March 24, 2021

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

Re: Valisure Citizen Petition on Hand Sanitizer Products Containing Benzene Contamination and Other Significant Issues

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), 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

Hand sanitizers are considered drugs that are regulated by the U.S. Food and Drug Administration ("FDA"). Valisure has tested and detected high levels of benzene and other contaminants in specific batches of hand sanitizer products containing active pharmaceutical ingredients of ethanol and isopropanol. 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.[1] 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." [2] 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." [3] However, due to the COVID-19 Public Health Emergency, FDA has issued guidance that allows interim limits of benzene[4] in aqueous solution ("liquid")[5] hand sanitizer products not to exceed 2 parts

[1] Centers for Disease Control and Prevention, *Facts About Benzene* (2018) (https://emergency.cdc.gov/agent/benzene/basics/facts.asp)
[2] 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).
[3] Food and Drug Administration (August 2018). *Q3C Tables and List Rev. 4*. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4)
[4] See Food and Drug Administration, *Guidance for Industry: Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)* (February 10, 2021) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-temporary-policy-preparation-certain-alcohol-based-hand-sanitizer-products-during).
[5] *Id*. See Footnote 37

per million ("ppm"). FDA's enforcement discretion in the aforementioned guidance does not extend to gel or non-liquid hand sanitizer products, and accordingly this suggests that for these products there is no acceptable level of benzene, since these are drug products that do not require benzene for their manufacture and do not constitute a significant therapeutic advance.[3] Valisure found hand sanitizer products that contain levels of benzene that significantly exceed the 2 ppm interim FDA restriction in both liquid and non-liquid formulation and detectable levels of benzene in many other hand sanitizer products. 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 or higher.[6, 7] Additionally, NIOSH defines benzene as a carcinogen and lists "inhalation, skin absorption, ingestion, skin and/or eye contact" as exposure routes.[8] Benzene is specifically associated with blood cancers such as leukemia,[9] making absorption through the skin particularly concerning as there have been multiple FDA studies showing that structurally similar chemicals in sunscreen products are found in the blood at high levels after application to exposed skin.[10] Furthermore, Valisure has tested and detected unacceptably high levels of methanol and acetaldehyde, a Group 2B carcinogen defined by the WHO and IARC as "possibly carcinogenic to humans," [2] in specific batches of hand sanitizer. The presence of benzene, a known human carcinogen, and multiple other contaminants, in products widely recommended for the prevention of spreading the SARS-CoV-2 virus causing COVID-19 and regularly used by adults and children in large volumes makes these findings especially troubling.

This Petition requests that the Commissioner take the following actions:

1) request a recall of identified batches of hand sanitizer products on the basis that, due to contamination with a known human carcinogen and other restricted contaminants, 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 submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)), in particular investigate issues of contamination and issues of hand sanitizer product formulation that is inconsistent with FDA guidance intended to restrict ingredients that could increase the risk of accidental ingestion by children, and effect labeling revisions as needed;

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[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/emergencyresponsecard_29750032.html)
[8] *Id*
[9] American Cancer Society. *Benzene and Cancer Risk* (January 5, 2016) (https://www.cancer.org/cancer/cancer-causes/benzene.html)
[10] Food and Drug Administration (1/21/2020). Shedding More Light on Sunscreen Absorption. (https://www.fda.gov/news-events/fda-voices/shedding-more-light-sunscreen-absorption)

3) review and update the current FDA guidance "Guidance for Industry: Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)" to clarify or provide additional guidance for non-aqueous solution hand sanitizers, including whether FDA intends to utilize similar enforcement discretion and ppm limits for these products or take other action to ensure they are safe and effective;

4) 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 hand sanitizer alternatives to contaminated products are available for protection against the spread of infectious diseases such as COVID-19;

5) review and update the current FDA guidance "Q3C – Tables and List, Guidance for Industry" to include non-emergency guidance for the acceptable concentration of benzene for drug products, such as hand sanitizers, 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;

6) review and update the current FDA guidance "Q3C – Tables and List, Guidance for Industry" to include non-emergency 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," such as hand sanitizers, and separately for drug products that require benzene for manufacturing and constitute a "significant therapeutic advance";

7) develop guidance documents defining the mass of a standard daily application of hand sanitizer so that a daily exposure of benzene and other contaminants can be calculated for hand sanitizer products;

8) support the increasing number of pharmacy-associated 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

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

Background on Petitioner

Valisure operates an analytical laboratory that is accredited to: 2017 International Organization for Standardization ("ISO") 17025 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 assays to test medications dispensed to patients 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 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.[3] Although the FDA guidance appears to indicate that there is no acceptable amount of benzene that can be present in drug products that do not constitute a significant therapeutic advance or where the use of benzene is unavoidable, such as hand sanitizers, FDA has responded to increased demand for hand sanitizers by consumers and health care personnel "experiencing difficulties accessing alcohol-based hand sanitizers" by issuing guidance under docket FDA-2020-D-1106, which outlines a temporary enforcement discretion policy applicable to certain liquid alcohol-based hand sanitizer products and uses an ostensibly less strict limitation on certain contaminants, including benzene, acetaldehyde, and methanol. FDA specifically stated in its June 1, 2020 press release that benzene is temporarily allowed up to 2.0 ppm "to reflect data submitted by fuel ethanol manufacturers producing ethanol via fermentation and distillation, indicating that at least some of their fuel ethanol products have harmful chemicals, including gasoline and benzene, which are known human carcinogens (cancer-causing agents)." [11]

This course of action is understandable considering the severe nature of the COVID-19 Public Health Emergency; however, any products that exceed these interim limits are particularly

[11] Food and Drug Administration (June 1, 2020). *Coronavirus (COVID-19) Update: FDA Takes Action to Protect Public Health; Increase Supply of Alcohol-Based Hand Sanitizer* (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-action-protect-public-health-increase-supply-alcohol-based)

concerning and warrant expeditious action from FDA, including the hand sanitizer products that are excluded from the guidance. In Footnote 37 of the guidance, FDA states that its "policy does not apply to hand sanitizer gel or foam products because different or additional ingredients may impact the quality and potency of the product."[4] Because many hand sanitizer products on the United States market are gel or other non-liquid formulations, FDA should provide similar guidance for these products or take further action expeditiously.

Since mid-2020, FDA has been aware of adulterated hand sanitizer products and has taken action to protect the American public from these products that contain unacceptable levels of contamination and subpotent amounts of alcohol.[12] Eleven FDA alerts from June 19, 2020 to January 26, 2021 have warned of subpotent formulations, microbial contamination, unacceptable levels of contamination with methanol and 1-propanol and have placed import alerts on country of origin for specific products.

A major focus of the FDA alerts has been products manufactured outside the United States and specifically in Mexico. As the data in this Petition shows, it appears that a very small number of poor quality hand sanitizer products in the United States were manufactured in Mexico, but the majority are either made in the U.S. or in China. Therefore, the FDA's January 26, 2021 declared import alert on hand sanitizer products from Mexico[13] will not likely address the issue of the majority of unacceptably contaminated hand sanitizer products currently on the market and further action from FDA is warranted.

Another major focus of FDA's concerns regarding hand sanitizer has been regarding methanol contamination. Serious adverse events, including death, can occur when hand sanitizer products contaminated with methanol are swallowed. U.S. health agencies such as the CDC have warned against the rise in cases of individuals ingesting hand sanitizer and being harmed, especially when the ingested products are contaminated.[14] As the CDC states, "Young children might unintentionally swallow these products [hand sanitizers], whereas adolescents or adults with history of alcohol use disorder might intentionally swallow these products as an alcohol (ethanol) substitute[15,16]." FDA stated in its Q&A for Consumers | Hand Sanitizers and COVID-19, "In March 2020 (during the COVID-19 pandemic), calls to Poison Control related to hand sanitizer

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[12] Food and Drug Administration, *FDA updates on hand sanitizers consumers should not use*. (March 10, 2021) (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use)

[13] Food and Drug Administration, *Coronavirus (COVID-19) Update: FDA Takes Action to Place All Alcohol-Based Hand Sanitizers from Mexico on Import Alert to Help Prevent Entry of Violative and Potentially Dangerous Products into U.S., Protect U.S. Consumers*. (January 26, 2021) (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-action-place-all-alcohol-based-hand-sanitizers-mexico-import)

[14] Yip, Luke et. al. (2020). Serious Adverse Health Events, Including Death, Associated with Ingesting Alcohol-Based Hand Sanitizers Containing Methanol — Arizona and New Mexico, May–June 2020. *Morbidity and Mortality Weekly Report (MMWR)*, *Centers for Disease Control and Prevention*. 2020 69(32);1070–1073 (https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e1.htm)

[15] Emadi A, Coberly L. Intoxication of a hospitalized patient with an isopropanol-based hand sanitizer. *New England Journal of Medicine*. 2007;356:530–1 (https://pubmed.ncbi.nlm.nih.gov/17267921/)

[16] Schneir AB, Clark RF. Death caused by ingestion of an ethanol-based hand sanitizer. *The Journal of Emergency Medicine*. 2013;45:358–60 (https://pubmed.ncbi.nlm.nih.gov/23706595/)

increased by 79% compared to March of 2019. The majority of these calls were for unintentional exposures in children 5 years of age and younger."[17]

FDA recognizes the danger of children ingesting hand sanitizer, and in FDA's guidance for the manufacture of liquid hand sanitizer during the declared COVID-19 Public Health Emergency the agency states in bold text that is emphasized beyond all other guidance in the document:[4]

> **The firm does not add other active or inactive ingredients, such as ingredients to improve the smell or taste, due to the risk of accidental ingestion in children.**

FDA should clarify, for the protection of children, that such stipulations on formulation apply to all hand sanitizer products during the declared COVID-19 Public Health Emergency, not only for liquid hand sanitizers. Petitioner has identified and tested hand sanitizer products that would be contrary to FDA's guidance and that utilize product labels that are clearly intended to appeal to children.

Figure 1. Hand sanitizer products "H066" on the left, and "H067" on the right. H066 contains blue coloring in the formulation and a product label containing trademarks of "STAR WARS" and "Mandalorian" and presumably a depiction of a Star Wars character. H067 contains green coloring in the formulation and a product label containing trademarks of "STAR WARS" and "Mandalorian" and presumably a depiction of a Star Wars character.

[17] Food and Drug Administration (12/15/2020). *Q&A for Consumers | Hand Sanitizers and COVID-19*. (https://www.fda.gov/drugs/information-drug-class/qa-consumers-hand-sanitizers-and-covid-19)

In addition to a risk of ingestion by children, the illustrative example above also contains levels of benzene that potentially pose a significant danger to children, or any individual using such products as intended, on exposed skin, through which benzene is known to absorb,[18, 19] and through inhalation of its fumes.[20]

Petitioner notes that FDA's interim limit on benzene of 2 ppm in liquid hand sanitizer is identical to the limit posed on special cases of drug products where benzene "use is unavoidable in order to produce a drug product with a significant therapeutic advance." [3] However, drug products are generally used in relatively small amounts when compared to beverages or drinking water. For drinking water or products that may be consumed as beverages, the Environmental Protection Agency ("EPA") has set significantly more strict limits for benzene than FDA's guidance for drug products. The Agency for Toxic Substances and Disease Registry ("ATSDR") authored a report on the toxicological profile for benzene[21] which stated:

> EPA has set 5 ppb [parts per billion] 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 as the maximum permissible level of benzene in water for short-term exposures (10 days) for children.

This EPA guidance may offer a rational approach to more strictly limiting benzene in liquid hand sanitizers during the declared COVID-19 Public Health Emergency to at least 0.2 ppm (equivalent of 200 ppb) to better protect individuals who may ingest such products, especially children.

Although considerations for ingestion of hand sanitizer should be undertaken, hand sanitizer products are not intended to be swallowed and are labeled only for topical use. Therefore, a contaminant such as benzene that can harm individuals through dermal absorption or inhalation is of great concern for public health as it can affect individuals that properly use hand sanitizer on exposed skin or breath its fumes.

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,

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[18] Kalnas, J; Teitelbaum, DT. (2000). Dermal absorption of benzene: implications for work practices and regulations. *International Journal of Occupational and Environmental Health.* Apr-Jun 2000;6(2):114-21 (https://pubmed.ncbi.nlm.nih.gov/10828140/)
[19] Nakai, J.S. et. al. (1996). Effect Of Environmental Conditions On The Penetration of Benzene Through Human Skin. *Journal of Toxicology and Environmental Health.* 1996 Volume 51, 1997 - Issue 5 pp447-462 (https://www.tandfonline.com/doi/abs/10.1080/00984109708984036)
[20] World Health Organization (2010). Exposure to Benzene: A Major Public Health Concern. (https://www.who.int/ipcs/features/benzene.pdf)
[21] Agency for Toxic Substances and Disease Registry (August 2007). *Toxicological Profile for Benzene*. (https://www.atsdr.cdc.gov/toxprofiles/tp3.pdf)

such as valsartan, irbesartan, losartan,[22] ranitidine, nizatidine,[23] and metformin,[24] due to the detection of the Group 2A "probable human carcinogen" N-Nitrosodimethylamine ("NDMA") in excess of FDA limits.[25, 26] 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.[27] Having a constant permissible daily intake or exposure is critical when there is variability in drug product size and exposures per day, a situation particularly relevant to an individual's application of hand sanitizer. Petitioner is not aware of any FDA guidance on a permissible daily exposure for benzene in any drug product, including hand sanitizer, and requests urgent action on behalf of FDA to issue guidance to fill this gap.

Although the dangers and carcinogenic potential of nitrosamines like NDMA have been well documented since the 1960s and there are important studies related to recent medication contamination findings,[28, 29] 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.[30] The hematotoxicity of benzene[31] 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," [32] which is a comment reiterated in a

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[22] 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).

[23] 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)

[24] 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)

[25] Light, David; Kucera, Kaury (September 9, 2019). Valisure Citizen Petition on Ranitidine. *Food and Drug Administration Citizen Petition*. (https://www.regulations.gov/document/FDA-2019-P-4281-0001)

[26] Light, David; Kucera, Kaury; Wu, Qian (March 2, 2020). Valisure Citizen Petition on Metformin. *Food and Drug Administration Citizen Petition*. (https://www.regulations.gov/document/FDA-2020-P-0978-0001)

[27] 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)

[28] 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)

[29] 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)

[30] 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)

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

[32] 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)

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." [33] According to the American Cancer Society:[34]

> 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 selected products using gas chromatography flame ionization detection ("GC-FID") instrumentation, the results of which are shown in Table 2 and Table 4. 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 hand sanitizer 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 based on *m/z* utilizing extracted ion chromatograms. Headspace sampling was used with exception for detection of methanol and acetaldehyde, which used direct injection. 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 sanitizer, which includes benzene analysis.[35] Valisure engaged the Chemical and Biophysical Instrumentation Center at Yale University to utilize the GC-MS analytical approach prescribed by FDA on multiple selected products, the results of which are shown in Table 2 and Table 4.

For Valisure's GC-MS headspace analysis method, the lower limit of detection ("LLOD") is 0.01 ppm, the limit of quantitation ("LLOQ") is 0.05 ppm, and the measurement uncertainty is ± 20%. Therefore, for the data presented in this Petition and using the aforementioned analytical methodology, Valisure is identifying hand sanitizer products with benzene detected at 0.1 ppm or above and quantifying the level of detection for such products. Information for other products tested at least once that had detection below 0.1 ppm or for which benzene was not detected is provided in Table 5. (Attachment A).

Valisure acquired hand sanitizer samples from many companies 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

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[33] 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)

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

[35] 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)

Valisure's analysis presented in this Petition. Even in this limited survey of certain available hand sanitizer products within the United States, multiple samples contained significantly detectable benzene and some batches contained over eight times the interim, emergency limit for liquid hand sanitizers and the conditionally restricted drug product 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 pharmaceutical products.

Petitioner requests FDA investigate the source of benzene and other contaminants identified in this Petition and notes that for benzene there are two potential sources suggested by existing research. Various chemical processes in the purification of alcohols are known to use benzene[36] and FDA has stated that at least some fuel ethanol is known to have harmful chemicals, including benzene.[11] Also of note is that many hand sanitizer products are "gels" where the product's high viscosity is often achieved through the addition of "carbomer."[37] Carbomer is often manufactured through the use of benzene[38] and analytical specification sheets have noted benzene impurity present in carbomer products measured in thousands of ppm;[39] therefore, even when used in low volumes, carbomer with high benzene content could still lead to significant benzene contamination in hand sanitizer products.

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 hand sanitizer products. The sample preparation and headspace (HS) gas chromatography (GC) methods were also validated for liquid and gel formulations and to allow shorter run time. Identification of benzene is based on the retention time matching to certified reference standards and mass spectral m/z matching to benzene. Quantification of benzene is performed by comparing peak area of benzene in a sample to a 10-point calibration curve from 0.01 to 200 ppm or at least 100-fold above and below the 2 ppm interim limit. Acetaldehyde and methanol quantification used a 5 and 7-point calibration curve respectively for concentration ranges of 3 - 1900 ppm (acetaldehyde with 50 ppm interim limit) and 5 - 26000 ppm (methanol with 630 ppm interim limit).

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[36] Gelling, Cristy (2012). Which type of ethanol should I use? *BiteSizeBio*. (https://bitesizebio.com/13518/which-type-of-ethanol-should-i-use/)
[37] Carbomer. *Elsevier B.V.* (Accessed March 13, 2021) (https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/carbomer)
[38] Berardi A, Perinelli DR, Merchant HA, et al. (2020) Hand sanitisers amid CoViD-19: A critical review of alcohol-based products on the market and formulation approaches to respond to increasing demand. *International Journal of Pharmaceutics*. 2020;584:119431. doi:10.1016/j.ijpharm.2020.119431 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229736/)
[39] Final Report on the Safety Assessment of Carbomers-934, -910, -934P, -940, -941, and -962. *Journal of the American College of Toxicology*. 1990;1(2):109-141. doi:10.3109/10915818209013151 (https://journals.sagepub.com/doi/abs/10.3109/10915818209013151)

Materials and Methods

Agilent 7890B Gas Chromatography (GC) system equipped with 7697A headspace autosampler coupled with 5977B Mass Selective Detector (MS) was utilized for sample analysis, and a DB-Select 624 UI, 60 m × 0.32 mm × 1.8 µm GC column (Agilent Technology, Santa Clara, CA) was used to separate benzene from other compounds. Dimethyl sulfoxide (DMSO, GC Headspace Grade) was used for sample preparation (Thermo Fisher Scientific, Waltham, MA). Standard of benzene (99.8 % purity) and isotopic labeled benzene standard (d_3-, 99.8% purity) was used for calibration, continuing calibration verification, retention time verification, and recovery checking. Certified reference material USP Class 1 residual solvents mixture was used for calibration confirmation (USP, Rockville, MD). All volumetric glassware used were Class A certified. For direct injection analysis of methanol and acetaldehyde, samples were prepared in acetonitrile (LC-MS Grade, Honeywell, Muskegon, MI) and analyzed using Agilent G1530A GC with 5973 MS. All reference standards were certified and sourced from Sigma-Aldrich, St. Louis, MO. Ultra high purity helium carrier gas was certified as 99.999% pure (The AERO ALL-GAS Co., Hartford, CT).

Hand sanitizer samples were sourced from online and retail vendors and only unique lots are represented in this Petition. The following product designations were determined to be duplicate lots and are intentionally not listed in Tables and Attachments: H045, H099, H182, H198, H232, H244, and H255.

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. Hand sanitizer samples were dispensed into the GC headspace vials at approximate 500 mg and weighed, followed by adding 4.5 mL of DMSO to make up the final volume to approximate 5 mL and vortex to mix. Five (5) mL of DMSO was used as blank sample. All blanks, samples, and calibration standards contained 0.25 ug of d_3-benzene in their 5 mL final extract. For direct injection analysis of methanol and acetaldehyde, samples were prepared gravimetrically to approximately 10% w/w in acetonitrile to a fixed volume, and centrifuged prior to analysis.

Instrumental Analysis

Table 1 summarizes the major instrumental parameters used for analysis of benzene, methanol, and acetaldehyde in the hand sanitizer samples.

Table 1. Instrumental parameters optimized for benzene, methanol, and acetaldehyde detection in hand sanitizer samples.

Headspace Sampling Method					
Headspace 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 min	Split ratio	5:1	Gain factor	1
Injection Duration	1 min	Oven Temp Gradient	60 °C (12 min) > 240 °C at 40 °C/min (2 min)	Solvent delay	3 min
Vial shaking	71 shakes/min	GC run time	18.5 min		
Fill pressure	15 psi				
Direct Injection Method					
Autosampler		GC		MS	
Injection Volume	1 µL	Carrier gas	Helium	Source Temp	230 °C
Solvent Washes	1	Inlet Temp	250 °C	Quad Temp	150 °C
Solvent Wash Vials	2	Column flow	2.7 mL/min	Acquisition type	SIM
		Split ratio	25:1	Gain factor	1
		Oven Temp Gradient	40 °C (5 min) > 240 °C at 30 °C/min (4 min)	Solvent delay	none
		GC run time	15.7 min		

Quality Assurance and Quality Control

Trace level of benzene was detected in isotopic labeled benzene standard (d3-benzene) and the background 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. For acetaldehyde and methanol analysis, quadradic fits were used. Calibration curves were accepted when the coefficient of determination R^2 was equal or greater than 0.999. Lower limit of detection (LLOD) and lower limit of quantification (LLOQ) were determined by spiking known amount of benzene into hand sanitizer samples that were pre-screened to be not detected for benzene or lower than the concentration of the lowest calibration standard. LLOD was 0.005 µg (equivalent to 0.01 ppm in hand sanitizer products) and LLOQ was 0.025 µg (equivalent to 0.05 ppm in hand sanitizer products). The measurement uncertainty was determined to be 20%. For acetaldehyde and methanol, the LLOQs were three times the LLOD with an upper bound of 35% and 15% applied respectively resulting in 12.7 ppm for acetaldehyde and 16.4 ppm for methanol USP Class 1 residual solvent mixture was analyzed against the calibration and result of benzene agreed with certified concentration. All hand sanitizer samples with benzene concentration above 2 ppm were analyzed in triplicates and reported herein. Values are given for quantification of 2-fold over LLOQ, or 0.1 ppm, analyzed at least one time.

Findings

Using the GC-MS method described above for the determination of benzene, Valisure analyzed 260 unique batches from 168 brands with the results detailed in the tables and figures below. In summary, 44 batches (17%) contain benzene at 0.1 ppm or above and 21 batches (8%), which include both liquid and gel formulations, contain benzene at 2 ppm or above. The highest level of benzene detected was 16.1 ppm, which is over eight times the interim limit temporarily used

during the declared COVID-19 Public Health Emergency. These findings are alarming and reveal a serious potential risk to public health for which Petitioner requests expeditious action from FDA to properly address.

Further analysis of hand sanitizer products that contain over 2 ppm of benzene revealed high levels of other impurities, specifically methanol and acetaldehyde. Some batches contained up to 8680 ppm of methanol, which is fourteen times the FDA interim limit, and 147 ppm of acetaldehyde, which is three times the FDA interim limit.

In addition to the detection of impurities, Valisure has identified both liquid and gel hand sanitizer products that implicate the concerns expressed by FDA in its guidance that hand sanitizer formulation that should not specifically appeal to children due to risk of ingestion. An illustrative example is provided in Figure 1 of this Petition for samples H066 and H067, which are also contaminated with benzene at approximately two times the FDA interim limit, as shown in Table 2 below. Of the 44 batches containing benzene, at least 20 (45%) have product labels that indicate the use of additional ingredients to improve the smell, taste, appearance or other properties which could make such hand sanitizer products more appealing to children, thereby increasing the risk of ingestion of specifically contaminated products. These labeling claims are highlighted in Table 2 and Table 4 in yellow. Images of all products are provided in Attachment C to better identify the products tested. Very few products were labeled with National Drug Codes ("NDC") so the NDCs listed in Table 2, Table 4, and Table 5 (Attachment A) are suggested based on information available to Valisure.

Regarding hand sanitizer formulation types, Table 2, Table 4 and Table 5 (Attachment A) designate the type according to information reasonably available to Valisure and through visual inspection. Valisure's data presented in Figure 2 suggests "gel" hand sanitizers constitute a substantial majority, approximately 73%, of hand sanitizer formulations being currently sold in the United States during the declared COVID-19 Public Health Emergency

Petitioner has also evaluated the country of origin for the hand sanitizer samples and listed this information when available. On January 26, 2021, FDA announced an import alert on all hand sanitizer products from Mexico and FDA has listed country of origin for the majority of its hand sanitizer product warnings.[12] Although Valisure could only reasonably sample a small fraction of the current market in the U.S., the data strongly suggests the origin of contaminated hand sanitizer products currently on the market is primarily China and the United States, with very few from Mexico. As of the date of this Petition, 83% of the 231 FDA product warnings are for products manufactured in Mexico, 7% in China and 3% in the United States. As the data in Figure 3 shows, of the 44 hand sanitizer products Valisure independently sourced and are contaminated with benzene, 2% are manufactured in Mexico, 50% in China, and 34% in the United States.

Valisure's analysis of benzene concentration matches closely with GC-MS results from Yale University's Chemical and Biophysical Instrumentation Center ("Yale") on 18 samples sent to Yale and analyzed from the same lot and specific product package. Data from four matched samples sent to Boston Analytical, Inc. for analysis using industry standard USP <467>

methodology of GC-FID confirms the high levels of benzene and the specific results closely match Valisure and Yale analysis for relatively low concentration of benzene; however, for benzene in excess of 10 ppm the analysis appears to significantly overestimate the concentration of benzene. As FDA suggests in its guidance for the analysis of hand sanitizer samples using GC-MS methodology,[35] the use of GC-FID according to USP <467> may not be appropriate for accurate detection of benzene, or potentially other impurities, in hand sanitizer products.

Table 2. Product description and results of benzene analysis on various batches of hand sanitizer in which benzene was detected above 2 ppm. At least three samples from each batch were tested individually and the amount of benzene detected is reported as an average of triplicates followed by the percent standard deviation. 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, Inc. from a sample of the same lot and specific product package. Label descriptions include a yellow highlight where claims are made that may fail to meet FDA guidance to avoid adding inactive ingredients, especially those with appeal to children. National Drug Code ("NDC") product codes are suggested based on information available to Valisure and displayed in brackets if the product labels had slight differences from those of tested products (see Attachment C for product images).

Sample ID	Benzene Mean (ppm ± %SD)	Brand and Label Description	Country of Origin	API and Percent	Product Code(s)	Lot	Exp.	Type	Manufacturing/Distributing Label Text
H127	16.1 ± 3% *17.7 **82	artnaturals hand sanitizer SCENT FREE NATURAL ELEMENTS + CLEANSING FORMULA 8 fl oz (236 ml)	China	Ethyl Alcohol 65%	UPC: 816820028205 NDC: 74642-000	Unknown	5/2023	Gel	DIST. BY artnaturals ® Gardena, CA 90248 MADE IN CHINA
H009	15.2 ± 2%	artnaturals hand sanitizer SCENT FREE NATURAL ELEMENTS + CLEANSING FORMULA 8 fl oz (236 ml)	China	Ethyl Alcohol 65%	UPC: 816820028205 NDC: 74642-000	Unknown	5/2023	Gel	DIST. BY artnaturals ® Gardena, CA 90248 MADE IN CHINA
H185	13.8 ± 2% *14.2 **40	SS LAVENDER & HERBS scented sanitizer ALCOHOL ANTISEPTIC 70% 3.38 FL. OZ. (100 mL)	USA	Ethanol Alcohol 70%	UPC: Unknown NDC: [75078-002, 75078-003, 75078-004]	20253	Unknown	Manual Pump Spray	Distributed by: Scentsational Soaps and Candles, Inc. Venice, FL 34292 Scentsational-Products.com
H139	11.4 ± 3% *11.7	huangjisoo HAND SANITIZER GEL TYPE HAND CLEANSER 62% ETHANOL 91% ORGANIC 500ml/16.9 FL.OZ	Korea	Ethanol 62%	UPC: 8809353931106 NDC: 73713-030	JE003	20230515	Gel	Manufacturer & Distributor: Newfeel Co., Ltd. Incheon, Korea Made in Korea

H258	6.2 ± 3% *7.4	TrueWash Instant Hand Sanitizer Natural 16 fl oz - (500 ml)	China	Ethyl Alcohol 75%	UPC: 817223010262 NDC: [75478-007]	202005JX01	05/2022	Gel	Manufacturer: Guangzhou Orchard Aromatherapy&Skin Care Co Distributed By: Supply Chain Sources LLC
H234	4.6 ± 2% *5.4	The Crème Shop Moisturizing Hand Sanitizer Peppermint Scented Infused with Aloe Vera & Vitamin E d	Korea	Ethyl Alcohol 70%	UPC: 849980064417 NDC: [74200-0014]	Item No.: HHSP6441-30	Unknown	Gel	Distributed by The Crème Shop USA
H066	3.9 ± 0% *4.5 **4	STARWARS MANDALORIAN HAND SANITZER (blue) 2.11 fl oz/60 mL	China	Ethyl Alcohol 68%	UPC: 042887437203 NDC: [74530-022]	20G1021	12-31-2022	Gel	[disney logo and starwars.com] © Best Brands Consumer Products, Inc. c/o Best Brands Sales Company LLC New York, NY 10001 RN #22195-Made in China-0620B
H067	3.8 ± 2%	STARWARS MANDALORIAN HAND SANITZER (green) 2.11 fl oz/60 mL	China	Ethyl Alcohol 68%	UPC: 042887437203 NDC: [74530-022]	20G1021	12-31-2022	Gel	[disney logo and starwars.com] © Best Brands Consumer Products, Inc. c/o Best Brands Sales Company LLC New York, NY 10001 RN #22195-Made in China-0620B
H220	3.7 ± 1% *4.3	BODY PRESCRIPTIONS Winter Mint Antibacterial Hand Sanitizer NET WT 12 GL OZ / 360 ML	China	Alcohol 75%	UPC: 192598534293 NDC: [50563-271]	BL091820-1	09/17/2022	Gel	Designed in the USA/Made in China Formulated exclusively and Distributed by: Enchante Accessories Inc., New York, NY 10016
H103	3.5 ± 5% *3.6	BORN BASIC ANTI-BAC HAND SANITIZER [70% ALCOHOL - 100% BASIC] 16.9 FL OZ [500 mL]	Mexico	Ethyl Alcohol 70%	UPC: 840038214563 NDC: [76891-111]	2933420	05-15-2021	Gel	MADE IN MEXICO DISTRIBUTED BY SCENT THEORY PRODUCTS, LLC. NEW YORK, NY 10018 WWW.MYSCENTTHEORY.COM
H181	3.2 ± 2% *4.0	beauty concepts Sugar Cookie ANTIBACTERIAL HAND SANITIZER 75% ALCOHOL NET WT 355ML/12 FL OZ	China	Alcohol 75%	UPC: 192598534286 NDC: 50563-272	BL091420-1	9/13/2022	Gel	Designed in the USA/Made in China Formulated exclusively and Distributed by: Enchante Accessories Inc., New York, NY 10016
H027	3.1 ± 1% *3.5	artnaturals hand sanitizer SCENT FREE NATURAL ELEMENTS + CLEANSING FORMULA 8 fl oz (236 ml)	China	Ethyl Alcohol 74%	UPC: 816820028205 NDC: Unknown	Unknown	5/2023	Gel	DIST. BY artnaturals ® Gardena, CA 90248 MADE IN CHINA
H149	2.9 ± 4% *2.3	PureLogic HAND SANITIZER ALOE + GREEN TEA 8 FL OZ (236ML)	China	Ethyl Alcohol 75%	UPC: 191205476339 NDC: 77731-039	Unknown	Unknown	Gel	©2020 Argento SC ® All rights reserved) Desined in NYC, Made in China Manufactured and distributed by Argento SC PURELOGIC is a division of Argento SC by Sicura Ing.

H088	2.7 ± 4% *2.0	MIAMI CARRY ON INSTANT SANITIZER GEL soothing gel - wash free - with aloe 75% Alcohol 16.9 FL OZ (500 mL)	USA	Ethyl Alcohol 75%	UPC: 848484050186 NDC: 75819-001	SCS200612 66	06/2022	Gel	DISTRIBUTED BY NAFTALI Miami Gardens, FL 33169 Made in China
H163	2.6 ± 1% *2.1	Natural Wunderz Triple Action Moisturizing Hand Sanitizer Aloe Vera 75% Alcohol Infused with 100% natural extracts 12.7 fl oz (375mL)	USA	Ethyl Alcohol 75%	UPC: 850016747150 NDC: [79360-101]	NW-20122	Unknown	Gel	NaturalWunderz.com Made in California, USA Distributed by NaturalWunderz, LLC Gardena, CA
H189	2.4 ± 3%	clean-protect-sanitize HAND SANITIZER 70% ALCOHOL ADVANCED FORMULA SULFATE FREE - VEGAN - PARABEN FREE 16.9 fl oz - 500 mL	USA	Ethyl Alcohol 70%	UPC: 805572180828 NDC: Unknown	H45220244	08/2022	Gel	Distributed & Manufactured Exclusively for: PII Healthcare 2323 Firestone Blvd South Gate, CA 90280 MADE IN USA
H191	2.4 ± 2%	clean-protect-sanitize HAND SANITIZER 70% ALCOHOL ADVANCED FORMULA SULFATE FREE - VEGAN - PARABEN FREE 16.9 fl oz - 500 mL	USA	Ethyl Alcohol 70%	UPC: 805572180828 NDC: Unknown	H45320245	09/2022	Gel	Distributed & Manufactured Exclusively for: PII Healthcare 2323 Firestone Blvd South Gate, CA 90280 MADE IN USA
H086	2.4 ± 0% *2.4	PURETIZE HandSanitizer 70% Alcohol Moisturizing Formula 16.9 FL OZ (500ml)	Korea	Ethyl Alcohol 70%	UPC: 810016711544 NDC: [76887-102]	WC 072005	April 30, 2023	Gel	Distributed by Puretize Los Angeles, CA Made in Korea for PURETIZE
H084	2.4 ± 2%	clean-protect-sanitize HAND SANITIZER 70% ALCOHOL ADVANCED FORMULA SULFATE FREE - VEGAN - PARABEN FREE 16.9 fl oz - 500 mL	USA	Ethyl Alcohol 70%	UPC: 805572180828 NDC: Unknown	H41020239	08/2022	Gel	Distributed & Manufactured Exclusively for: PII Healthcare 2323 Firestone Blvd South Gate, CA 90280 MADE IN USA
H190	2.2 ± 4% *1.5	clean-protect-sanitize HAND SANITIZER 70% ALCOHOL ADVANCED FORMULA SULFATE FREE - VEGAN - PARABEN FREE 16.9 fl oz - 500 mL	USA	Ethyl Alcohol 70%	UPC: 805572180828 NDC: Unknown	H39720239	08/2022	Gel	Distributed & Manufactured Exclusively for: PII Healthcare 2323 Firestone Blvd South Gate, CA 90280 MADE IN USA
H267	2.1 ± 2%	Hand Clean 100 Ethanol Gel Cos Nine	Korea	Ethyl Alcohol 68%	UPC: 8809591351124 NDC: 73330-0004	20F05001	20230604	Gel	Manufactured and distributed by COSNINE, Inc.

Table 3. Analysis results of products from Table 2 for methanol and acetaldehyde. Values in parenthesis reflect the respective interim FDA limits for liquid hand sanitizers during the COVID-19 Public Health Emergency.

	Sample ID	Methanol (630 ppm)	Acetaldehyde (50 ppm)
Exceeds Interim Limit	H185	8680 ± 2%	147 ± 3%
	H103	709 ± 1%	< LOQ
Below Interim Limit	H220	175 ± 1%	< LOQ
	H181	111 ± 1%	< LOQ
	H190	83 ± 3%	< LOQ
	H191	78 ± 3%	< LOQ
	H189	78 ± 5%	< LOQ
	H086	56 ± 3%	< LOQ
	H127	56 ± 6%	< LOQ
	H234	52 ± 2%	14.3 ± 4%
	H009	49 ± 2%	14.3 ± 17%
	H088	45 ± 3%	< LOQ
	H027	40 ± 4%	< LOQ
	H149	36 ± 7%	< LOQ
	H084	27 ± 1%	< LOQ
	H163	27 ± 2%	< LOQ
	H258	27 ± 7%	< LOQ
	H139	19 ± 3%	< LOQ
	H066	< LOQ	< LOQ
	H067	< LOQ	< LOQ

Table 4. Product description and results of benzene analysis on various batches of hand sanitizer in which benzene was detected between 0.1 ppm and 2.0 ppm. When reported with percent standard deviation, the average of triplicate measurements are reported, otherwise results from one measurement are reported. 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, Inc. from a sample of the same lot and specific product package. Label descriptions include a yellow highlight where claims are made that may fail to meet FDA guidance to avoid adding inactive ingredients, especially those with appeal to children. National Drug Code ("NDC") product codes are suggested based on information available to Valisure and displayed in brackets if the

product labels had slight differences from those of tested products (see Attachment C for product images).

ID	Benzene Mean (ppm ± %SD)	Brand and Label Description	Country of Origin	API and Strength	Product Code(s)	Lot	Expiration	Type	Manufacturing/Distributing Label Text
H112	1.8 ± 1% *1.2 **2	i-Softto Instant Hand Sanitizer Ethyl alcohol 75% (V/V) 16.9 fl.oz/500 ml Premium Quality By Softto Group	China	Ethyl Alcohol 75%	UPC: 810046820353 NDC: 73931-001	FE0401D DI	20220503	Gel	Manufacturer: Guangdong Essence Daily Chemical Co.,Ltd Distributed by: Guangzhou Softkiss cosmetics Co.,Ltd Suntisfy Inc. Irvine, California 92614 Made in China
H085	1.6 ± 4%	HAND-SAN Hand Sanitizer Alcohol Based MADE IN USA 16 fl oz (473 ml)	USA	Alcohol 70%	UPC: Unknown NDC: 76948-0006	2058733	08/19/2021	Gel	Dist. by J&S Chemical Canton, Georgia 30115 info@jschemical.com
H057	1.6	viridipharm from HEMP to HEALTH hand SANITIZER ANTIBACTERIAL 16 FL OZ (473 mL)	USA	Ethyl Alcohol 70%	UPC: 850001701648 NDC: 73267-001	Unknown	Unknown	Gel	Manufactured for: Viridipharm - Elmwood Park, NJ
H020	1.3 ± 19%	Smart Care Hand SANITIZER Aloe Vera & Vitamin E 2FL OZ (59mL)	China	Ethyl Alcohol 62%	UPC: 850016923127 NDC: [70108-048]	GX201326 3003	04/2022	Gel	International copyrights and trademarks granted or pending worldwide Distributed by Ashtel Studios Inc. Ontario, California 91761 Designed in U.S.A. - Made in China
H208	0.9 *1.1	BODY PRESCRIPTIONS Antibacterial Hand Sanitizer Vanilla Mint NET WT 12 GL OZ / 360 ML	China	Alcohol 75%	UPC: 192598534309 NDC: 50563-273	BL091620 -1	09/15/2022	Gel	Designed in the USA/Made in China Formulated Exclusively and Distributed by: Enchante Accessories Inc., New York, NY 10016
H256	0.9	artnaturals hand sanitizer SCENT FREE NATURAL ELEMENTS + CLEANSING FORMULA Infused with Aloe Vera 8 fl oz (236 ml)	China	Ethyl Alcohol 63%	UPC: 816820028205 NDC: Unknown	Unknown	05/2023	Gel	DIST. BY artnaturals (R) Gardena, CA 90248 MADE IN CHINA
H153	0.8	Oomph Antiseptic Instant Hand Sanitizer Gel	Australia	Ethyl Alcohol 80%	UPC: 9300764052712 NDC: 79319-000	Unknown	Unknown	Gel	Distributed By: Trendsformers LLC
H055	0.6	i-Softto Instant Hand Sanitizer Ethyl alcohol 75% (V/V) 16.9 fl.oz/500 ml Premium Quality By Softto Group	China	Ethyl Alcohol 75%	UPC: 810046820353 NDC: 73931-001	Unknown	Unknown	Gel	Manufacturer: Guangdong Essence Daily Chemical Co.,Ltd Distributed by: Guangzhou Softkiss cosmetics Co.,Ltd Suntisfy Inc. Irvine, California 92614 Made in China

H237	0.6	Smart Care Hand SANITIZER Aloe Vera & Vitamin E 16.9 FL OZ (500mL)	China	Ethyl Alcohol 62%	UPC: 850010842387 NDC: [70108-040]	JCK20133 50704	2022-04-28	Gel	International copyrights and trademarks granted or pending worldwide Distributed by Ashtel Studios Inc. Ontario, California 91761 Designed in U.S.A. - Made in China
H200	0.5	Clean Hands ULTRO CLEAN	China	Ethyl Alcohol 75%	UPC: 6939563201170 NDC: 50563-195	Unknown	14/03/2023	Gel	Made in China
H042	0.4	Livpure Extra Strength Germ Protection Hand Sanitizer (with Vanillin and Lemon Essential Oil)	USA	Ethyl Alcohol 80%	UPC: 850011432198 NDC: [74451-467]	ROS-LIV-20043051-02 43	230501	Gel	Distributed by Believue Parfums, NJ Manufactured By: Roselle Parfums Inc
H155	0.4	Kendall + Kylie Hand Sanitizer Gel Cucumber Scent	China	Alcohol 75%	UPC: 1949491818048 NDC: Unknown	Unknown	01/08/22	Gel	Distributed By: 2253 Group
H033	0.3	Defendr+ Hand Sanitizer Unscented + Moisturizing	China	Ethyl alcohol 70%	UPC: 190430038954 NDC: 74825-2020	20191-0624	06/24/2022	Gel	Manufactured for & Distributed by: Taste Beauty, LLC. 12 East 33rd Street, NY, NY 10016 Made in China
H184	0.3 *0.5	The Skinny all natural Hand Sanitizer Now with eucalyptus and spearmint essential oils	USA	Ethyl alcohol 80%	UPC: 850017809345 NDC: Unknown	Unknown	Unknown	Manual Pump Spray	Manufactured by: Skinny & Co., Inc. Indianapolis
H186	0.2	CALA Advanced Hand Sanitizer Moisturizing with Aloe Vera Extract Moisturizing & Refreshing	Korea	Alcohol 70%	UPC: 616513676511 NDC: 58241-0009 74985-676	20H0301	08 2023	Gel	CALA Products
H035	0.2	Smart Care Hand SANITIZER Aloe Vera & Vitamin E 8 FL OZ (236mL)	China	Ethyl Alcohol 62%	UPC: 850016923110 NDC: 70108-035	JLB20130 51803	04/2022	Gel	International copyrights and trademarks granted or pending worldwide Distributed by Ashtel Studios Inc. Ontario, California 91761 Designed in U.S.A. - Made in China
H048	0.2	artnaturals hand sanitizer SCENT FREE NATURAL ELEMENTS + CLEANSING FORMULA 8 fl oz (236 ml)	China	Ethyl Alcohol 74%	UPC: 816820028205 NDC: Unknown	Unknown	05/2023	Gel	DIST. BY artnaturals ® Gardena, CA 90248 MADE IN CHINA
H002	0.2	frida HAND SANITIZER 78% Alcohol 8oz (236.5 mL)	USA	Ethyl Alcohol 78%	UPC: 810028770454 NDC: Unknown	MFY02 S2	2021/06	Gel	Manufactured for: Fridababy, LLC, Miami FL 33137 Made in the USA From domestic and imported ingredients frida.com
H052	0.2	clean n' natural Hand Sanitizer 70% Alcohol Based With moisturizers and vitamin E	USA	Ethyl Alcohol 70%	UPC: 038488704011 NDC: 67385-023	01896017	07/2022	Gel	Clean n' Natural Products, CA Made in USA of U.S. and Imported parts.
H030	0.2	Defendr+ Hand Sanitizer Unscented + Moisturizing	China	Ethyl Alcohol 70%	UPC: 190430037971 NDC: 74825-2020	20170-0602	06/02/2022	Gel	Manufactured for & Distributed by: Taste Beauty, LLC. 12 East 33rd Street, NY, NY 10016 Made in China

H115	0.2	Zep Instant Hand Sanitizer Gel	USA	Ethanol 60%	UPC: 690858087829 NDC: Unknown	E4020196 B	Unknown	Gel	Distributed by Zep Inc.
H254	0.1	artnaturals hand sanitizer SCENT FREE NATURAL ELEMENTS + CLEANSING FORMULA 8 fl oz (236 ml)	China	Ethyl Alcohol 74%	UPC: 816820028205 NDC: Unknown	Unknown	05/2023	Gel	DIST. BY artnaturals ® Gardena, CA 90248 MADE IN CHINA
H044	0.1	Soapbox Hand Sanitizer Light Citrus Scent With Moisturizers & Vitamin E	USA	Ethyl Alcohol 62%	UPC: 850002771428 NDC: [75115-772]	2016052	06/22	Gel	Dist. by Soapbox Soaps LLC

Table 5. Product description of various batches of hand sanitizer for which benzene was detected below 0.1 ppm or 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.

Figure 2. Chart describing the distribution of all hand sanitizer types for 260 products evaluated by Valisure.

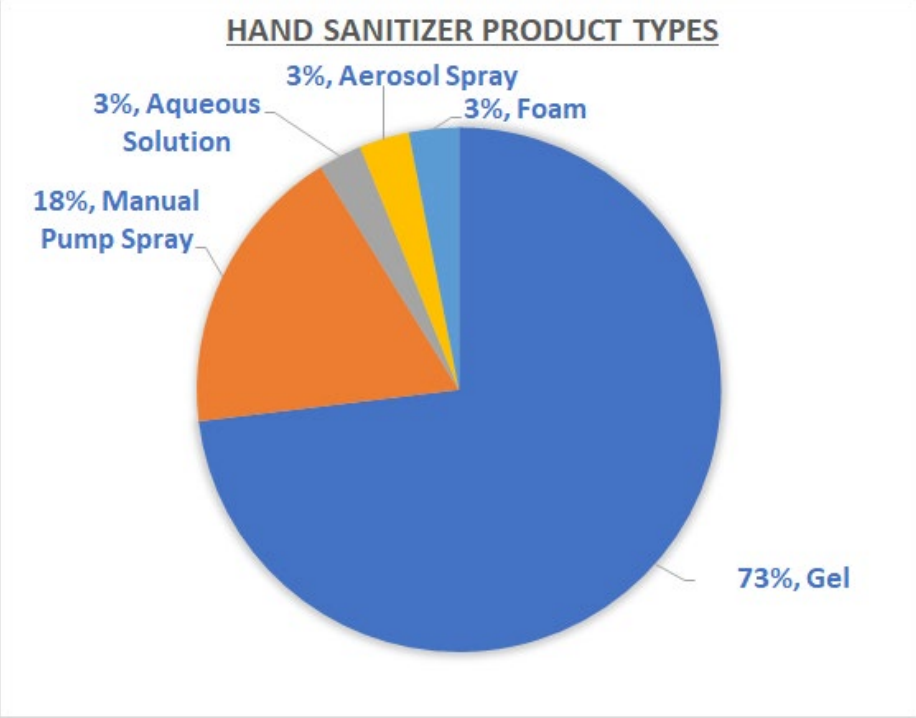
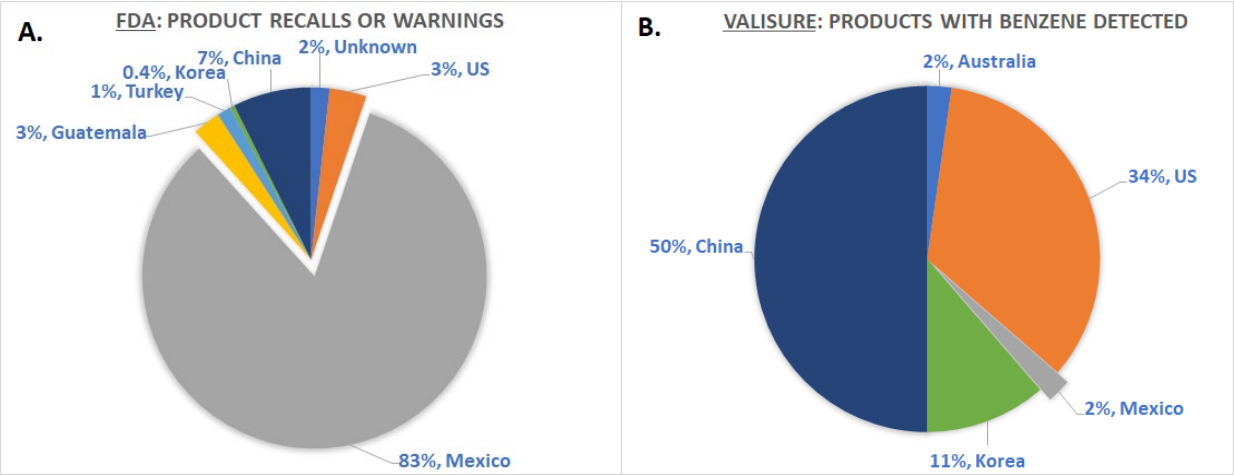


Figure 3. Charts describing A. Countries of origin for products listed by FDA with warning to the public not to use, and B. Countries of origin for products listed in Table 2 and Table 4 which contain detectable levels of benzene contamination and were independently sourced by Valisure.



Recall Request and Other Actions

This Petition seeks to have the Commissioner and FDA request recalls for the identified batches of hand sanitizer products, consistent with FDA's mandate to ensure the safety of the drug supply in the United States. The 44 batches highlighted in Table 2 and Table 4 should be expeditiously recalled. Table 2 products clearly exceed both FDA's interim limits on liquid hand sanitizer products during the declared COVID-19 Public Health Emergency and FDA's guidance for all drug products where a conditionally restricted limit for benzene is set for drugs that constitute a significant therapeutic advance and require benzene for their manufacture. Table 4 products appear to violate FDA guidance suggesting there is no acceptable level of benzene for drug products, such as hand sanitizer, that do not constitute a significant therapeutic advance and require benzene for their manufacture.

Such recalls are important for public safety. As indicated in Table 2, Table 4, and Table 5, there is significant batch-to-batch variation in benzene content, but many batches of hand sanitizer contain no detectable benzene and thus recalls should not overly burden the distribution chain or impact the availability of hand sanitizer 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 hand sanitizer, whose manufacture does not require benzene and that do not constitute a significant therapeutic advance. FDA has specified an interim limit on benzene of 2 ppm for liquid hand sanitizer during the declared COVID-19 Public Health Emergency; however, there is no guidance for any drug product whose manufacture does not require benzene and that does not constitute a significant therapeutic advance, nor is there guidance for gel or non-liquid hand sanitizers that Valisure's data suggests

are the majority of hand sanitizer products sold in the United States. Petitioner requests FDA provide guidance for such products in general and specifically for hand sanitizer when the COVID-19 Public Health Emergency expires.

Importantly, exposure of an individual to hand sanitizer products can vary widely and relates 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 potentially carcinogenic nitrosamine impurities. To properly quantify daily exposure, FDA should provide further guidance on the amount of hand sanitizer product used per application and the number of applications per day.

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. Hand sanitizer products are typically used in many times greater volume than standard drug products like tablets or capsules, so even a relatively low concentration limit could result in very high total exposure. This strongly underscores the need for a daily limit in addition to a concentration limit. Furthermore, FDA should clarify the non-emergency limit for benzene and the limit for non-liquid hand sanitizer formulations, both in terms of concentration and total exposure limit. It appears through the non-emergency FDA statement that benzene "should not be employed in the manufacture of drug substances" for drug products that do not require benzene for manufacture and do not constitute a significant therapeutic advance,[3] that there is no currently acceptable level of benzene for such drug products that include hand sanitizer.

In addition, for the reasons stated above, Valisure requests that FDA conduct examinations and investigations 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. As noted in the Petition, there are many products on the market with characteristics that conflict with FDA guidance aimed at preventing accidental ingestion by children.

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 CDC recommendation for use of hand sanitizer to protect against the spread of COVID-19 when hand washing with soap is not available,[40] and the potential that the alarming nature of this Petition's findings could deter individuals from using any hand sanitizer, Valisure would maintain that it is important for information provided to the public to clarify and underscore that contamination has not been detected in all hand sanitizer products and that unadulterated hand sanitizer products are available and should continue to be utilized.

[40] Centers for Disease Control and Prevention (November 4, 2020). *Hand Sanitizer Use Out and About*. (https://www.cdc.gov/handwashing/hand-sanitizer-use.html)

Independent, Batch-level Testing and Verification 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 hand sanitizer products that are regulated as drugs by FDA. In the interim, while these are pending, FDA should issue formal guidance recommending such testing and verification.

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.

In addition, Petitioner requests that FDA support the expanding number of independent drug quality analysis programs, including the program recently announced at The University of Kentucky,[41] 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.

[41] 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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