October 30, 2019

RE: Hearing on "Safeguarding Pharmaceutical Supply Chains in a Global Economy"
116th Congress
Energy and Commerce Committee

Dear Chairman Pallone and Subcommittee Chair Eshoo,

Thank you for the opportunity to submit this written testimony to you. Valisure commends the Committee for shedding light on the growing issues of pharmaceutical safety and quality for the American people and the imperative need to institute safeguards.

With 80 percent of ingredients in U.S. medications manufactured in India and China, medication quality and authenticity are constantly called into question. It's an issue that affects everyone. There are roughly three drug recalls in the U.S. every day and about 100 of those recalls every year are "Class I," which are considered potentially life threatening.

Part of the issue related to these recalls is that the chemical quality of medications is only checked occasionally on a limited number of batches at the manufacturer level, which relies on a system of self-reporting. And as you are aware, most manufacturers are located overseas where oversight by the Food and Drug Administration is difficult and fraud is commonplace. Widespread abuse of this self-reporting system by manufacturers in India and China has been extensively detailed in the recently published book, *Bottle of Lies*, which describes a 10-year investigative report on these issues.[1]

According to a 2015 white paper published by the FDA, the agency acknowledged that, "the FDA has no formal means for quality surveillance, except through inspections," and "inspection findings have not been a reliable predictor of the state of quality."[2] The paper also stated that, "product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design; these data further indicate failures in the implementation of manufacturing process scale-up as well as routine production."

Valisure believes that the only immediately effective way to address these concerns about poor quality control is chemical batch testing at the end of the supply chain. Valisure, located at Yale Science Park in New Haven, Connecticut, is the first analytical pharmacy that analyzes the chemical quality of every batch of every medication before dispensing to patients. Valisure's laboratory is ISO 17025 accredited by the International Organization on Standardization and DEA and FDA registered. Currently, Valisure rejects over 10% of the batches it analyzes due to issues with dosage variance, incorrect drug dissolution, mislabeled inactive ingredients, or the presence of carcinogenic contaminants.

Although all these rejections are concerning and underscore fundamental problems throughout the manufacturing system, the particularly alarming issue of carcinogens contaminating medications has been garnering the most public attention. In addition to increasing media coverage, such as the cover of

the September 16, 2019 issue of Bloomberg Businessweek,[3] carcinogens in our drugs unfortunately illustrate the depth and pervasiveness of the vulnerabilities in the pharmaceutical supply chain.

Since July 2018, the FDA and industry has continued to issue recalls in the -sartan class of drugs from numerous manufacturers due to the presence of the cancer-causing contaminant N-Nitrosodimethylamine (NDMA) and other similar "nitrosamines." These common blood pressure medications include valsartan, losartan, and irbesartan and belong to the class of drug known as angiotensin II receptor blockers (ARBs).

While there are an infinite number of possible impurities that medications can be tested for, some, like NDMA, are obvious and have been studied in medications for decades. Valisure proactively investigates other scientifically commonplace impurities and carcinogens, and recently demonstrated its utility by discovering a fourth carcinogen, N,N-Dimethylformamide (DMF), in several on-market valsartan drugs. DMF is an industrial solvent that was reclassified in 2018 as a Group 2A "probable human carcinogen" by the World Health Organization (WHO) and International Agency for Research of Cancer (IARC). DMF is classified by the FDA as a Class 2 solvent and is commonly used in the production of pharmaceutical active ingredients, including valsartan. According to the FDA, Class 2 solvents "should be limited in pharmaceutical products because of their inherent toxicity."

In a Citizen Petition filed with the FDA on June 13, 2019, Valisure submitted its findings that high levels of DMF exist in certain lots of valsartan medication.[4] In this case, Valisure tested over 30 batches of valsartan medications and about two thirds of them contained high levels of DMF. The solvent DMF has been implicated as the source of the more commonly discussed carcinogens like NDMA. Although progress has been made to reduce NDMA, the continued presence of DMF exemplifies that, even after a year of recalls, the fundamental manufacturing processes have not been significantly improved. Manufacturers continue to be more motivated to use cheap solvents like DMF for cost savings rather than focusing on improving drug quality and safety.

Furthermore, the presence of the carcinogenic solvent DMF in Novartis's brand name version of valsartan (Diovan) illuminates the particularly complex nature of the pharmaceutical supply chain and the difficulty in maintaining quality control. Below is a statement from Novartis to Bloomberg News[5] in response to Valisure's FDA citizen petition on DMF:

"Novartis doesn't use DMF in making Diovan and documents provided by suppliers it purchases ingredients from indicate that they don't, either, said spokesman Althoff. But companies that its suppliers buy from could."

Even a brand name manufacturer with strong measures of quality control is susceptible to the immense complexities of the global supply of pharmaceutical components, which can be contaminated at any juncture. The simple review of paperwork in a self-reported system is not sufficient to safeguard our nation's drug supply; independent chemical analysis is needed within the United States.

The FDA appears to recognize the necessity to improve quality with a recent announcement highlighting "We Need Manufacturers to Sell Quality — Not Just Medicine."[6] In this document published October 24, 2019, Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, outlines a plan for rating manufacturers based on "quality management maturity."

Although the recognition that not all manufacturers are equal is commendable, in Valisure's opinion, focusing on a self-reported "quality management maturity" rating unfortunately misses the point. It's almost certain that the "quality management maturity" of manufacturers like GSK, Sanofi and Novartis is extremely high - yet all of them have just instituted world-wide recalls of their Zantac/ranitidine products due to the presence of a potent carcinogen, NDMA. This carcinogen was very likely present in the drug for decades and only discovered now with chemical analysis done by Valisure,[7] an independent entity that is not part of the standard quality management system, often referred to as "cGMP." Participants of cGMP primarily self-report their analysis and will largely self-regulate what they decide to analyze in the first place. If anything, any rating system should be first and foremost based on real, chemical quality data and, importantly, come from independent entities outside of cGMP.

The medical community has also begun calling for increased transparency in the pharmaceutical supply chain, as evidenced by a recent resolution from the American College of Cardiology calling for legislation requiring independent testing and verification of the chemical content of batches of pharmaceuticals. According to the resolution submitted on May 9, 2019, "RESOLVED, That our AMA advocate for legislation requiring independent testing and verification of the chemical content of batches of pharmaceuticals."[8]

Currently, Valisure is the only entity in the United States that independently verifies and proactively analyzes the chemical quality and safety of each batch of medication in a pharmacy. In only the past six months, Valisure has already identified a fourth major carcinogen in valsartan and discovered the presence of the potent carcinogen NDMA in Zantac/ranitidine, which triggered recalls throughout the United States and the world. Government and regulators must start working with and encourage private industry to undertake the independent analysis of medication quality. Valisure has already proven the immense impact and critical need for such work and welcomes any engagement to help ensure the safety and quality of our medications in the United States.

Respectfully submitted,

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References

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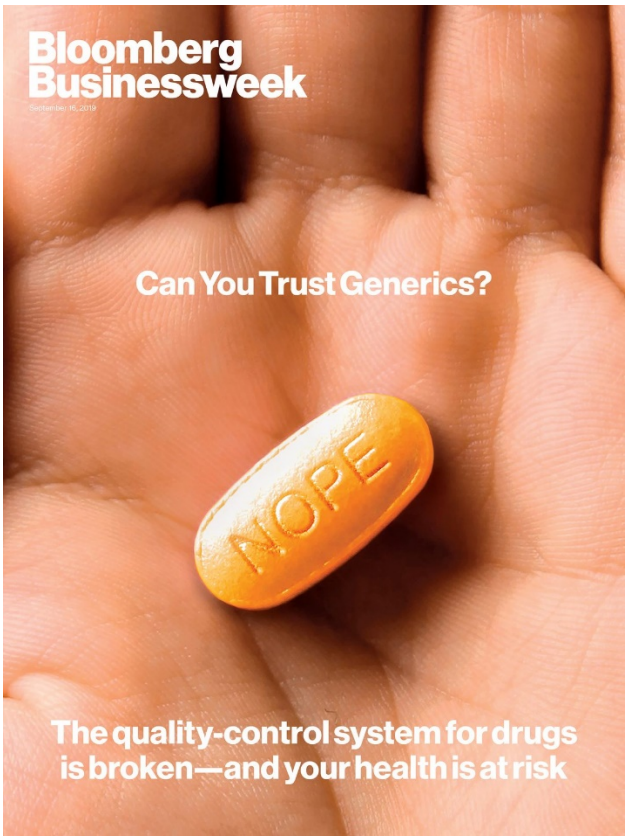

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