeffrey. (2023). Dermal Irritation, Sensitization, and Safety of Fixed-Dose Triple-Combination Clindamycin Phosphate 1.2%/Benzoyl Peroxide 3.1%/Adapalene 0.15% Gel in Healthy Participants. *SKIN The Journal of Cutaneous Medicine*. 7. s227. 10.25251/skin.7.sup.227.

benzene concentrations of 7.2 ppm – 11.0 ppm for the AG of Onexton and 4.6 ppm – 7.8 ppm for Cabtreo.

Results – SIFT-MS

As aforementioned in this Petition, Valisure observed evidence that some BPO containing acne treatment products may have packaging that is porous to benzene, enabling some portion of benzene contained in the product, or formed in the product during stability testing, to escape into the environment or air around the package. To test this hypothesis and to further validate the overarching theory that current benzoyl peroxide drug products produce substantial amounts of benzene at “temperatures the product may be exposed to during distribution and handling by consumers,”⁶⁵ Valisure utilized SIFT-MS technology to evaluate levels of benzene in the air surrounding an incubating BPO product contained in a closed, 528 liter environmental chamber.

Figures 7 and 8 below show results from this analysis at 70°C and 40°C. 70°C is particularly relevant as it is within the known temperature range of a hot car,⁶⁶ and 40°C is within the known temperature range of bathroom during a hot shower, both being reasonable environments where a BPO containing product may be stored by a consumer. The results of these tests clearly show that benzene can leak outside of unopened BPO containing acne treatment products at concerning high levels.

⁶⁵ Food and Drug Administration. *FDA Requests Removal of All Ranitidine Products (Zantac) from the Market* (April 1, 2020) (<https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market>)

⁶⁶ Grundstein A, Meentemeyer V, Dowd J. Maximum vehicle cabin temperatures under different meteorological conditions. *Int J Biometeorol*. 2009 May;53(3):255-61. doi: 10.1007/s00484-009-0211-x. Epub 2009 Feb 21. PMID: 19234721.

Figure 7. SIFT-MS analysis of benzene in the air within a 528L environmental chamber while a product is incubated at 70°C for 16.7 hours. Two products were separately analyzed, Equate Beauty, 4 oz, 10% BPO, acne wash, and Proactiv, 5.5 oz, 2.5% BPO, cleanser. Detected benzene is displayed in ppb and as a moving average of 1 minute of detection (20 detections occurring at 3-second intervals in real-time). Both products were incubated without modification from original packaging; notably their caps were not opened.

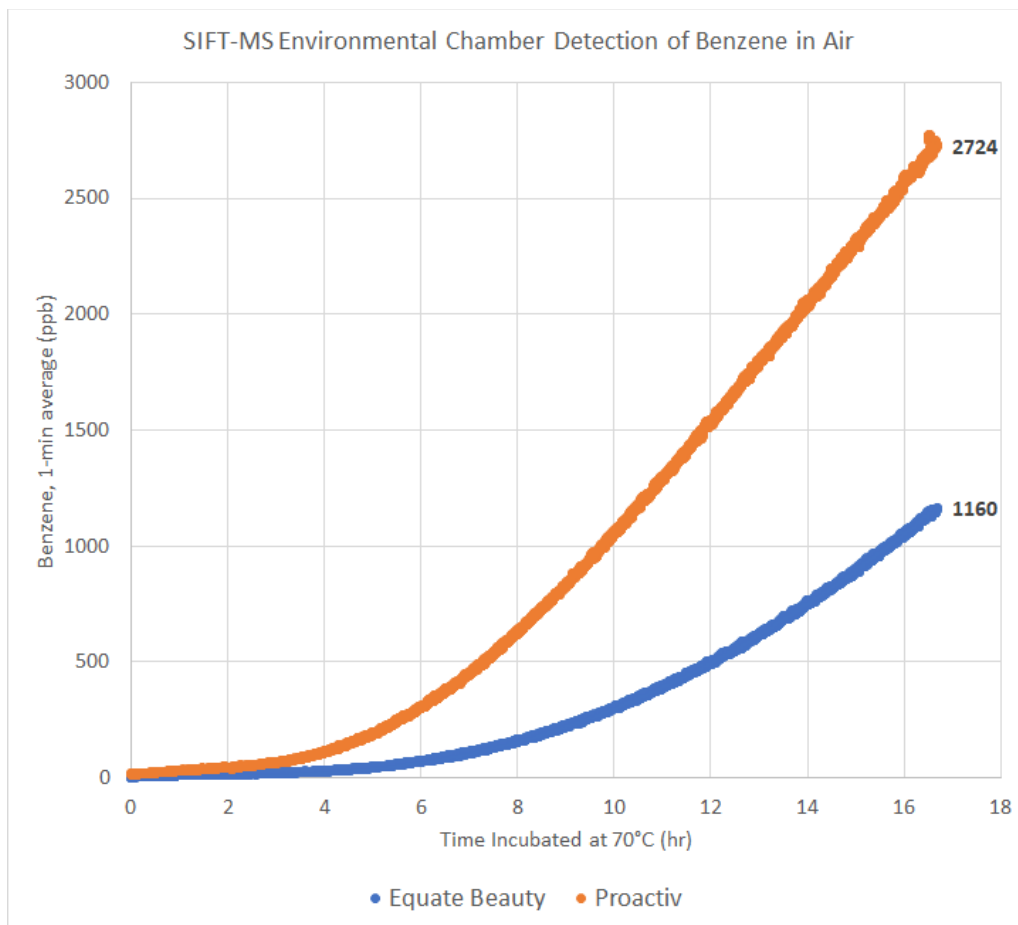
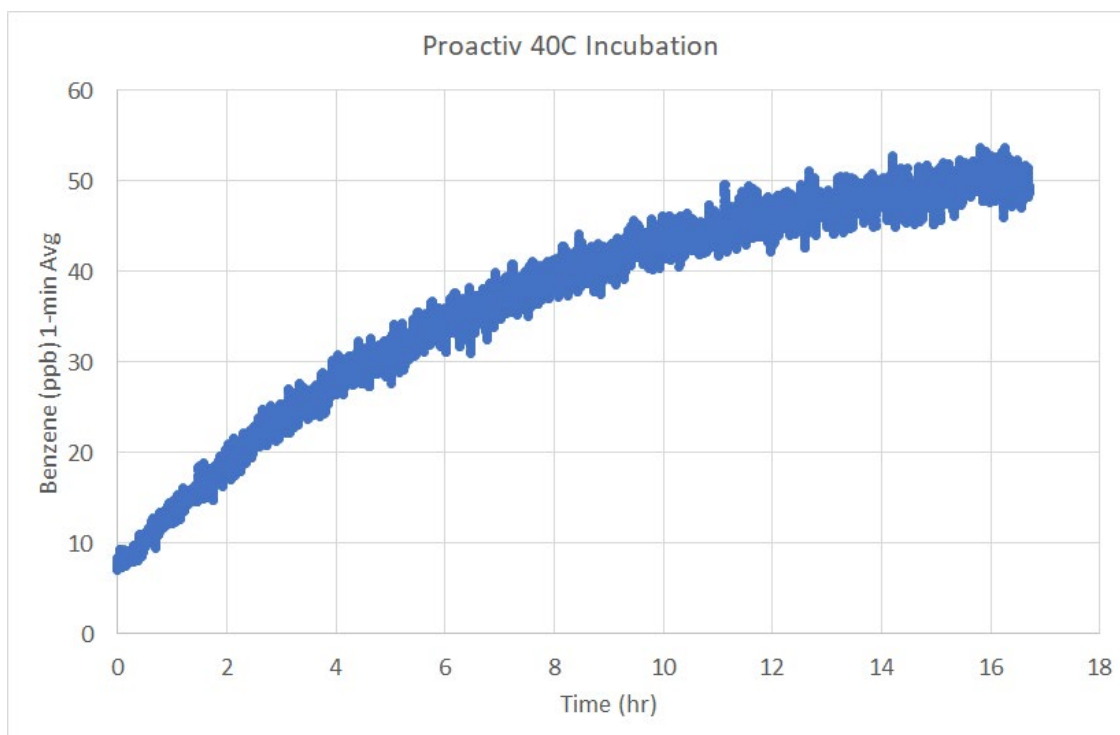


Figure 8. SIFT-MS analysis of benzene in the air within a 528L environmental chamber while a product (Proactiv, 5.5 oz, 2.5% BPO, cleanser) is incubated at 40°C for 16.7 hours. Detected benzene is displayed in ppb and as a moving average of 1 minute of detection (20 detections occurring at 3-second intervals in real-time). Product was incubated without modification from original packaging; notably the cap was not opened.



The data from the SIFT-MS testing suggests that high levels of gaseous benzene could be generated from a BPO containing product and emanate into a consumer environment such as a hot car or bathroom during a hot shower. Using the data from the Proactiv product incubated at 70°C for 16.7 hours, the 2,724 ppb of benzene detected in the 528 L chamber would be the equivalent of approximately 508 ppb of benzene in a 100 cubic foot compact car,⁶⁷ which is approximately 1,270 times the previously mentioned EPA calculated threshold for increased cancer risk by long-term inhalation exposure to benzene. Using the data from the 40°C incubation, the approximate temperature a bathroom can reach during a hot shower,⁶⁸ and assuming the same amount of total heating time and an 8 ft x 8ft x 8ft bathroom (512 cubic feet), the concentration of benzene in the bathroom could reach approximately 1.5 ppb, or

⁶⁷ US Department of Energy. *Frequently Asked Questions, Office of Energy Efficiency & Renewable Energy.* (<https://www.fueleconomy.gov/feg/info.shtml#sizeclasses>)

⁶⁸ Aizawa, Y., Tanabe, S., Amai, H., Watanabe, K., & Yokoo, K. (2006). Thermal environment and moisture production in the bathroom. In *HB 2006 - Healthy Buildings: Creating a Healthy Indoor Environment for People*, Proceedings (pp. 119-124).

approximately 4 times the EPA calculated threshold for increased cancer risk by long-term inhalation exposure to benzene.

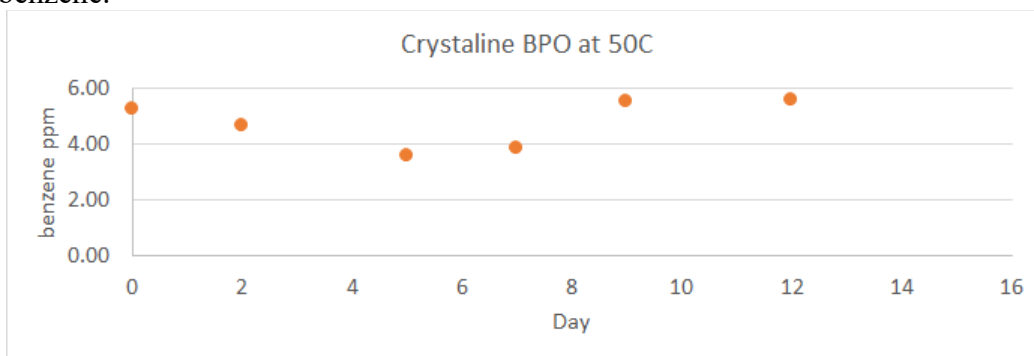
Furthermore, calculating the total benzene present in the air from the detected benzene level in the 528 L chamber during the 70°C incubation, approximately 4.59 mg of benzene was generated, which is the equivalent of producing approximately 29 ppm of benzene in the 5.5 oz Proactiv cleanser product in less than a single day of incubation.

Potential to Address BPO Instability for Future Formulations of BPO

On-market formulations of BPO containing acne treatment products tested by Valisure appear to be fundamentally unstable and generally form unacceptably high levels of benzene; however, it is possible that future reformulations of BPO drug products could address this issue. FDA has recently issued guidance requesting reformulation of drug products containing the raw material carbomer due to suspicion of it being contaminated with benzene,⁶⁹ lending precedent for a potential future guidance on reformulating BPO containing drug products.

Benzoyl peroxide as a raw material is known to be thermally stable at purities as high as 75% up to temperatures of 98°C.⁷⁰ Valisure also evaluated pure BPO reference powder in its GC-MS analytical system and found no evidence of the instability and formation of benzene seen in formulated final products of BPO containing acne treatments. See Figure 9.

Figure 9. Crystalline benzoyl peroxide incubated at 50°C for 12 days and analyzed for benzene.



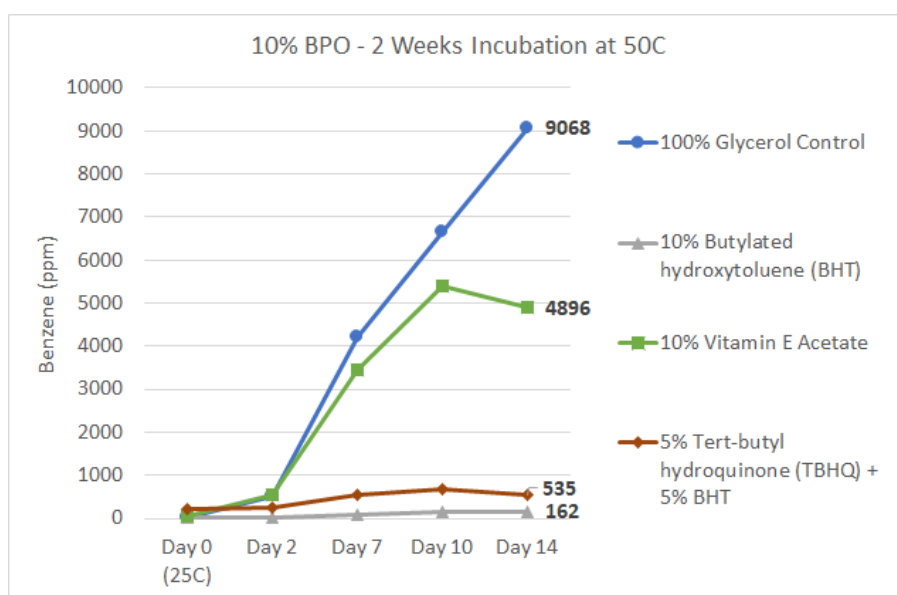
If BPO is inherently stable as a pure, crystalline powder, then a reformulated product that focuses on substantially reducing or entirely preventing the degradation of BPO into benzene could potentially be developed. Antioxidants are often used to prevent or inhibit thermal

⁶⁹ Food and Drug Administration. *Reformulating Drug Products That Contain Carbomers Manufactured With Benzene* (December 27, 2023) (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reformulating-drug-products-contain-carbomers-manufactured-benzene>)

⁷⁰ Yueqi Shen, et. al., Thermal decomposition of solid benzoyl peroxide using Advanced Reactive System Screening Tool: Effect of concentration, confinement and selected acids and bases. *Journal of Loss Prevention in the Process Industries*. Volume 60, 2019, pp 28-34, ISSN 0950-4230, <https://doi.org/10.1016/j.jlp.2019.04.001>

degradation processes⁷¹ and Petitioner investigated a few common antioxidants in a model system of therapeutically relevant 10% BPO in glycerol. The results summarized in Figure 10 below show that the addition of an antioxidant can substantially reduce the formation of benzene by over 98% in a formulation representative of a drug product. These and other techniques that could help address the BPO degradation problem in drug product formulations have been detailed in a recent patent filing.⁷²

Figure 10. Incubation at 50°C for 14 days of simple formulations of 10% BPO in glycerol where antioxidants were added individually or in combination and benzene concentration was evaluated by GC-MS.



Industry, Academic, Regulatory and Physician Concern

Petitioner is not aware of any actions by finished dosage form manufacturers on this issue. In other industries, the issue of BPO decomposition into benzene has been previously identified and acted upon. At least one patent application was filed by the chemical company Akzo Nobel N.V. in 1997 which “relates to a method for reducing the rate of free benzene and/or benzene derivative formation in BPO formulations based on organic plasticizers, such as pastes, emulsions, suspensions, dispersions and the like.”⁷³

⁷¹ Anshuman Shrivastava (2018). *Introduction to Plastics Engineering*. Elsevier Inc. ISBN: 978-0-323-39500-7. DOI: <https://doi.org/10.1016/C2014-0-03688-X>

⁷² Light, D et. al. “SHELF-STABLE FORMULATIONS OF BENZOYL PEROXIDE AND METHODS OF PRODUCING SAME.” PCT/US2023/015111

⁷³ Borys F. SchafranBryce Milleville (1997). “Reduction of benzene formation in dibenzoyl peroxide formulations.” Akzo Nobel N.V. Worldwide application, WO1997032845A1. (<https://patents.google.com/patent/WO1997032845A1/en>)

In the polymer manufacturing industry, BPO's decomposition into benzene has been studied and concern was raised specifically regarding the carcinogenic implications of the presence of benzene. In 1994, a paper was published⁷⁴ by researchers at Denmark's Department of Environmental Chemistry titled "Formation of benzene by hardeners containing benzoyl peroxide and phthalates" and stated:

"Recently, during the investigation of benzene residues in chemical products (Rastogi 1993a),⁷⁵ it was observed that the benzene content in benzoyl peroxide containing hardeners of two component repair-sets (fillers, elastomers) were >2 % (w/w) [20,000 ppm]. Benzene is carcinogenic (IARC 1982), and its use in consumer and industrial products is generally avoided."

The study continues with heating of various BPO-containing products at 34°C, 50°C and 80°C finding substantial benzene formation at elevated temperatures, even exceeding levels found in this Petition. Furthermore, similar to Valisure's results, Rastogi finds that only formulations of BPO are unstable, while BPO alone is relatively stable:⁷⁶

"Even heating of BPO-phthalate mixtures at 50°C produced significant amounts of benzene (approximately 0.3% [3,000 ppm]), while no benzene production was detected when benzoyl peroxide was heated alone at this temperature (Table 2)."

The referenced 1993 Rastogi article above, titled "Residues of Benzene in Chemical Products," has also been flagged by the US EPA as part of its Health & Environmental Research Online ("HERO") system.⁷⁷

Petitioner is not aware of any epidemiological studies suggesting a link between BPO use and cancer in humans; however, chemical evidence of carcinogenicity has been reported since at least 1981.⁷⁸ Multiple studies in the 1980s were conducted using animal models that suggested

⁷⁴ Rastogi SC. Formation of benzene by hardeners containing benzoyl peroxide and phthalates. *Bull Environ Contam Toxicol*. 1994 Nov;53(5):747-52. doi: 10.1007/BF00196949. PMID: 7833612.

⁷⁵ Rastogi, S.C. Residues of benzene in chemical products. *Bull. Environ. Contam. Toxicol*. 50, 794–797 (1993). <https://doi.org/10.1007/BF00209940>

⁷⁶ *Id.*

⁷⁷ US Environmental Protection Agency. Health & Environmental Research Online (HERO). "Residues of Benzene in Chemical Products." HERO ID 2894703 (https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/2894703)

⁷⁸ Slaga TJ, Klein-Szanto AJ, Triplett LL, Yotti LP, Trosko KE. *Skin tumor-promoting activity of benzoyl peroxide, a widely used free radical-generating compound*. *Science*. 1981 Aug 28;213(4511):1023-5. doi: 10.1126/science.6791284. PMID: 6791284.

carcinogenic potential of benzoyl peroxide, including the use of commercial drug formulations of BPO like that of PanOxyl Gel.^{79 80 81 82}

In 1991, FDA posted an amendment to the monograph for OTC topical acne drug products because, “the agency became aware of a 1981 study by Slage, et al. ([FDA] Ref. 1) that raised a safety concern regarding benzoyl peroxide as a tumor promoter in mice and a 1984 study by Kurokawa, et al. ([FDA] Ref. 2) that reported benzoyl peroxide to have tumor initiation potential,” leading FDA to determine that “further study is necessary to adequately assess the tumorigenic potential of benzoyl peroxide.”⁸³

By 2010, FDA published a final monograph on benzoyl peroxide along with summarizing results from further studies on the potential carcinogenicity of benzoyl peroxide and actions of the FDA Advisory Committee. This final monograph stated, “The Committee recommended, by a four-to-three vote (with one abstention), that the known safety data regarding the tumor promoting potential of benzoyl peroxide should be communicated to consumers. Because this data was inconclusive, the Committee unanimously agreed that the word, “cancer” should not be included in the labeling of acne drug products containing benzoyl peroxide. The Committee was concerned that the word “cancer” would cause consumers to avoid using these products (even though the data were inconclusive).”⁸⁴

Petitioner notes that the lack of epidemiological evidence and the FDA Advisory Committee’s conclusion that the BPO carcinogenicity in animal studies displayed inconclusive data could potentially be due, at least in part, to the newly discovered variable nature of BPO formulation instability and variable rates of formation of benzene.

Investigators at Yale University and Long Island University are actively studying BPO products and their propensity to form benzene. One researcher and dermatologist from Yale University commented to Valisure:

⁷⁹ Kurokawa Y, Takamura N, Matsushima Y, Imazawa T, Hayashi Y. *Studies on the promoting and complete carcinogenic activities of some oxidizing chemicals in skin carcinogenesis*. *Cancer Lett.* 1984 Oct;24(3):299-304. doi: 10.1016/0304-3835(84)90026-0. PMID: 6437666.

⁸⁰ Pelling JC, Fischer SM, Neades R, Strawhecker J, Schweickert L. *Elevated expression and point mutation of the Ha-ras proto-oncogene in mouse skin tumors promoted by benzoyl peroxide and other promoting agents*. *Carcinogenesis*. 1987 Oct;8(10):1481-4. doi: 10.1093/carcin/8.10.1481. PMID: 3115617.

⁸¹ O’Connell JF, Klein-Szanto AJ, DiGiovanni DM, Fries JW, Slaga TJ. *Enhanced malignant progression of mouse skin tumors by the free-radical generator benzoyl peroxide*. *Cancer Res.* 1986 Jun;46(6):2863-5. PMID: 3084079.

⁸² Iversen OH. *Carcinogenesis studies with benzoyl peroxide (Panoxyl gel 5%)*. *J Invest Dermatol.* 1986 Apr;86(4):442-8. doi: 10.1111/1523-1747.ep12285787. PMID: 3091706.

⁸³ Food and Drug Administration. *Proposed Rule: Reclassifies benzoyl peroxide from GRASE to Category III*. (August 7, 1991) Federal Register, 56FR37622. pp 37622 - 37635

(<https://cdn.loc.gov/service/ll/fedreg/fr056/fr056152/fr056152.pdf#page=178>)

⁸⁴ Food and Drug Administration. *Final Monograph*. (March 4, 2010) Federal Register, 75FR9767.

(<https://www.gpo.gov/fdsys/pkg/FR-2010-03-04/pdf/2010-4424.pdf>)

“I want to reiterate first and foremost that there is not a safe level of benzene that can exist in any skin care product, over the counter or prescription. Benzene is highly carcinogenic, and recently we've seen the U.S. Food and Drug Administration agree with this position this by taking action to ensure removal of carbomers contaminated with benzene from manufacturing processes. The current data on BPO degrading into high levels of benzene is extremely concerning given its prominent use in skin care, and this study should serve as another wake-up call for improved manufacturing and quality control of consumer healthcare products.”⁸⁵

Recall Request and Other Actions

This Petition seeks to have the Commissioner and FDA request recalls and a suspension of sales for products containing the active pharmaceutical ingredient benzoyl peroxide, consistent with FDA’s mandate to ensure the safety of prescription and over the counter the drugs in the United States.

Such actions are extremely important for public safety. The elimination of benzoyl peroxide from the market is not expected to create a significant impact to the U.S. healthcare system or patients currently using the drug due to the fact that many alternatives exist for the treatment of acne vulgaris. As mentioned earlier in this Petition, Valisure specifically tested other drug products, like salicylic acid, and did not find any evidence of benzene formation.

Petitioner notes that there is precedent for recalling widely used medications due to concern over carcinogenic properties. In 1979 the FDA and industry jointly announced a recall due to the suspected carcinogenic properties of methapyrilene, an “antihistamine that for years has been the active ingredient of such nonprescription [i.e. OTC] sleeping pills as Sominex, Excedrin P.M. and Compoz.”⁸⁶ According to the announcement, the recall followed a conclusion by the National Cancer Institute (“NCI”) two months earlier, that methapyrilene causes liver cancer in rats and mice and should be presumed to do so in humans; after evaluating the NCI’s data, the FDA reached the same conclusion.⁸⁷ Methapyrilene’s link to cancer was widely believed to be associated with the probable human carcinogen, NDMA, formed by an unstable DMA group on the molecule.^{88 89}

⁸⁵ Email from Dr. Christopher Bunick, MD, PhD, Associate Professor of Dermatology at Yale University, New Haven, CT.

⁸⁶ U.S., Industry Recall Sleep Aids Containing Cancer-Causing Agent (June 9, 1979). *The New York Times*, New York, NY. (<https://www.nytimes.com/1979/06/09/archives/us-industry-recall-sleep-aids-containing-cancercausing-agent.html>)

⁸⁷ *Id.*

⁸⁸ Lijinsky, W. (1974). Reaction of drugs with nitrous acid as a source of carcinogenic nitrosamines. *Cancer Research*. Vol. 34, p. 255-258 (<https://cancerres.aacrjournals.org/content/34/1/255>)

⁸⁹ Mergens, WJ. *et. al.* (1979) In vitro nitrosation of methapyrilene. *Journal of Pharmaceutical Sciences*. Vol. 68, p. 827-832. (<https://www.ncbi.nlm.nih.gov/pubmed/458597>)

Molecular instability and the formation of a potent carcinogen was also the case with ranitidine (brand name Zantac), for which FDA requested a full market withdrawal in 2019.⁹⁰ Commentary published in the Journal of the American Medical Association following the publication of ranitidine's NDMA formation phenomenon⁹¹ was titled "Ranitidine's N-nitrosodimethylamine Problem May be Tip of the Iceberg"⁹² and suggested that drug molecules displaying fundamental instabilities and forming potent carcinogens could be a pervasive issue that warrants further investigation; a concern certainly supported by the findings in this Petition.

Published data shows that Zantac was stability tested at 70°C for two weeks and formed approximately 1 time the regulatory limit for NDMA;⁹³ whereas data in this Petition shows that BPO products can form over 800 times the conditional regulatory limit for benzene in two weeks at the lower temperature of 50°C.

In addition, for the reasons stated above, FDA should 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 medications under Section 705(b) of the FDCA (21 U.S.C. § 375(b)).

Petitioner urges the Commissioner and the FDA to expeditiously request recalls of benzoyl peroxide products to protect the American public from further exposure to the potentially carcinogenic properties of benzoyl peroxide products containing or forming benzene, which is not labeled for such risk and, in light of such risk, would not likely be acceptable for most, if not all, its intended treatments, and to take other such actions outlined in this Petition as deemed appropriate.

Independent Testing and Verification of Drug Products in the United States

Petitioner is also requesting that the FDA promulgate regulations requiring robust independent chemical testing and verification of medications. In the interim, while these regulations are pending, FDA should issue formal guidance recommending such testing and verification.

This is necessary to serve public health and help protect Americans from adulterated and poor-quality drug products, an issue of growing concern. European regulators have recognized the

⁹⁰ Food and Drug Administration. *FDA Requests Removal of All Ranitidine Products (Zantac) from the Market* (April 1, 2020) (<https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market>)

⁹¹ Braunstein LZ, Kantor ED, O'Connell K, et al. Analysis of Ranitidine-Associated N-Nitrosodimethylamine Production Under Simulated Physiologic Conditions. *JAMA Netw Open*. 2021;4(1):e2034766. doi:10.1001/jamanetworkopen.2020.34766

⁹² White CM. Ranitidine's N-nitrosodimethylamine Problem May be Tip of the Iceberg. *JAMA Netw Open*. 2021;4(1):e2035158. doi:10.1001/jamanetworkopen.2020.35158

⁹³ Emery Pharma (January 3, 2020). Citizen Petition from Emery Pharm on behalf of Najafi Pharma. (<https://www.regulations.gov/document/FDA-2020-P-0042-0001>)

importance of independent testing and established a multi-state system of over 70 “Official Medicines Control Laboratories (“OMCLs”) which are discussed in a European Medicines Directorate document:⁹⁴

“By testing medicines independently of manufacturers (that is, without conflicts of interest and with guaranteed impartiality), the OMCLs have a fundamental role in ensuring the quality, safety and efficacy of medicines. When it comes to medicines in Europe, OMCLs play a major role in contributing to the overall welfare of patients and animals.”

Additionally, recent record levels of drug shortages in the US have been linked to drug quality issues as the most common root cause.⁹⁵ Congressman Morgan Griffith commented during a recent House Energy and Commerce Oversight and Investigations Subcommittee Hearing: “Examining the Root Causes of Drug Shortages: Challenges in Pharmaceutical Drug Supply Chains” that:

“In our race to save a few pennies here and there, we are sacrificing both availability and quality ... GPOs [Group Purchasing Organizations] can help end drug shortages by prioritizing generic drug's availability and quality. Instead they use their market power to force a race to the bottom pricing, without consideration for quality or availability.”⁹⁶

Witnesses at this hearing emphasized that the majority of drug shortages are due to quality problems, that about 25% of US generics are produced at plants currently under an FDA warning letter and that these are fundamental problems that existed well before Covid.⁹⁷ Further following up on drug shortages and GPOs, the Federal Trade Commission announced on February 14, 2024 that “FTC, HHS Seek Public Comment on Generic Drug Shortages and Competition Amongst Powerful Middlemen. Joint request seeks information on impact of group purchasing organizations and drug wholesalers on access to generic pharmaceuticals.”⁹⁸

Congressman Andy Harris of the House Appropriations Subcommittee on FDA specifically asked FDA Commissioner Califf why drugs coming into the US aren't independently batch-

⁹⁴ European Directorate for the Quality of Medicines & Healthcare. *The European Network of Official Medicines Control Laboratories (OMCLs)*. (<https://www.edqm.eu/documents/52006/83062/brochure-omcl.pdf/a41e2402-7a62-6105-955f-c5edaa0f6116>)

⁹⁵ United States 118th Congress. *Oversight and Investigations Subcommittee Hearing: “Examining the Root Causes of Drug Shortages: Challenges in Pharmaceutical Drug Supply Chains.”* (May 11, 2023) House Energy & Commerce (<https://energycommerce.house.gov/events/oversight-and-investigations-subcommittee-hearing-examining-the-root-causes-of-drug-shortages-challenges-in-pharmaceutical-drug-supply-chains>)

⁹⁶ *Id.*

⁹⁷ *Id.*

⁹⁸ Federal Trade Commission. *FTC, HHS Seek Public Comment on Generic Drug Shortages and Competition Amongst Powerful Middlemen*. (February 14, 2024). (<https://www.ftc.gov/news-events/news/press-releases/2024/02/ftc-hhs-seek-public-comment-generic-drug-shortages-competition-amongst-powerful-middlemen>)

tested, and commented that some US hospital systems are already doing their own import testing because of their concern about the purity of some of the generic products.⁹⁹

Looking towards finding solutions to these issues, the American Society of Health-system Pharmacists (“ASHP”) recently published results of a nationwide survey of health system pharmacies that concluded that 90% of health systems believed that drug shortages were substantively increasing costs in their drug and labor budgets and that quality recognition programs are highly desired, with 85% of respondents willing to spend at least 5% more on products with quality recognition.¹⁰⁰ The ASHP report states:¹⁰¹

“Despite speculation that purchasers may not pay more for products from manufacturers that achieve quality recognition, the survey data emphasize that quality is important to purchasers — and many are willing to spend more for the assurance of manufacturer quality.”

Furthermore, the recently announced actions to incorporate independent chemical testing of medications and quality recognition derived from it by large private health care systems like Kaiser Permanente, and large government healthcare systems like the Military Health System through the Department of Defense (“DoD”), strongly underscore the utility and feasibility of this broadly recognized recommendation.¹⁰² Petitioner recently announced its collaboration with DoD that emphasized:¹⁰³

“By creating much-needed transparency in drug quality, this study will enable conscientious manufacturers to be able to better compete and allow major purchasers of drugs, like the Department of Defense and Veterans Administration, to reward good manufacturers and exclude substandard medicines from being consumed by the military and veterans, and serve as a model for broader adoption throughout the United States to benefit all American patients.”

⁹⁹ Sarah Karlin-Smith. *Batch Testing Of All Imported Drugs Floated At House Appropriations Hearing*. (March, 29, 2023). Pink Sheet. (<https://pink.citeline.com/PS147972/Batch-Testing-Of-All-Imported-Drugs-Floated-At-House-Appropriations-Hearing>)

¹⁰⁰ Paul W. Abramowitz. *ASHP Calls for Action on Drug Shortages, Releases New Recommendations and Survey Findings*. (August 10, 2023) American Society of Health-system Pharmacists. (<https://www.ashp.org/about-ashp/ceo-blogs/recent-blogs/ashp-calls-for-action-on-drug-shortages-releases-new-recommendations-and-survey-findings>)

¹⁰¹ American Society of Health-system Pharmacists. *Severity and Impact of Current Drug Shortages*. (June/July 2023). (<https://www.ashp.org/-/media/assets/drug-shortages/docs/ASHP-2023-Drug-Shortages-Survey-Report.pdf>) (<https://www.ashp.org/-/media/assets/drug-shortages/docs/ASHP-2023-Drug-Shortages-Survey-Report.pdf>)

¹⁰² Anna Edney and Riley Griffin. *Drug Safety Fears Spur Pentagon Plan to Test Widely Used Meds* (June 7, 2023) (<https://www.bloomberg.com/news/articles/2023-06-07/drug-safety-fears-spur-pentagon-plan-to-test-widely-used-meds>)

¹⁰³ Valisure. *VALISURE SIGNS AGREEMENT WITH DEPARTMENT OF DEFENSE TO INDEPENDENTLY TEST & QUALITY SCORE DRUGS*. (August 8, 2023). PR Newswire. (<https://www.prnewswire.com/news-releases/valisure-signs-agreement-with-department-of-defense-to-independently-test--quality-score-drugs-301895301.html>)

“In this Defense Department collaborative study, quality will be assessed through a robust, multi-step process of independently testing the chemical properties of samples of drug products from suppliers to the DoD and objectively scoring the respective National Drug Codes (NDC) of each supplier. Scoring will be conducted according to a recently published paper authored by a consortium of healthcare key opinion leaders, including individuals at Department of Defense, Long Island University, Yale University, Stanford University, Columbia University, Ohio State University, University of Connecticut, University of Utah, NYU Langone, and Cleveland Clinic, titled, "A data-driven quality-score system for rating drug products and its implications for the health care industry."¹⁰⁴ Scoring NDCs will not only provide a quality risk assessment but do so in a manner that is actionable for both pharmaceutical distribution and contracting.”

Valisure hopes to work collaboratively with FDA on the issues identified in this Petition and generally on improving the quality and reliability of the nation’s drug supply chain.

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

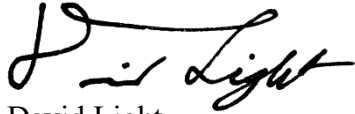
Pursuant to 21 C.F.R. § 10.30(b), economic impact information will be submitted by the Petitioner only upon request of the Commissioner following review of this Petition.

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.

¹⁰⁴ Arash Dabestani, et. al. *A data-driven quality-score system for rating drug products and its implications for the health care industry*. Journal of the American Pharmacists Association, Volume 63, Issue 2, 2023, Pages 501-506, ISSN 1544-3191, <https://doi.org/10.1016/j.japh.2022.10.001>. (<https://www.sciencedirect.com/science/article/pii/S1544319122003272>)

Respectfully submitted,



David Light

Valisure

President

5 Science Park

New Haven, CT 06511

Phone: 833-497-7370

Fax: 203-497-7371



Wolfgang Hinz, PhD

Valisure

Chief Scientific Officer

5 Science Park

New Haven, CT 06511

Phone: 833-497-7370

Fax: 203-497-7371



Kary Kucera, PhD

Valisure

Scientific Advisor

5 Science Park

New Haven, CT 06511

Phone: 833-497-7370

Fax: 203-497-7371