



COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process
Hearing before the United States Senate Committee on Finance
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Testimony of David Light, Founder and CEO, Valisure

Chairman Grassley, Ranking Member Wyden, and distinguished Members of the Senate Finance Committee, thank you for holding this important hearing. My name is David Light, and I am the Founder and CEO of Valisure.

At Valisure, our mission is to help ensure the safety, quality, and transparency of medications, and we do this with a very simple but novel approach: we check. Valisure is an online pharmacy attached to an analytical laboratory. We are the first and only pharmacy in America that chemically batch-validates every medication we sell, and we do it at no additional cost to consumers. Founded in 2015, Valisure is headquartered at Yale Science Park in New Haven, Connecticut. Valisure is ISO-17025 accredited by the International Organization for Standardization (ISO) and is registered with the Drug Enforcement Administration (Pharmacy: FV7431137, Laboratory: RV0484814) and the Food and Drug Administration (FDA) (FEI #: 3012063246).

In response to rising concerns about medication quality, counterfeit medications, and overseas manufacturing, Valisure developed proprietary analytical technologies that we use in addition to the FDA's standard assays to test every batch of every medication we dispense. Valisure tests medications for correct dosage, major inactive ingredients, proper dissolution, and the presence of carcinogens such as N-Nitrosodimethylamine (NDMA). Currently, we reject over 10% of on-market medication batches based on these testing standards.

With roughly 80 percent of ingredients in U.S. medications manufactured in India and China,¹ medication quality is constantly called into question. 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. These recalls can be attributed, at least in part, to the fact that the chemical quality of medications is primarily checked by manufacturers, which self-report the results. Most manufacturers are located overseas, where oversight by the FDA is difficult and fraud is commonplace. These general difficulties are only made worse by the COVID-19 pandemic.

¹ Gibson, Rosemary. *China Rx: Exposing the Risks of America's Dependence on China for Medicine*. Prometheus. Buffalo, New York. 2018



A useful metaphor for understanding the immense complexity of the drug supply chain and the critical need for independent analysis is to think of a bottle of medication like a used car. When you go to pick up a medication from your local pharmacy, it will often be a year or two old, have traveled thousands of miles, and touched dozens of hands all around the world. No one who buys a used car is satisfied to know that the original manufacturer vouched for its quality. Buyers want a Carfax report; a 100-point inspection on that specific car, or more. None of that transparency is available for medications. To ensure quality, we must do more than just review a manufacturer's paperwork and facilities: we need independent chemical analysis of the medication itself.

In a 2015 FDA white paper, the FDA acknowledged that it “has no formal means for quality surveillance, except through inspections” and conceded that “inspection findings have not been a reliable predictor of the state of quality.”² The paper also noted 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.”

Inspections by FDA at overseas plants are often announced months in advance and are typically conducted less frequently than the inspections of U.S. facilities, which are unannounced.³ Even these infrequent overseas inspections have been halted as a result of the COVID-19 crisis,⁴ making the need for greater oversight and quality assurance of the drugs coming into our country more imperative than ever.

Recent drug quality issues have threatened the health and safety of American consumers, including the widespread contamination of critical blood pressure medications,⁵ gastroesophageal reflux disease drugs,⁶ and diabetes medications⁷ tainted with carcinogens.⁸ Not only do drug quality issues place patients' lives at risk, they also account for over 60% of

² FDA *Pharmaceutical Quality Oversight*, page 2 <https://www.fda.gov/media/91721/download>

³ Government Accountability Office. *Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections*. 2019. (<https://www.gao.gov/assets/710/703077.pdf>)

⁴ FDA *Updates and Press Announcements on Coronavirus Disease 2019 (COVID-19) Update: Foreign Inspections*. (<https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-covid-19-update-foreign-inspections>)

⁵ FDA *Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)*. <https://bit.ly/38MRM6C>.

⁶ FDA *Updates and Press Announcements on NDMA in Zantac (ranitidine)*. February 27, 2020. <http://bit.ly/3b92dIP>

⁷ Reuters. “Online Pharmacy Valisure Says Tests Show Carcinogen in Diabetes Drug Metformin.” *The New York Times*. March 2, 2020. (<https://nyti.ms/2UhtwDw>)

⁸ Edney, Anna; Berfield, Susan; Yu, Evelyn. “Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.” *Bloomberg Businessweek*. September 12, 2019. (<https://bloom.bg/2x7P11z>)



drug shortages⁹ and generate fear and mistrust that is a contributing factor to medication non-adherence.¹⁰

We believe Valisure's work has only scratched the surface of the troubling drug quality issues in the U.S. supply chain. In less than a year, Valisure has identified a fourth major carcinogen in valsartan, discovered the fundamental instability of Zantac/ranitidine leading it to break down into a carcinogen, detected high levels of NDMA in roughly 40% of analyzed batches of the diabetes drug metformin, and uncovered many other serious issues. The immense impact of and critical need for independent chemical testing of medications has become extremely clear.

The Recall of Zantac/Ranitidine: Case Study in the Need for Independent Chemical Testing

The idea of independently checking drug products may be new to industry, but in the academic world, it has been done for decades. However, warnings from academics have unfortunately largely been ignored. A grim but perfect example of this relates to the drug Zantac and its generics, ranitidine.

In 1977, Senators sat in Dirksen Senate Office Building and listened to testimony from the prominent scholar Dr. William Lijinsky, Director of the Chemical Carcinogenesis Laboratory at Frederick Cancer Research Center. Dr. Lijinsky presented strong evidence that certain drugs are unstable and prone to forming the extremely potent nitrosamine carcinogen NDMA. In his opening remarks, Dr. Lijinsky testified:

Methapyrilene, like many similar antihistaminic drugs, is a tertiary amine. Being a tertiary amine, it reads [reacts] with nitrites in mildly acid solution to form a nitrosamine, dimethylnitrosamine [NDMA], which is one of the most potent carcinogens known, inducing liver cancer in rats.¹¹

Like methapyrilene, Zantac is an antihistamine, has a tertiary amine, and it reacts with nitrites (commonly found in many foods) in mildly acid solution (like a full stomach) to form NDMA.

⁹ See Dr. Patrizia Cavazzoni, F.D.A., The Importance of Pharmaceutical Quality 11. (2020). <https://bit.ly/37LwrJB>

¹⁰ Brown MT, Bussell J, Dutta S, Davis K, Strong S, Mathew S. Medication Adherence: Truth and Consequences. *Am J Med Sci.* 2016;351(4):387–399. doi:10.1016/j.amjms.2016.01.010 (<https://www.ncbi.nlm.nih.gov/pubmed/27079345>)

¹¹ *Senate Hearings Before the Subcommittee on Monopoly and Anticompetitive Activities of the Select Committee on Small Business on Effect of Promotion and Advertising of Over-the-Counter Drugs on Competition, Small Business, and the Health and Welfare of the Public.* June 1977. <https://drive.google.com/file/d/1dTw6mwdMVFmoGAM1tQvHieohLiuzicgn/view>

A year later, in 1978, the World Health Organization (WHO) and the United Nations held a global summit on nitrosamine carcinogens¹² where leading scientists from around the world expressed concern about NDMA and its formation from some common drugs.

By 1979, methapyrilene, the drug Dr. Lijinsky used as an example in his testimony, was removed from the market after 25 years of use due to concerns that it was carcinogenic¹³ and forming NDMA.^{14 15}

Despite these multitudes of warnings, Zantac/ranitidine, which had practically the same, if not worse, chemical instability and NDMA formation issues, was approved in 1981 in the UK and in 1983 in the U.S.¹⁶ The first of many academic studies raising the possibility of Zantac/ranitidine being carcinogenic were published in 1982 and 1983.^{17 18 19 20} Dozens of studies in top journals followed, including clinical²¹ and epidemiological studies.²² Another series of studies started in 1982 and investigated the use of “nitrosatable drugs” (Zantac/ranitidine is highly

¹² Nitrates, Nitrites and N-Nitroso Compounds (1978). World Health Organization and the United Nations Environment Programme. (<http://www.inchem.org/documents/ehc/ehc/ehc005.htm>)

¹³ “U.S., Industry Recall Sleep Aids Containing Cancer-Causing Agent.” *The New York Times*. June 9, 1979. (<https://www.nytimes.com/1979/06/09/archives/us-industry-recall-sleep-aids-containing-cancer-causing-agent.html>)

¹⁴ Lijinsky, William (1974). Reaction of Drugs with Nitrous Acid as a Source of Carcinogenic Nitrosamines. *Cancer Research*. Volume 34, Issue 1 (<https://cancerres.aacrjournals.org/content/34/1/255>)

¹⁵ 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>)

¹⁶ Original NDA and Original BLA Approvals June 1983 (Accessed May 31, 2020). (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=reportsSearch.process&rptName=2&reportSelectMonth=6&reportSelectYear=1983&nav>)

¹⁷ Brambilla G., Cavanna M., De Flora S. (1982). Genotoxic Effects of Drugs: Experimental Findings Concerning Some Chemical Families of Therapeutic Relevance. In: Nicolini C. (eds) *Chemical Carcinogenesis*. NATO Advanced Study Institutes Series (Series A: Life Sciences), Vol 52. Springer, Boston, MA (https://link.springer.com/chapter/10.1007/978-1-4684-4334-9_11).

¹⁸ Brambilla, G. et al. (1983). Genotoxic effects in rodents given high oral doses of ranitidine and sodium nitrite. *Carcinogenesis*. Vol. 4, 10, p. 1281-1285 (<https://academic.oup.com/carcin/article-abstract/4/10/1281/2391364>).

¹⁹ Martelli, A., Fugassa, E., Voci, A., Brambilla, G. (1983). Unscheduled DNA synthesis induced by nitrosated ranitidine in primary cultures of rat hepatocytes. *Mutation Research Letters*. Vol. 122, 3-4, p. 373-376 (<https://www.sciencedirect.com/science/article/pii/0165799283900222>).

²⁰ Maura, A. et al. (1983). DNA damage induced by nitrosated ranitidine in cultured mammalian cells. *Toxicology Letters*. Vol. 18, 1-2, p. 97-102 (<https://www.sciencedirect.com/science/article/pii/0378427483900772>).

²¹ Zeng, T. and Mitch, W.A. (2016). Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. *Carcinogenesis*. Vol. 37, p. 625-634 (<https://www.ncbi.nlm.nih.gov/pubmed/26992900>).

²² Mathes, RW., et. al. (2008) Relationship between histamine2-receptor antagonist medications and risk of invasive breast cancer. *Cancer Epidemiology Biomarkers & Prevention*, a publication of the American Association for Cancer Research. Vol. 17(1): p. 67-72. (<https://www.ncbi.nlm.nih.gov/pubmed/18199712#>)



“nitrosatable”) being used during pregnancy and found links to childhood tumors,^{23 24} birth defects,^{25 26} and other serious negative effects.^{27 28} However, the multitude of studies had little, if any, practical impact on the pharmaceutical and regulatory world. Despite the loud warnings from academics, Zantac/ranitidine became one of the best-selling drugs in history²⁹ and among the most commonly prescribed drugs to treat acid reflux in pregnant women³⁰ and infants.³¹

It was not until 2019, 38 years after Zantac/ranitidine was first approved and 42 years after Dr. Lijinsky delivered his warnings to the U.S. Senate, that Valisure’s analytical pharmacy performed the simple act of independently checking a bottle of generic Zantac syrup prescribed to one of our co-founder’s infant daughter. The results were so dramatic that we immediately took the drug off our formulary and tasked our full scientific staff to investigate.

After we realized the magnitude of the problem, we were not satisfied by simply publishing our findings in a scientific journal. We petitioned the FDA directly;³² we spoke to press; and we did not back down from the crystal-clear science that Zantac/ranitidine is fundamentally unstable, forms a potent carcinogen, and should be taken off the market. Two months ago, after dozens

²³ Preston-Martin, S., et. al. (1982). N-Nitroso compounds and childhood brain tumors: a case-control study. *Cancer Research*. Vol. 42(12) p. 5240-5. (<https://www.ncbi.nlm.nih.gov/pubmed/7139628/>)

²⁴ Olshan AF, Faustman EM. (1989) Nitrosatable drug exposure during pregnancy and adverse pregnancy outcome. *International Journal of Epidemiology*. Vol. 18(4) p. 891-9. (<https://www.ncbi.nlm.nih.gov/pubmed/2621027/>)

²⁵ Brender, JD. et. al. (2012) Nitrosatable drug exposure during the first trimester of pregnancy and selected congenital malformations. *Birth defects research. Part A, Clinical and molecular teratology*. Vol. 94(9) p. 701-13 (<https://www.ncbi.nlm.nih.gov/pubmed/22903972/>)

²⁶ Shinde, MU. et. al. (2013) Prenatal exposure to nitrosatable drugs, vitamin C, and risk of selected birth defects. *Birth defects research. Part A, Clinical and molecular teratology*. Vol. 97(8) p. 515-31 (<https://www.ncbi.nlm.nih.gov/pubmed/?term=23716465>)

²⁷ Brender, JD. et. al. (2011). Nitrosatable Drug Exposure During Early Pregnancy and Neural Tube Defects in Offspring. *American Journal of Epidemiology*. Vol. 174(11) p. 1286–1295 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3254159/>)

²⁸ Thomsen, AML. et. al. (2019). Nitrosatable drug exposure during pregnancy and risk of stillbirth. *Pharmacoepidemiology & Drug Safety*. Vol. 28(9) p. 1204-10 (<https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4867>)

²⁹ Wright, Richard (1996). How Zantac became the best-selling drug in history. *Journal of Health Care Marketing*. Vol. 16, Iss. 4, (Winter 1996): 24-29 (<https://search.proquest.com/openview/74cd4d4d4bff6f0807d9e1f952890bc1/1?pq-origsite=gscholar&cbl=36770>)

³⁰ Koenig, Clint (2001). What medications are safe and effective for heartburn during pregnancy? MDedge. (<https://www.mdedge.com/familymedicine/article/60506/womens-health/what-medications-are-safe-and-effective-heartburn-during>)

³¹ Baird, Drew, et. al. (2015). Diagnosis and Treatment of Gastroesophageal Reflux in Infants and Children. *American Family Physician*. 92(8):705-717 (<https://www.aafp.org/afp/2015/1015/p705.html>)

³² Valisure FDA Citizen Petition Requesting Recall of Ranitidine and Other Actions. September 9, 2019. Regulations.gov. (<https://www.regulations.gov/docket?D=FDA-2019-P-4281>)



of countries had already banned the drug,³³ the FDA finally granted our petition,³⁴ and this potentially dangerous drug was officially taken off the U.S. market.³⁵

Without independent testing and the drive to make it broadly transparent and recognized, Zantac/ranitidine could have remained on the market for many more decades to come.

The Prevalence of Contaminants in Medications in the U.S. Supply Chain

Valisure's investigation into Zantac/ranitidine's link to NDMA was a result of our general interest in analyzing medications for carcinogens, which began as a response to the rampant recalls of the blood pressure medications valsartan, losartan, and irbesartan. These recalls, which began in the summer of 2018, eventually expanded to over 1,000 lots of the -sartan class of drugs from numerous manufacturers due to the presence of NDMA and other similar nitrosamines.³⁶

While there are an infinite number of possible impurities that a laboratory could test medications for, some, like NDMA, are obvious. NDMA has been studied in medications for decades,³⁷ and the technology to detect it down to parts per billion and beyond has been widely available since at least 1970.^{38 39}

Other commonplace carcinogens are also logical to investigate, such as N,N-Dimethylformamide (DMF). DMF is an industrial solvent that was reclassified in 2018 by the WHO and International Agency for Research of Cancer (IARC) as a Group 2A "probable human carcinogen," the same category as NDMA. The FDA classifies DMF as a Class 2 solvent, which

³³ Newkirk, Margaret; Berfield, Susan; Edney, Anna . "The FDA Drug Recall System is Voluntary, Haphazard, and Broken." *Bloomberg Businessweek*. December 13, 2019. (<https://www.bloomberg.com/graphics/2019-voluntary-drug-recalls-zantac/?sref=RD3S4ThO>)

³⁴ *Final Response Letter from FDA CEDR to Valisure, LLC*. Regulations.gov. April 1, 2020. <https://www.regulations.gov/document?D=FDA-2019-P-4281-0008>

³⁵ *FDA News Release on 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>

³⁶ Edney, Anna; Berfield, Susan; Yu, Evelyn. "Carcinogens Have Infiltrated the Generic Drug Supply in the U.S." *Bloomberg Businessweek*. September 12, 2019. (<https://bloom.bg/2x7P11z>)

³⁷ Lijinsky, William, *et. al.* (1972) Carcinogenic Nitrosamines formed by Drug/Nitrite Interactions. *Nature*. (<https://www.nature.com/articles/239165b0>)

³⁸ Sen, N.P. (1970). Gas-liquid chromatographic determination of dimethylnitrosamine as dimethylnitramine at picogram levels. *Journal of Chromatography*. Vol 51, pp 301-304 (<https://www.sciencedirect.com/science/article/abs/pii/S0021967301968682>)

³⁹ Bassir, Olumbe and Maduagwu, Emmanuel N. (1978). Occurrence of nitrate, nitrite, dimethylamine, and dimethylnitrosamine in some fermented Nigerian beverages. *Journal of Agricultural and Food Chemistry*. American Chemical Society. Vol 26, pp 200-203 (<https://pubs.acs.org/doi/pdf/10.1021/jf60215a052#>)



“should be limited in pharmaceutical products because of their inherent toxicity.”⁴⁰ However, DMF is nonetheless used in the production of pharmaceutical active ingredients, including valsartan. Residual solvents are known issues in pharmaceutical processing, and, because DMF was implicated as a source of NDMA formation in valsartan, it was one of the first impurities to be added to Valisure’s standard impurities analysis. As soon as we started looking for DMF, we found it.

Valisure tested over 30 batches of valsartan medications and found that approximately two-thirds contained high levels of DMF. We included these findings in a Citizen Petition filed with the FDA on June 13, 2019.⁴¹ Our analysis suggests that although progress has been made to reduce NDMA in -sartan medications, even after two years of recalls, the fundamental manufacturing processes have not been significantly improved. In the absence of independent scrutiny and regulatory action, manufacturers continue to be motivated to use cheap solvents like DMF rather than investing in improving drug quality and safety.

Valisure’s analysis found DMF not just in medications produced by generic manufacturers but also in Diovan, the branded version of valsartan produced by Novartis. This finding illuminates the immense complexity of the drug supply chain and the difficulty faced even by manufacturers who are proactive about ensuring quality. A spokesperson for Novartis provided the following comment to *Bloomberg News* regarding the DMF finding:

Novartis doesn’t use DMF in making Diovan and documents provided by suppliers indicate that they don’t, either, said spokesman Althoff. But companies that its suppliers buy from could.⁴²

The vast and incredibly complex web of the pharmaceutical manufacturing industry has been recognized as a danger for many years, but it has resisted a slew of new technologies that attempted to “secure it.”⁴³ Therefore, independent, proactive chemical analysis of medications that is made transparent to all in the healthcare ecosystem is critical, and not just for generic manufacturers in a handful of overseas countries, but as an overall industry standard.

⁴⁰ FDA (June 2017). Q3C – Tables and List, Guidance for Industry. (<https://www.fda.gov/media/71737/download>)

⁴¹ Valisure FDA Citizen Petition on Valsartan. Regulations.gov. June 16, 2019.

<https://www.regulations.gov/docket?D=FDA-2019-P-2869>

⁴² Edney, Anna. Fourth . Discovered in Heart Pills Used by Millions. *Bloomberg News*. June 18, 2019(<https://www.bloomberg.com/news/articles/2019-06-18/fourth-carcinogen-discovered-in-heart-pills-used-by-millions>)

⁴³ Light, David.. “Blockchain Won’t Solve Pharma Quality Concerns.” *MoneyInc*. February 27, 2018. (<https://moneyinc.com/blockchain-wont-solve-pharma-quality-concerns/>)



Metformin: A Current Crisis for Roughly 18 Million Type 2 Diabetics in the U.S.

Metformin is an oral diabetes medication that helps control blood sugar levels in adults and adolescents with type 2 diabetes. Metformin is taken by over 18 million Americans and is prescribed over 90 million times a year, making it the fourth-most prescribed drug in the U.S.⁴⁴

Amid actions by regulators worldwide to step up vigilance on drug quality, the Ministry of Health of Singapore was the first to publicly identify NDMA contamination in metformin and issued recalls in early December 2019.⁴⁵ Switzerland announced recalls weeks later⁴⁶ and, by February 2020, Canada had followed suit.⁴⁷

The FDA announced it would investigate metformin contamination in December 2019.⁴⁸ In February 2020, the FDA released a laboratory method for the analysis of metformin⁴⁹ and published lab results.⁵⁰ The FDA reported that it had analyzed 16 batches of metformin from seven companies and found no NDMA beyond acceptable levels. However, it is important to note that the FDA may have acquired the medication samples through voluntary submission direct from manufacturers, which can introduce significant sampling bias and would not be an independent measure of quality.

To independently evaluate the state of metformin contamination, Valisure acquired 38 batches of metformin from 22 companies through our pharmacy's distributors. The results from this analysis were included in a FDA Citizen Petition filed on March 2, 2020.⁵¹ In our analysis, Valisure utilized the FDA's published testing protocol but modified it to improve sensitivity and, importantly, to add an internal control.⁵² Our results showed that 42% of the batches analyzed (16 of 38) contained NDMA exceeding the FDA's daily acceptable intake limit, with the highest

⁴⁴ Graedon, Joe. "ALERT | Metformin Carcinogen Contamination Confirmed!". *The People's Pharmacy*. May 28, 2020. (<https://www.peoplespharmacy.com/articles/alert-metformin-carcinogen-contamination-confirmed>)

⁴⁵ Health Sciences Authority of Singapore, *HSA Recalls Three out of 46 Metformin Medicines*. December 4, 2019. (<https://www.hsa.gov.sg/announcements/news/hsa-recalls-three-out-of-46-metformin-medicines>)

⁴⁶ Swissmedic, *Trace amounts of a nitrosamine impurity found in individual diabetes medicines*. December 6, 2019. (<https://www.swissmedic.ch/swissmedic/en/home/news/mitteilungen/info-diabetesmedikamente-nitrosamine.html>)

⁴⁷ Government of Canada. *Certain Metformin diabetes drugs recalled due to the presence or possible presence of NDMA*. March 11, 2020. (<https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/72287a-eng.php>)

⁴⁸ U.S. Food and Drug Administration. *Statement from Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research, on impurities found in diabetes drugs outside the U.S.* 2019.

⁴⁹ LC-HRMS Method for the Determination of NDMA in Metformin Drug Substance and Drug Product (<https://www.fda.gov/media/134914/download>)

⁵⁰ Laboratory Tests | Metformin (February 3, 2020) (<https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-metformin>)

⁵¹ *Valisure FDA Citizen Petition on Metformin*. Regulations.gov. March 2, 2020. (<https://www.regulations.gov/document?D=FDA-2020-P-0978-0001>)

⁵² Wu, Qian (February 27, 2020). *Valisure LC-HRMS Method for Determination of NDMA in Metformin* (<https://www.regulations.gov/document?D=FDA-2020-P-0978-0003>)



detected amount over 16 times the permissible limit. To further validate this data, Valisure sent samples from a contaminated batch of metformin to be independently verified by Emery Pharma, an FDA registered/inspected, cGMP/GLP compliant analytical laboratory.⁵³ Emery's results showed slightly higher NDMA levels than what Valisure found, confirming the severity of the contamination.

Valisure's analysis of its pharmacy batches significantly widened the number of sampled products and companies beyond the FDA's original report and likely reduced the sampling bias but was still limited by the availability of the drug from Valisure's pharmacy distributors. Therefore, Valisure conducted a direct-to-consumer crowdsourcing study in which we called for individuals to send us samples of metformin for free analysis. This effort resulted in the evaluation of 128 samples of metformin from individuals located in 30 states. The results of Valisure's analysis of these samples were detailed in a study co-authored with a researcher at The University of Maryland School of Pharmacy and posted on medRxiv.org, a pre-publication server maintained by Yale University.⁵⁴ As summarized in the study abstract,

42% of all medication samples contained detectable levels of NDMA and, when scaled to maximum daily tablet dose, 36% of all medication samples contained NDMA levels exceeding the FDA daily acceptable intake limit. The highest NDMA detection from the tested samples was 1565 ng per tablet, which, when commonly taken four times a day, is 65 times the United States Food and Drug Administration (FDA) acceptable daily intake limit. Results underscore the need for immediate product recalls of tainted medications and an overall investigation of metformin manufacturing practices.

These results largely mirror the findings from the analysis of pharmacy samples in Valisure's FDA Citizen Petition, and again illustrate the importance of independent testing derived from independently sourced samples.

The FDA recognized the importance of Valisure's Citizen Petition, and, in response, requested samples from the batches we analyzed. On April 1, 2020, Valisure voluntarily supplied tablets from each of the 38 identified batches. On May 28, 2020, the FDA announced that it was in contact with five metformin manufacturers and was urging them to voluntarily recall their products.⁵⁵ It appears that this action was spurred in large part by the Agency's analysis of the

⁵³ Emery Pharma (February 28, 2020). (<https://emerypharma.com/>)

⁵⁴ Wu, Qian, et. al. (2020). Analysis of Crowdsourced Metformin Tablets from Individuals Reveals Widespread Contamination with N-Nitrosodimethylamine (NDMA) in the United States. MedRxiv. (<https://www.medrxiv.org/content/10.1101/2020.05.22.20110635v1>)

⁵⁵ FDA Alerts Patients and Health Care Professionals to Nitrosamine Impurity Findings in Certain Metformin Extended-Release Products. May 28, 2020. (<https://www.fda.gov/news-events/press-announcements/fda-alerts-patients-and-health-care-professionals-nitrosamine-impurity-findings-certain-metformin>)



samples provided by Valisure. Valisure applauds this decision and hopes there will be future opportunities for collaboration between the FDA and independent laboratories like ours. However, a disconnect regarding the severity and breadth of the metformin contamination issue unfortunately persists due to discord over analytical methodologies.

In the case of metformin, the current FDA statements target only the extended release (ER) formulations of metformin, which account for about one quarter of prescriptions,⁵⁶ and not the immediate release (IR) formulations, which have also been identified by Valisure to contain unacceptable levels of NDMA. Furthermore, the Agency states that their findings of NDMA in metformin “were generally lower than reported by the private laboratory [Valisure].” Both these discrepancies are likely explained by the Agency’s published method for the analysis of metformin not including an internal control.

Internal controls are considered scientific best practice by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),⁵⁷ and are industry standard for the analysis of NDMA in complex samples like drinking water,⁵⁸ wastewater,⁵⁹ soil,⁶⁰ food⁶¹ and beverages,⁶² biological samples,⁶³ and pharmaceutical products⁶⁴ (including Singapore’s published method for NDMA analysis in metformin⁶⁵).

⁵⁶ Edney, Anna. “FDA Finds Carcinogen in Some Versions of Popular Diabetes Drug.” *Bloomberg News*. May 27, 2020. (<https://www.bloomberg.com/news/articles/2020-05-27/fda-finds-carcinogen-in-some-versions-of-popular-diabetes-drug>)

⁵⁷ M10 Bioanalytical Method Validation (June 27, 2019). Regulations.gov. (<https://www.regulations.gov/document?D=FDA-2019-D-1469-0002>)

⁵⁸ U.S. Environmental Protection Agency, Method 521, Determination of Nitrosamines in Drinking Water by Solid Phase Extraction and Capillary Column Gas Chromatography with Large Volume Injection and Chemical Ionization Tandem Mass Spectrometry (MS/MS), Version 1.0, September 2004.

⁵⁹ Ngongang AD, Duy SV, Sauvé S. Analysis of nine N-nitrosamines using liquid chromatography-accurate mass high resolution-mass spectrometry on a Q-Exactive instrument. *Analytical Methods*. 2015;7(14):5748-59.

⁶⁰ Bednar et al., Determination of Low Level NOMA in Soils, U.S. Army Corps of Engineers, ERDC TN-EQT-09-01, December 2009. <https://erdc-library.erdc.dren.mil/jspui/bitstream/11681/3699/1/ERDC-TN-EQT-09-01.pdf>

⁶¹ Chen et al., High Sensitivity Analysis of Nitrosamines Using GC-MS/MS, ThermoFisher Scientific Application Note 10315.

⁶² Tipler, A., The Determination of Low Levels of Nitrosamines in Beer Using the Clarus 680 GC/MS and a D-Swafer System, PerkinElmer Application Note.

⁶³ Zeng T, Mitch WA. Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. *Carcinogenesis*. 2016 Jun 1;37(6):625-34.

⁶⁴ U.S. Food and Drug Administration, Combined Direct Injection N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosoethylisopropylamine (NEIPA), N-Nitrosodiisopropylamine (NDIPA), and N-Nitrosodibutylamine (NDBA) Impurity Assay by GC-MS/MS. 2019. <https://www.fda.gov/media/123409/download>

⁶⁵ Singapore Health Science Authority, Determination of N-nitrosodemethylamine (NDMA) in Metformin Products by HRAM-GCMS, Ver002, May 2020. <https://www.hsa.gov.sg/docs/default-source/announcements/safety-alerts/determination-of-ndma-in-metformin-products-by-hram-gcms.pdf>



To understand the importance of an internal control more simply, it is useful to employ the metaphor of taking a picture of a fish to show its size. To properly portray the size of the fish, one can place a penny or a dollar bill next to it. The penny is acting as an “internal control” because it is a known size, so now a person can properly appreciate the size of the fish in the picture.

In Valisure’s study of metformin, the internal control was highly influential to obtain proper quantification of NDMA and the internal control had the greatest influence on IR tablets.⁶⁶ This implies that without the use of an internal control, NDMA levels will incorrectly appear significantly lower overall and, in particular for IR formulations, potentially to the point that unacceptable levels of contamination may not be detected at all in IR tablets if the control is not used.

These details may sound overly technical, but the consequences are profound. While debate ensues over analytical methodologies, roughly 13 million Americans are currently taking IR formulations of metformin and are at risk of continued exposure to unacceptable levels of NDMA. This situation is very similar to what occurred with Zantac/ranitidine nearly a year ago, in which the product remained on the market for months while the FDA contested analytical techniques.

Another critical component of the importance of independent analysis is the flexibility to improve upon regulatory guidance for analytics which may not always follow the latest best practices.

Proposed Solutions: Certified Drugs, Drug Quality Scores, and Regulatory Interventions

While the problems with the U.S. supply chain are significant, we believe there are several straightforward steps that would either stop these issues before products even leave the manufacturing plant or enable immediate, real-time action by buyers and payers to avoid purchasing low-quality products.

Certified Drugs

As aforementioned, Valisure conducts batch-testing of every product dispensed to our customers before it leaves the pharmacy, and we do so without adding any cost to patients. We believe this could be replicated on a larger scale, creating “certified drugs” that are independently chemically analyzed and certified before being sold to a patient, pharmacy,

⁶⁶ Light, David; Kucera, Kaury; Wu, Qian. Valisure FDA Citizen Petition Comment Letter. May 31, 2020. (<https://www.valisure.com/wp-content/uploads/Valisure-FDA-Citizen-Petition-Comment-Letter-May-31-2020.pdf>)



wholesaler, or health care system.

Ideally, this independent analysis would be done immediately after the original manufacturer produces the product, when the full size of the batch is in one location and before the product is dispensed to wholesalers and other down-market entities. The results of this analysis – in the form of a simple certificate – could be a desired, value-add mark that follows the product through the supply chain and into the hands of the patient receiving the medication, thus ensuring transparency and recognition of quality.

This independent analysis is already possible at less than a penny per pill at Valisure’s pharmacy, and the cost could easily be borne by manufacturers or large entities in the supply chain. Manufacturers could stand to gain market share for these certified products either by standard market drivers or through new requirements or incentives by health systems and large private or government purchasers.

Health systems are constantly plagued by drug quality issues and are impacted both tangibly (e.g. drug recalls) and intangibly (e.g. doctor and pharmacist time dealing with recalls; patient mistrust; readmissions; poor treatment of patients’ conditions). Leading health centers like The Cleveland Clinic have identified so many issues that “Cleveland Clinic pharmacists developed a confidential black list of drugs it would no longer buy.”⁶⁷ Prominent health systems or other major entities in the drug supply chain that are concerned about quality and patient safety could demand certified drugs and either require or incentivize having independent certification in their purchasing processes.

Certified drugs not only have the advantage of removing potentially dangerous products from the market but would inject much-needed transparency into the U.S. drug supply chain. As noted by Professor John Gray of Ohio State University in a statement submitted for the record for this hearing:

Unlike many consumer products, consumers/patients generally cannot know if there is a problem with their drug by looking at it. Further, even after taking the drug, it is hard to pinpoint that any side effects are the result of drug quality. This lack of quality visibility makes testing more critical in the drug industry than in many other industries. It also increases the risk that manufacturers, facing cost and delivery pressures, allow drugs to be shipped that did not meet all process and/or product specifications.

⁶⁷ Eban, Katherine. “These pills could kill you.” *The Boston Globe*. May 24, 2019. (<https://www.bostonglobe.com/ideas/2019/05/24/ideas-katherine-eban-these-pills-could-kill-you/d4gYXkoMR24n1uoLUkbnqj/story.html>)



The opacity of drug quality and the difficulty it can cause providers is exemplified by the many clinical examples observed by distinguished doctors at the Cleveland Clinic.⁶⁸ In the book *Bottle of Lies* by Katherine Eban, a whole chapter is dedicated to term coined by a Cleveland Clinic doctor called “the X factor:”

visualize each patient’s case as an algebraic equation. A new symptom put an unknown variable, an “X,” into the equation. ... generics seemed to be a new X that threw off the whole equation.

In other words, potential quality problems resulting from drug manufacturing present a further “X factor” that can frustrate proper diagnosis and treatment. As such, the visible mark of quality a certified drug offers would provide immense value to patients, doctors, payers, and the broader health care system.

Drug Quality Scores

Although we believe that Valisure’s independent chemical analysis of pharmaceuticals could be replicated on a larger scale, in the near term, certified drugs are likely only realistic for a handful of high-volume, high-impact drugs. However, data is available today that provides valuable insights on practically all drug products in the U.S.

On February 3, 2020, Valisure had the honor to be a plenary speaker at an event hosted by the Duke Margolis Center for Health Policy in partnership with FDA, *Understanding How the Public Perceives and Values Pharmaceutical Quality*.⁶⁹ At this event, a broad group of leaders from health care systems, the pharmaceutical supply industry, payers, universities, and non-profits strongly agreed there is a troubling lack of transparency into medication quality, and that the development of medication “quality scores” would be a powerful solution.

The FDA’s Task Force on Drug Shortages has endorsed the creation of a voluntary “rating system.... to inform purchasers, group purchasing organizations (GPOs) for health care systems, and even consumers, about the quality management maturity of the facilities making the drugs.”⁷⁰ We believe that this would be an important first step. However, data on quality

⁶⁸ Sweeney, James. “Sheriff’ Cardiologist Sounds the Alarm on Ineffective Generics.” *Medscape*. October 28, 2019. (<https://www.medscape.com/viewarticle/920470>)

⁶⁹ Understanding How the Public Perceives and Values Pharmaceutical Quality (2020). *Duke Margolis Center for Health Policy*. (<https://healthpolicy.duke.edu/events/understanding-how-public-perceives-and-values-pharmaceutical-quality>)

⁷⁰ Dr. Janet Woodcock, FDA, *To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality — Not Just Medicine*. Oct. 24, 2019. (<https://bit.ly/2SOEy3P>)



management maturity – in other words, a manufacturer’s paperwork – falls far short of the transparency on drug quality demanded by supply chain stakeholders.

Independent quality rating systems should be developed through a process that includes robust stakeholder feedback, including patients, providers, academic institutions, and health systems. These ratings systems should rely on objective, science-based data that is not solely voluntarily provided by manufacturers but generated by independent third parties. To accomplish this, results from independent chemical analysis of drug products could be combined with publicly available regulatory data and turned into drug quality scores that could be as simple as a “red/yellow/green” rating for each drug made by each manufacturer. Any buyer or payer could simply strive to buy green, occasionally yellow, and just avoid red.

A recent paper, *Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems*,⁷¹ [ATTACHMENT B] written by authors from NYU Langone Health, Columbia University, Defense Health Agency, University of Utah Health Care, Cleveland Clinic, Yale School of Public Health, and University of Connecticut School of Pharmacy, illustrates how such an independent system of quality ratings could work. Valisure contributed data and expertise to this paper. As explained in the extract:

The quality of drug products in the United States, which are largely produced overseas, has been a matter of growing concern. Buyers and payers of pharmaceuticals, whether they are health-systems, insurers, PBMs, pharmacies, physicians, or patients, have little to no visibility into any quality metrics for the manufacturers of drug products or the products themselves. A system of “quality scores” is proposed to enable health-systems and other purchasers and payers of medication to differentiate among drug products according to evidence-based metrics. Metrics influencing the quality scores described herein include both broadly applicable regulatory information and more drug-specific, third-party chemical analysis information. The aggregation of these metrics through a proposed set of rules results in numerical values on a 0-100 scale that may be further simplified into a red/yellow/green designation. The simplicity of such scores enables seamless integration into existing healthcare systems and an integration scheme is proposed. Using real-world data from currently on-market valsartan drug products, this proposed system generated a variety of quality scores for six major manufacturers. These scores were further evaluated according to their current market price showing no significant correlation between quality score and price. The implementation of drug quality scores at

⁷¹ Dabestani, Arash; et. al. (May 26, 2020). Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems. MedRxiv. (<https://www.medrxiv.org/content/10.1101/2020.05.22.20110775v1>)

SEE ATTACHMENT B



healthcare institutions in the United States and their potential utilization by regulators, could create a much-needed, market-driven incentive for pharmaceutical manufacturers to produce quality medications that would reduce drug shortages and improve public health.

This landmark paper is attached to this testimony and offers the first real blueprint of how independently generated, evidence-based drug quality scores can be built and utilized by healthcare systems throughout the US.

Regulatory Interventions

Finally, we believe there are a number of actions that the FDA and Congress could take that would bolster the effectiveness of the solutions above and further strengthen federal oversight of drug quality.

First, the proposed industry-driven solutions of certified drugs and drug quality scores could be significantly strengthened by incentives or requirements put in place by government payers. For example, the Department of Defense (DoD), which purchases its own medications, could require independent certification prior to purchase or provide incentives for manufacturers to do so. These concepts could also be included in legislation currently proposed to reform government purchasing of drugs (including for DoD) to incentivize sourcing from the U.S. and move pharmaceutical manufacturing to America.⁷²

Second, legislation could fill critical voids in the FDA's current ability to enforce appropriate measures for ensuring the safety and quality of the nation's drug supply. In the aforementioned Duke Margolis Center event, representatives from the FDA presented data from a survey of physicians. When asked, "Which, if any, of the following are functions of the FDA in terms of regulating drug quality?" the top answer was, "Remove a drug from market if unexpected risks are detected."⁷³ It is a sad irony that this is one power that the FDA does not have.

⁷² Costantino RC. The U.S. Medicine Chest: Understanding the U.S. Pharmaceutical Supply Chain and the Role of the Pharmacist. J Am Pharm Assoc. Under Review; see S. 3537, Protecting our Pharmaceutical Supply Chain from China Act; S. 3538, Strengthening America's Supply Chain and National Security Act; H.R.6731, Securing America's Pharmaceutical Supply Chain Act; H.R.6630, Securing America's Critical Minerals Supply Chain Act; and H.R. 4710, Pharmaceutical Independence Long-Term Readiness Reform Act.

⁷³ https://healthpolicy.duke.edu/sites/default/files/atoms/files/pharmaceutical_quality_slides_final.pdf



Congresswoman Rosa DeLauro (D-CT) has introduced H.R. 1108, the Recall Unsafe Drugs Act,⁷⁴ which would remedy this situation by providing the FDA with the authority it lacks to conduct the mandatory recalls of drugs. The bill was reintroduced in January 2020, along with a call from the Congresswoman to recall all ranitidine products.⁷⁵ Valisure strongly supports this legislation, which would mirror the mandatory recall authority FDA already has over medical devices, food, and biological products, but lacks for drugs.

Finally, another avenue where independent batch-level validation of drugs could easily be applied is drug importation. Drug importation is a unique opportunity to reimagine the drug supply chain and rebuild it in a way that helps ensure drug quality by incorporating independent chemical analysis of all imported products – essentially making all imported drugs certified drugs. We believe that drug importation is not only an important opportunity to provide lower-cost drugs to American consumers, but to enable even higher quality assurance than is presently possible in the current domestic drug supply.

In general, Valisure supports the framework set forth in the Administration’s Importation of Prescription Drugs Proposed Rule, particularly the proposed batch-level testing of all imported products. However, it is critical that the rule is revised to ensure that this testing is performed by independent laboratories rather than requiring further cGMP testing conducted by manufacturers that would be subject to the same conflicts of interest and errors as under our current system.⁷⁶ [ATTACHMENT A]

Valisure is greatly honored by the engagement it has received from government agencies and legislators and is open to exploring any avenues in which it can help to increase quality assurance and transparency in medications.

COVID-19 and the Impact on Medication Quality

In addition to its devastating toll on global health and economies, the COVID-19 pandemic has had significant impacts on the drug supply chain. Although finding treatments and vaccines for the virus and caring for the sick are the immediate first-order problems to address, it is becoming increasingly clear that one of the biggest second-order issues will be serious

⁷⁴ *H.R. 1108 Recall Unsafe Drugs Act*. Rep. Rosa L. DeLauro (D-CT-03). February 16, 2017. (<https://www.congress.gov/bill/115th-congress/house-bill/1108>)

⁷⁵ DeLauro Reiterates Call to Ban Ranitidine Sales, Reintroduces Bill to Giving FDA Mandatory Recall Authority Over Drugs .January 10, 2020. (<https://delauro.house.gov/media-center/press-releases/delauro-reiterates-call-ban-ranitidine-sales-reintroduces-bill-giving>)

⁷⁶ See Valisure’s comments to the proposed rule, *Importation of Prescription Drugs Proposed Rule*, Docket No. FDA–2019–N–5711. (<https://www.regulations.gov/document?D=FDA-2019-N-5711-1247>)

SEE ATTACHMENT A



disturbances to the U.S. pharmaceutical supply chain. Drug shortages are already affecting Americans prescribed medications being repurposed for COVID-19 treatment,⁷⁷ and the shutdown of overseas manufacturing will likely create dozens of widespread shortages in the months to come – many of which we have little visibility into today.

In addition to the challenge of drug shortages, existing pharmaceutical quality problems may be exacerbated by the COVID-19 crisis. Many safety and quality issues stem from overseas manufacturers cutting corners, and it is certainly possible that many more corners will be cut in the scramble to ramp back up production and fill backorders. The potential for the market to be flooded with counterfeit, substandard, and tainted products is a serious concern, particularly in light of the suspension of routine FDA inspections,⁷⁸ the approval of previously banned manufacturers, and dramatically increased demand for specific drugs.

Through Emergency Use Authorization Act (EUA) authority, the FDA has chosen to make decisions now for the good of public health that will undoubtedly impact public safety in the future. For example, in its efforts to authorize production of large quantities of several drugs, the FDA has lifted its ban on one overseas manufacturer, Ipca Laboratories. The FDA had previously banned products from three Ipca manufacturing facilities because of rampant data manipulation and what the FDA in a warning letter called a “cascade of failure” at its plant in Silvassa.⁷⁹ One potential solution could be a mandate that any drugs produced under an EUA should be independently tested and certified before entering the U.S. market.

We are also concerned about quality problems resulting from escalated production of products used to treat COVID-19. Many of these drugs are also used broadly for the treatment of other medical issues by non-COVID patients. In the race to produce large amounts of these drugs, quality may be sacrificed for quantity, thereby exposing a large population to substandard products. Further, when new COVID treatments, preventives, and vaccines are developed, manufacturers will face enormous pressure to produce large volumes quickly. Without careful regulatory oversight and independent analysis, this could result in quality problems from rushed manufacturing.

⁷⁷ Erman, Michael. “Potential coronavirus treatment touted by Trump already in shortage, pharmacists say.” *Reuters*. March 19, 2020. <https://www.reuters.com/article/us-health-coronavirus-usa-shortages-excl/exclusive-potential-coronavirus-treatment-touted-by-trump-already-in-shortage-pharmacists-idUSKBN2163JD>

⁷⁸ *FDA Updates and Press Announcement on Coronavirus Disease 2019 (COVID-19) Update: Foreign Inspections*. March 10, 2020. <https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-covid-19-update-foreign-inspections>

⁷⁹ *FDA Warning Letters on Ipca Laboratories Limited*. January 29, 2016. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/ipca-laboratories-limited-01292016>



It is important to note that manufacturing problems that arise from the escalated production of drugs and a lack of FDA inspectors on the ground at foreign plants could produce a domino effect for years to come. The lifecycle of a drug in the supply chain is many years and it could be many more before significant and serious issues are found, let alone addressed.

Conclusion

Since Valisure's founding, our mission has been to bring quality assurance and increased transparency into the opaque world of the nearly \$2 trillion global pharmaceutical industry. While we initially brought these benefits directly to patients through our online pharmacy, we are encouraged by the growing awareness of these problems by public and private stakeholders and increased opportunities for collaboration. By working together, we strongly believe that we can bring critically needed quality and transparency in medications to all Americans.

We are grateful to the Senate Finance Committee's commitment to ensuring the safety and quality of the U.S. drug supply chain and hope to continue working with you towards this critical goal.

Respectfully submitted,

David Light

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March 9, 2020
VIA ELECTRONIC FILING TO:
www.regulations.gov

Stephen M. Hahn, MD
Commissioner
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Importation of Prescription Drugs Proposed Rule, Docket No. FDA–2019–N–5711

Dear Dr. Hahn,

On behalf of Valisure, the nation's first and only analytical pharmacy, I appreciate the opportunity to comment on the FDA's proposed rule on the importation of prescription drugs. We commend the FDA's thoughtful approach to the rule, particularly the focus on batch-level testing of imported products. Drug importation is not only an important opportunity to provide lower-cost drugs for American consumers, but to enable even higher quality assurance than is presently possible with the domestic drug supply. We urge speedy implementation of the rule to allow states and stakeholders the opportunity to assemble Section 804 Implementation Programs (SIPs) as quickly as possible.

I. Background on Valisure

Valisure is an online pharmacy attached to an analytical laboratory, and is the first and only pharmacy in America that chemically batch-validates every medication it sells at no additional cost to consumers. Founded in 2015, Valisure is headquartered at Yale Science Park in New Haven, Connecticut. Valisure is ISO-17025 accredited by the International Organization for Standardization (ISO) and is registered with the Drug Enforcement Administration (Pharmacy: FV7431137, Laboratory: RV0484814) and the 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, the quality of generics, and overseas manufacturing, Valisure developed proprietary analytical technologies that it uses in addition to FDA standard assays to test every batch of every medication it dispenses. Valisure tests medications for correct dosage, major inactive ingredients, proper dissolution, and for the presence of carcinogens such as N-Nitrosodimethylamine (NDMA). Valisure currently rejects over 10% of medication batches based on these testing standards.

Over the past year, Valisure identified a fourth major carcinogen in valsartan and discovered the presence of NDMA in Zantac/ranitidine, which led to recalls of the drug



throughout the United States and the world. Most recently, Valisure detected high levels of NDMA in specific lots of the drug metformin.

In an August 7, 2018 inspection of Valisure's facilities by the FDA, the FDA 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 the FDA. Valisure also received guidance that since it operates outside of the manufacturing industry using the appropriate ISO guidelines as opposed to Good Manufacturing Practices (GMPs), any product failures or concerns that Valisure identifies should be reported back to the pharmaceutical industry. Valisure has complied with this guidance and regularly provides reports to applicable parties in the pharmaceutical industry.

II. Comments on the Proposed Rule

Valisure supports the importation framework proposed by the rule. In particular, we support the rule's proposed batch-level testing of all imported products, which will help ensure the integrity and safety of the medication. Below, we offer specific comments on several key provisions of the rule, including suggestions to help ensure that importation can be done both efficiently and cost-effectively.

A. SIP Sponsors

Valisure supports the proposal to allow pharmacies and wholesalers to co-sponsor SIPs. Pharmacies, in particular, have significant expertise acquiring and distributing prescription drugs, as well as ensuring the quality of these products; this makes pharmacies uniquely well-suited to partner with state SIP sponsors. We also believe that a pharmacy could safely serve as both a co-sponsor and an Importer within an SIP. To help safeguard these arrangements, we recommend requiring states to establish sufficient oversight mechanisms to ensure that this dual role does not present a conflict of interest.

Valisure also supports the proposal to allow pharmacies and wholesalers to sponsor a SIP independent of a state ("Option 2" under §251.2). We recommend limiting this option to pharmacies that can demonstrate the ability to manage the administrative aspects of the program, develop sustainable partnerships with reputable Foreign Sellers, and administer the required Statutory Testing with high-quality independent laboratories.

Finally, Valisure supports the proposal to allow pharmacies and wholesalers to serve as Importers, for all the reasons enumerated above. We agree that part of Importers' responsibilities should include an initial screening of imported products. In addition to a visual comparison of each product to the HPFB-approved drug, on-site laser spectroscopy-based techniques could be used to quickly screen products as a first-pass screening using handheld devices. This would require a relatively minimal investment by the Importer, but would add an additional level of security. However, this would not replace the need for significantly more detailed analysis by a qualified laboratory.



B. Covered Products

Valisure believes that the rule's restrictions on covered products would still allow the importation of many commonly used medications that not only provide significant opportunities for price savings, but have already been subject to critical quality and safety issues (for example, valsartan, losartan, and metformin). The proposed Statutory Testing for imported products could result in even safer products than are currently available for sale in the United States.

In particular, Valisure supports the FDA's decision not to exclude modified-release drugs and narrow-therapeutic index drugs from the definition of covered products. These are precisely the types of products that Valisure often hears quality complaints about from doctors and patients. Batch-to-batch variation in drug dissolution and dosage in narrow-therapeutic index drugs can translate into significant adverse events and negatively impact patients' clinical outcomes. Valisure's testing has revealed substantial quality and safety issues with many of these products: for example, products with significantly different dissolution rates across batches, and batches of narrow-therapeutic drugs, like anticonvulsants, that fall outside the manufacturers' stated ranges. As noted above, we believe this rule is an opportunity to add an additional layer of testing that can actually improve the quality and safety of imported products versus the current domestic supply.

C. Statutory Testing

Valisure believes that the Statutory Testing is a critical component of the proposed rule that will help ensure that imported products are safe and high quality. In particular, Valisure supports batch-level testing of all imported drugs, which will provide an important safeguard that goes beyond the requirements for domestically marketed drugs. However, Valisure has several suggestions to ensure that this testing is additive and not redundant and is conducted by independent third-party laboratories.

a. Qualifying Laboratories

Valisure strongly agrees with the proposal that all qualifying laboratories should have an inspection history and must have satisfactorily addressed any objectionable conditions or practices identified during its most recent inspection. Valisure agrees that qualifying laboratories should be held to rigorous standards, namely ISO 17025 accreditation.

However, Valisure disagrees that qualifying laboratories should be required to hold Current Good Manufacturing Practice (CGMP) certification. CGMP laboratories, by definition, contract with pharmaceutical manufacturers. This raises a potential conflict of interest that could lead CGMP laboratories to compromise the integrity of their testing. Moreover, CGMP testing follows manufacturer specifications rather than scientific and physiological best practice. In the past year alone, academics and independent laboratories like Valisure have discovered serious drug quality issues that were missed by CGMP testing, including potent carcinogens found in losartan, valsartan, ranitidine, and metformin. In some cases, these carcinogens were found because FDA testing guidelines had not yet been updated; in other cases, carcinogen contamination was



widespread but apparently missed during CGMP testing.¹ Regardless, these lapses have profound consequences for patient health.

In addition to raising a potential conflict of interest and possibly neglecting critical testing that is not prescribed by manufacturers, pharmaceutical companies placing their products for sale in the U.S. are already required to conduct a GMP analysis, making the testing in the proposed rule redundant in many cases. GMP testing is also particularly expensive; most contract research organizations (CROs) will charge more for a GMP test than a non-GMP test, even though the only substantive difference is the paperwork. As such, requiring qualifying laboratories to hold CGMP certification will unnecessarily raise the cost of the Statutory Testing and lower cost savings to American consumers.

ISO-17025 accreditation is rigorous, and actually goes beyond GMP by not only setting standards for laboratory and analytical methodology, but also governing quality systems company-wide including business practices. As such, Valisure urges the FDA to eliminate the requirement that qualifying laboratories hold CGMP certification in order to ensure that the sponsors of SIPs have the option of contracting with truly independent and unbiased laboratories.

b. Laboratory Testing Requirements

Valisure recognizes that 21 U.S.C. §384 permits laboratory testing to be done by the Importer or by the manufacturer. However, Valisure remains concerned that permitting the testing to be conducted by the manufacturer significantly increases the risk of inadequate scrutiny (at best) and fraud (at worst). As discussed above, this is especially true if the testing is conducted by a CGMP laboratory that routinely contracts with the pharmaceutical industry or is itself owned or controlled by the manufacturer selling the product.

To lower the risk that manufacturer testing might allow low-quality products to be imported into the U.S., Valisure reiterates its recommendation that testing should be permitted to be conducted by ISO-17025 certified labs rather than restricted only to labs that hold CGMP certification. This would allow SIP sponsors the option of requiring any imported products to be tested by independent laboratories free of potential conflicts of interest. Additionally, Valisure urges that the rule clarify that manufacturers cannot satisfy the Statutory Testing requirements through pre-existing release or conformance testing. To the extent products have already undergone release or conformance testing at a qualifying laboratory in the U.S., the FDA should stipulate that the Statutory Testing should be conducted at a separate, independent laboratory to ensure thorough analysis before the products enter the United States market. Valisure also strongly supports the

¹ See VALISURE, *Valisure Citizen Petition*, June 19, 2019 (finding high levels of the carcinogen DMF in lots of valsartan); VALISURE, *Valisure Citizen Petition on Ranitidine*, Sept. 9, 2019 (finding extremely high levels of NDMA in ranitidine); VALISURE, *Request that the FDA recall of identified batches of metformin on the basis that, due to contamination with a probable human human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA*, March 2, 2020 (finding high levels of the carcinogen NDMA in lots of metformin).



requirement in the proposed §251.16(e) that if testing is done by manufacturers, detailed data should be provided to the FDA.

D. Product Labeling

Finally, Valisure supports labeling imported products appropriately to allow pharmacists to be able to distinguish them on a shelf. However, Valisure suggests that the required language on each box include the stipulation that each product was batch-tested to help ensure safety and quality.

* * *

Valisure appreciates the opportunity to provide comments on the proposed rule and looks forward to working with the FDA and states to help implement the safe and affordable importation of drugs from Canada. If you have any questions or if we can provide any further information that would be useful, please do not hesitate to contact me at david.light@valisure.com or 833-497-7370.

Sincerely,

David Light
Founder and CEO
Valisure

ATTACHMENT B

Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems

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Abstract

The quality of drug products in the United States, which are largely produced overseas, has been a matter of growing concern.¹ Buyers and payers of pharmaceuticals, whether they are health-systems, insurers, PBMs, pharmacies, physicians, or patients, have little to no visibility into any quality metrics for the manufacturers of drug products or the products themselves. A system of "quality scores" is proposed to enable health-systems and other purchasers and payers of medication to differentiate among drug products according to evidence-based metrics. Metrics influencing the quality scores described herein include both broadly applicable regulatory information and more drug-specific, third-party chemical analysis information. The aggregation of these metrics through a proposed set of rules results in numerical values on a 0-100 scale that may be further simplified into a red/yellow/green designation. The simplicity of such scores enables seamless integration into existing healthcare systems and an integration scheme is proposed. Using real-world data from currently on-market valsartan drug products, this proposed system generated a variety of quality scores for six major manufacturers. These scores were further evaluated according to their current market price showing no significant correlation between quality score and price. The implementation of drug quality scores at healthcare institutions in the United States and their potential utilization by regulators, could create a much-needed, market-driven incentive for pharmaceutical manufacturers to produce quality medications that would reduce drug shortages and improve public health.

¹ Conti RM, Berndt ER, Kaygisiz NM, Shivdasani Y. "We Still Don't Know Who Makes This Drug," Health Affairs Blog, February 7, 2020. (<https://www.healthaffairs.org/doi/10.1377/hblog20200203.83247/full/>)

Introduction

As most of the United States' complex drug supply chain has moved overseas, especially to countries such as India and China, quality and safety concerns have become more pressing. Eighty percent of active pharmaceutical ingredients ("API") for products sold in the U.S. now come from outside the country, the vast majority from China.² As Dr. Janet Woodcock, Director of the Food and Drug Administration ("FDA") Center for Drug Evaluation and Research ("CDER"), has noted, this "use of foreign-sourced materials creates vulnerabilities in the U.S. drug supply."³ Recent drug quality issues have threatened the health and safety of American consumers, including the widespread contamination of critical blood pressure medications,⁴ gastroesophageal reflux disease drugs,⁵ and diabetes medications⁶ with carcinogens.⁷ Not only do drug quality issues place patients' lives at risk, they also account for over 60% of drug shortages⁸ and generate fear and mistrust that is an important cause of medication non-adherence.⁹

Certain manufacturers have exhibited substantive quality issues and even engaged in data manipulation. This issue is highlighted by the record \$500 million fine imposed on the generics manufacturer, Ranbaxy, after it pleaded guilty to failing to report its drugs did not meet specifications. The firm also made false statements to the FDA. Ranbaxy knowingly manufactured drugs that tested out-of-specification, had unknown impurities, and would not maintain their expected shelf life.¹⁰

Although significant attention is given to overseas manufacturers, American companies are not immune from quality issues. Numerous cases exist of serious quality

² U.S.-CHINA ECONOMIC AND SECURITY REVIEW COMMISSION, 2019 REPORT TO CONGRESS 250 (2019).

³ *Statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, F.D.A., Before the Subcommittee on Health Committee on Energy And Commerce, U.S. House of Representatives, Safeguarding Pharmaceutical Supply Chains in a Global Economy 2* (Oct. 30, 2019), available at <https://bit.ly/2SYjqyq>.

⁴ *FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)*, <https://bit.ly/38MRM6C>.

⁵ *FDA Updates and Press Announcements on NDMA in Zantac (ranitidine)* (February, 27, 2020). <http://bit.ly/3b92dlP>

⁶ Reuters (March 2, 2020). Online Pharmacy Valisure Says Tests Show Carcinogen in Diabetes Drug Metformin. *The New York Times* (<https://nyti.ms/2UhtwDw>)

⁷ Edney, Anna; Berfield, Susan; Yu, Evelyn (September 12, 2019). Carcinogens Have Infiltrated the Generic Drug Supply in the U.S. *Bloomberg Businessweek*. (<https://bloom.bg/2x7P11z>)

⁸ See Dr. Patrizia Cavazzoni, F.D.A., THE IMPORTANCE OF PHARMACEUTICAL QUALITY 11 (2020), at <https://bit.ly/37LwrJB>.

⁹ Brown MT, Bussell J, Dutta S, Davis K, Strong S, Mathew S. Medication Adherence: Truth and Consequences. *Am J Med Sci*. 2016;351(4):387-399. doi:10.1016/j.amjms.2016.01.010 (<https://www.ncbi.nlm.nih.gov/pubmed/27079345>)

¹⁰ White CM. Generic Drugs Not as Safe as FDA Wants You to Believe. *Annals Pharmacotherapy* 2020;54(3):283-286 (<https://journals.sagepub.com/doi/full/10.1177/1060028019881692>)

problems affecting American consumers caused by poor manufacturing practices at facilities in the United States.¹¹

For these reasons, we applaud the FDA’s recent recognition of the need for more transparency with regard to drug manufacturing.¹² Recalls and FDA investigations have made clear that not all manufacturers are alike in their capacity to reliably produce high-quality pharmaceutical products. However, purchasers of pharmaceutical products – including drug distributors, pharmacies, and health systems – often have no reliable way to distinguish between high- and low-quality manufacturers or their drug products.

The FDA’s Task Force on Drug Shortages has endorsed the creation of a voluntary “rating system.... to inform purchasers, group purchasing organizations (GPOs) for health care systems, and even consumers, about the quality management maturity of the facilities making the drugs.”¹³ This underscores the importance of the fundamental principle of having a quality score that can differentiate between manufacturers. However, since the FDA proposal is voluntary, it may not achieve broad implementation. Furthermore, it is important that the criteria used be evidence-based. Announcements have also been made by private industry for the creation of a commercially available drug quality scores platform intended for use by health systems.¹⁴

Any reliable rating system should draw upon objective, science-based, independently generated data that is not voluntarily provided by manufacturers but collected by independent parties. Although a quality score system may include voluntarily furnished data, it must be primarily based on independent data to be broadly applicable and thus optimally useful to healthcare systems. The American College of Cardiology stressed the need for “independent testing and verification of the chemical content of batches of pharmaceuticals” in a recent resolution¹⁵ that emphasizes the necessity to rely on more than just the manufacturer’s self-reported data.

These independent quality rating systems should be developed through a process that incorporates robust stakeholder feedback, including patients, providers, academic institutions, regulatory agencies and health systems. In order to spur such discussion and make meaningful progress towards establishing a viable system for use among an array of healthcare providers, the authors propose criteria for the creation of evidence-based quality scores, examples of use on existing drug products, and a mechanism for utilization exemplified by a proposed workflow for Health Systems.

¹¹ FDA Updates on Multistate Outbreak of Burkholderia cepacia Infections (August 2, 2017). (<http://bit.ly/33pjhkK>)

¹² Dr. Janet Woodcock, FDA, *To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality — Not Just Medicine*, Oct. 24, 2019, at <https://bit.ly/2SOEy3P>.

¹³ *Id.*

¹⁴ Press Release (January 8, 2020). Valisure And Govzilla Announce A Collaboration Focused On Creating A Platform For Evidence-Based Quality Scores For Drug Products. *PR Newswire*. (<https://prn.to/2xAuZgw>)

¹⁵ American College of Cardiology resolution to the American Medical Association (May, 9, 2019)

Methods

Quality Score Overview

Evidence collected in this proposed system originates from both broad manufacturer-level data and from specific product information. The combination of this data is intended to influence scores for specific drug products of a particular drug from a specific manufacturer. Although the evidence can be aggregated to evaluate a given manufacturer as a whole, the greatest utility to healthcare purchasers and payers is likely achieved by focusing on specific products. This is due to the immense complexity and opacity of the pharmaceutical supply chain. The source of ingredients used in any one drug product is considered proprietary and is therefore not easily accessible.

The specificity down to a drug product is not intended to directly describe a given National Drug Code (“NDC”), which further defines a drug product’s dosage form and packaging. It is assumed that evidence gathered on a specific drug product will be applicable to all NDCs related to that drug product from the specific manufacturer, regardless of dosage level or packaging. As an illustrative example, if negative information is gathered for “manufacturer X’s” valsartan 160mg tablets packaged in 100 count bottles, this will influence quality scores on NDCs for all valsartan tablets in all package sizes for manufacturer X. When substantially more data is available, future iterations of quality scores may directly describe individual NDCs or individual dosage forms.

The proposed system would generate a quality score on a numerical scale from 0 to 100, with 100 being the most desirable and highest achievable score and 0 being the lowest and least desirable score. Since all drug products legally sold in the United States are FDA-approved and produced at registered facilities certified as conforming to Current Good Manufacturing Practices (“cGMP”), the default assumption is that, absent evidence to the contrary, all products receive a default score of 100.

Criteria proposed herein are all based on information that is negative in nature and thus produces evidence for reducing a starting score of 100. Future iterations of such quality scores may also include criteria based on positive information that generates evidence for raising a score. The default value of such scores may be subsequently lowered to add opportunity for particularly well-performing manufacturers or products to outperform the default. It is also contemplated that temporal considerations be given to modify the impact of negative information and to eventually remove or significantly reduce its influence. The intention for a reliable quality score system would be to continuously incorporate new regulatory and chemical analysis data to enable optimal, real-time, guidance of drug product quality.

Quality Score Criteria

Proposed below are detailed criteria and their influence on a default score. These are based on independently gathered evidence from regulatory information and chemical analysis of on-market drug products obtained from a licensed pharmacy.

Category	Criteria	Qualifiers	Score Influence
Regulatory Information	Warning Letter ratio to total inspections	>1.5X 3-yr industry average	-10
		>2X 3-yr industry average	-30
	Form 483 ratio to total inspections	>10% 3-yr industry average	-10
		>20% 3-yr industry average	-30
	GMP related Consent Decree/ CIA in place		-50
Public Product Quality complaints	e.g. % "bad odor" > 2X competitors	-10	
	e.g. % "bad odor" > 4X competitors	-30	
Serious Adverse event	e.g. % "death" > 2X competitors	-10	
	e.g. % "death" > 4X competitors	-30	
Chemical Analysis	Dosage failure	Single batch	-10
		>33% of batches	-30
		All batches	-61
	Dissolution failure of USP	Single batch	-10
		>33% of batches	-30
		All batches	-61
	Dissolution failure of Physiological Conditions	>33% of batches	-10
		All batches	-30
	Carcinogen failure of FDA levels	Single batch	-30
		>33% of batches	-61
	Carcinogen failure at evidence-based, stricter levels	Single batch	-10
		>33% of batches	-30
All batches		-61	
Heavy metals failure of FDA levels	Single batch	-30	
	>33% of batches	-61	
Microbial detection failure by FDA method	Single batch	-30	
	>33% of batches	-61	
Microbial detection failure by PCR method	Single batch	-10	
	>33% of batches	-30	
	All batches	-61	
Ingredients ID failure, API	Single batch	-30	
	>33% of batches	-61	
Ingredients ID failure, excipient	Single batch	-10	
	>33% of batches	-30	
	All batches	-61	

Table 1. Proposed quality score criteria are categorized by information derived from regulatory data and chemical analysis data. For most criteria, the severity of negative influence on the score is dependent on qualifiers on the information gathered.

The specific criteria proposed above are primarily self-explanatory. Criteria requiring clarification are discussed below.

Form 483 and Warning Letter Ratio of Inspections – The 3-year average of total drug industry inspections, Form 483 letters and warning letters is aggregated and the ratios of Form 483 letters to total inspections and warning letters to total inspections is calculated. These same values are also calculated for an individual manufacturer and if the ratios for the manufacturer are higher than the global average by a set qualifier, a negative score influence is triggered. Future iterations may utilize total drug industry inspections within geographic regions as opposed to a global average. This could be an important refinement given the differences in inspection practices within the United States and overseas; such as domestic inspections are unannounced whereas foreign inspections often come with months of advanced warning.¹⁶

Public Product Quality Complaints or Serious Adverse Events – The ratio of this complaint or event to all others for this product is compared to other manufacturers of the same product. If the ratio for a concerning complaint or serious event is significantly higher than the average ratio of its competitors, a negative score influence is triggered.

Dissolution Failure of Physiological Conditions – This differs from dissolution failure of USP conditions for a variety of products where the registered USP monograph for dissolution testing does not conform to industry standard physiologically relevant conditions. For example, industry standard simulated gastric fluid is often used for 2 hours and has a pH of 1.2 and simulated intestinal fluid is often used for the remainder of dissolution testing thereafter and has a pH of 6.8. However, USP dissolution media for ibuprofen tablets prescribes using only one solution with a pH of 7.2 without any exposure to acid. Although testing ibuprofen tablets in USP solution may yield a passing test, performing dissolution testing in physiologically relevant media has been shown to yield certain specific products taking over 24 hours to dissolve whereas others dissolve quickly, as expected.¹⁷

Carcinogen Failure at Evidence-based, Stricter Levels – FDA regulations for acceptable daily exposures or intakes of various carcinogen compounds generally follow internationally accepted guidelines. However, there are cases where organizations such as the World Health Organization (“WHO”) and the International Agency for Research on Cancer (“IARC”) will provide guidance which differs from that listed by the FDA. This is currently the case with N,N-Dimethylformamide¹⁸ (“DMF”) which is classified by WHO and IARC as a Group 2A probable human carcinogen.¹⁹ For the purposes of this proposed quality score system, a negative score influence is triggered when DMF levels exceed 96 nanogram but are less than 1,000 nanograms and a more severe negative score influence is triggered when DMF levels exceed 1,000 nanograms.

¹⁶ Government Accountability Office (2019). Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections. (<https://www.gao.gov/assets/710/703077.pdf>)

¹⁷ Your Medication May Not Be Dissolving Properly (2018). *The Valisure Notebook*. <http://bit.ly/38XVDNm> (accessed March 15, 2020)

¹⁸ Light, David; Kucera, Kaury (June, 13, 2019). Request that the FDA to issue a regulation, revise industry guidance, and take such other actions. *FDA Citizen Petition filed by Valisure, LLC*. (<https://www.regulations.gov/docket?D=FDA-2019-P-2869>)

¹⁹ International Agency for Research on Cancer and World Health Organization, *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*, Volume 47, 71, 115 (2018) (<https://monographs.iarc.fr/list-of-classifications-volumes/>).

Category	Criteria	Qualifiers	Score Influence
Chemical Analysis	Carcinogen failure: DMF >96 ng, < 1,000ng	>33% of batches	-10
		All batches	-30
	Carcinogen failure: DMF >1,000 ng	Single batch	-10
		>33% of batches	-30
	All batches	-61	

Table 2. Quality score criteria definitions for “Carcinogen failure at evidence-based, stricter levels” specific for DMF

Notably absent from the proposed quality score criteria is information regarding recalls. Although the existence of high volumes of recalls for a particular manufacturer of a drug product may intuitively induce a negative score influence, this may, in fact, be an indication of responsible quality surveillance. Furthermore, a lack of recalls may be indicative of overly lax quality assurance measures for a given manufacturer as opposed to a truly quality product. In the United States, drug product recalls are almost all voluntary and performed at the discretion of pharmaceutical manufacturers.²⁰ This conundrum warrants a deeper investigation. A retroactive review of chemical data compared with recall data could potentially better inform the correct view of product recalls. While such insights are yet to be elucidated, it was deemed best to leave such information out of the currently proposed quality score system.

Also absent from the quality score criteria is the FDA-proposed concept of quality management maturity. Indicators of quality management maturity have been proposed but appear to primarily rely on manufacturers’ proprietary information.²¹ To the authors’ knowledge, there is no existing metric that uses publicly available inputs other than recalls which are discussed above. The lack of available information to assess the merits of quality management maturity for use in an independently derived and broadly applicable, evidence-based quality score system precludes it from inclusion in this proposal; however, future iterations may add such criteria when the information required for evaluation is made available or new indicators are elucidated.

It is envisioned that a drug quality score system or platform could include a mechanism for health system users to report potential drug quality issues, adverse events or send suspect medication samples for chemical analysis. This could create a much broader net to identify quality issues and if broadly utilized, such information could be valuable for the creation of new criteria to influence quality scores.

²⁰ Newkirk, Margaret; Berfield, Susan (December 13, 2019) The FDA Drug Recall System is Voluntary, Haphazard and Broken. Bloomberg Businessweek (<https://www.bloomberg.com/graphics/2019-voluntary-drug-recalls-zantac/>)

²¹ ISPE Drug Shortages Prevention Plan (October 2014)
<http://www.ispe.org/DrugShortagesPreventionPlan>

Quality Score Mechanics

To enable further ease of use and straightforward implementation within established healthcare systems, the proposed numerical quality score output can be categorized in a red/yellow/green fashion according to the following table:

Color Designation	Quality Score Range
Green	80-100
Yellow	40-79
Red	0-39

Table 3. Quality scores receive a color designation dependent on their numerical value.

Recognizing that a drug product receiving a red designation could induce significant impact within a healthcare system; special consideration was given to criteria which can trigger a red. In this proposal, only the quality score criteria within the category of Chemical Analysis is allowed to trigger a red designation. Even if the sum of Regulatory Information criteria resulted in a score influence of -61 or below, the reported quality score would be a minimum of 40, yielding a yellow designation. The logic for this is rooted in the assumption that regulatory findings and public reporting can be influenced by many factors and do not have a well-established correlation to product quality, which is defined by its chemical composition. Supporting this is an excerpt from a 2015 White Paper from the FDA Office of Pharmaceutical Quality:²²

“FDA has only limited information about the current state of pharmaceutical quality. FDA has no formal means for quality surveillance, except through inspections

...

Furthermore, inspection findings have not been a reliable predictor of the state of quality.”

Proposed Implementation for Health Systems

The intended use of the proposed quality scores system in an established healthcare system would be to inform and enable pharmacy procurement teams so that decision trees could be enacted. Decision trees could be implemented through healthcare IT systems that standalone or are integrated into the health systems’ existing vender or purchasing system. A proposal of a decision tree utilizing such quality scores in order to purchase primarily green, occasionally yellow after manager review and completely avoid red is proposed for a health system where a robust process exists for

²² Food and Drug Administration (2015). FDA Pharmaceutical Quality Oversight: One Quality Voice. (<https://www.fda.gov/media/91721/download>)

managing drug shortages . Such drug shortage processes may include identification of substitute products, determination of alternative drugs or treatments and other remedies for mitigating or minimizing the impact of a drug shortage. In extreme cases that are reviewed by management, a poorly scoring medication product where there is no alternative could be treated by the health system as a drug shortage instead of purchasing a product designated red. Depending on the healthcare system, it may require a different decision tree and may elect to utilize different criteria, or adopt the same criteria with different degrees of influence on the quality score values.

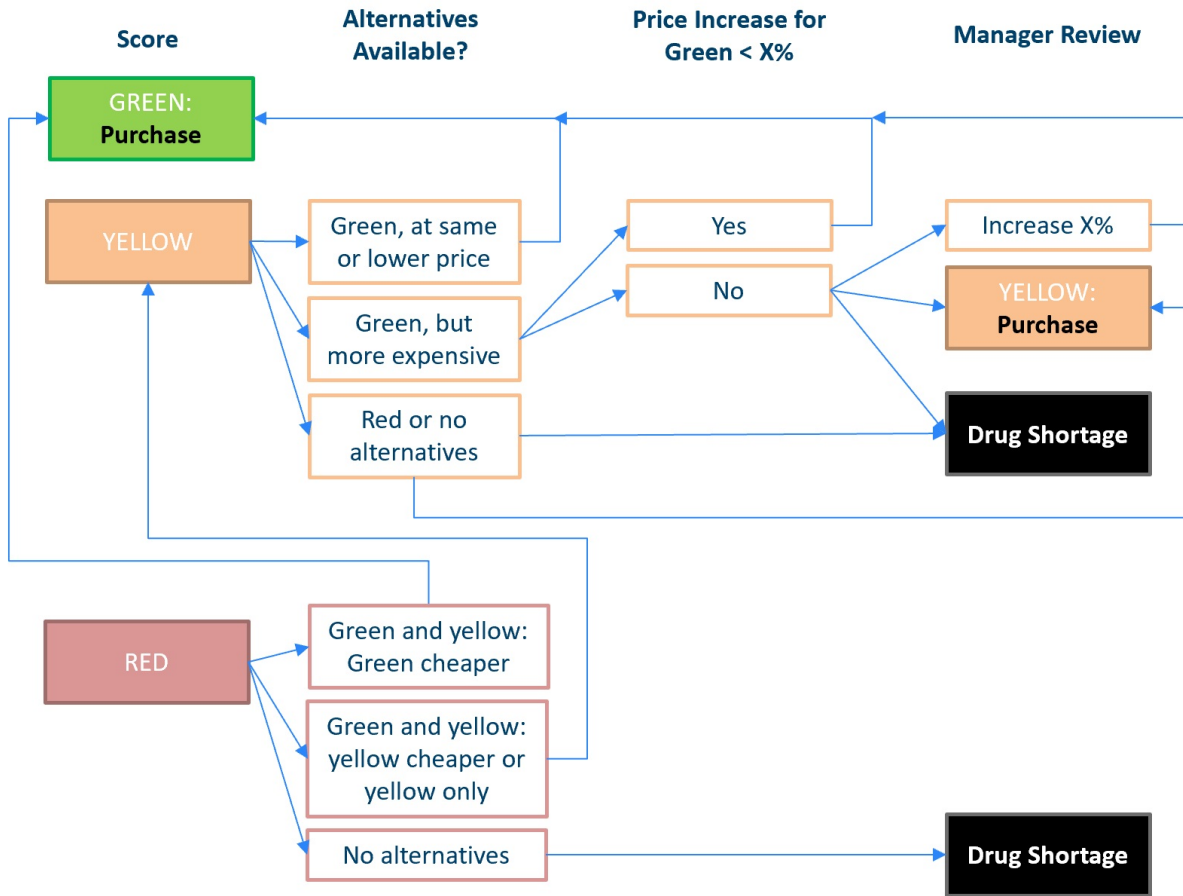


Figure 1. Proposed decision tree implementing red/yellow/green quality score designations. The first column describes the color designation of a drug product that is the default selection for the health system, which then triggers the decision tree.

Results

The angiotensin receptor blocker drug, valsartan, has been subject to heavy scrutiny over quality due to a multitude of recalls after carcinogenic impurities were found.²³ This drug has been selected here for analysis using available data to generate a limited number of quality score criteria which give illustrative examples of how such quality scores can be derived. Regulatory information was gathered by Govzilla and chemical analysis information was acquired from Valisure’s analytical laboratory that is attached to a licensed pharmacy.

Table 4A	Regulatory Information (2017 – 2020)						
	Inspections	Form 483	Warning Letter	Form 483 Ratio	Warning Letter Ratio	Form 483 % Above Global Ratio	Warning Letter % Above Global Ratio
Company A	38	20	0	0.526	0.000		
Company B	6	1	0	0.167	0.000		
Company C	36	24	1	0.667	0.028	26%	
Company D	15	9	1	0.600	0.067	13%	181%
Company E	10	3	0	0.300	0.000		
Company F	53	27	0	0.509	0.000		
Global 3-year	6,967	3,691	257	0.530	0.037		

Table 4B	Chemical Analysis						
	Batches Analyzed	DMF >96ng, <1000ng	DMF >1000ng	NDMA >96ng	Dosage	Dissolution	Ingredients
Company A	6	1	0	1	0	0	0
Company B	2	2	0	0	0	0	0
Company C	9	9	0	0	0	0	0
Company D	7	0	0	0	0	0	0
Company E	7	0	7	0	0	0	0
Company F	2	2	0	0	0	0	0

Table 4. Detailed regulatory information (Table 4A) and chemical analysis information (Table 4B) on available manufacturers of valsartan. Although the names have been deidentified, the data describes real manufacturers of valsartan drug products being currently sold in the United States.

²³ See Food and Drug Administration, *Search List of Recalled Angiotensin II Receptor Blockers (ARBs) Including Valsartan, Losartan and Irbesartan* (<http://bit.ly/3aUIbLF>).

Table 5	Quality Scores						
	Impactful Criteria Findings (Score Influence)						
	Quality Score	% of Batches DMF >96, <1000ng	% of Batches DMF >1000ng	% of Batches NDMA > 96ng	Form 483 >10%	Form 483 >20%	Warning Letters >1.5X
Company A	70			17% (-30)			
Company B	70	100% (-30)					
Company C	40	100% (-30)				26% (-30)	
Company D	80				13% (-10)		1.8X (-10)
Company E	39		100% (-61)				
Company F	70	100% (-30)					

Table 5. Data output for criteria triggering an influence on quality scores and the corresponding numerical influence on the scores denoted in parentheses, regarding current, on-market valsartan drug products from specific manufacturers. The final calculated quality scores are displayed and given their corresponding color designation.

Even with a drug such as valsartan that has had many quality issues, some of which appear to persist, the use of the proposed quality score system is able to identify a supplier that scores a green. Even among potentially mediocre product quality choices, those that appear to perform particularly poorly are identified by a red and can be reasonably avoided.

To further evaluate the impact on pricing by using the proposed quality score system, the relative costs of the valsartan drug products were analyzed across the six companies. Four dosage forms (40mg, 80mg, 160mg and 320mg) were evaluated using pricing from three different distributors and ensuring packaging size was consistent among all companies.

Price vs Quality Score

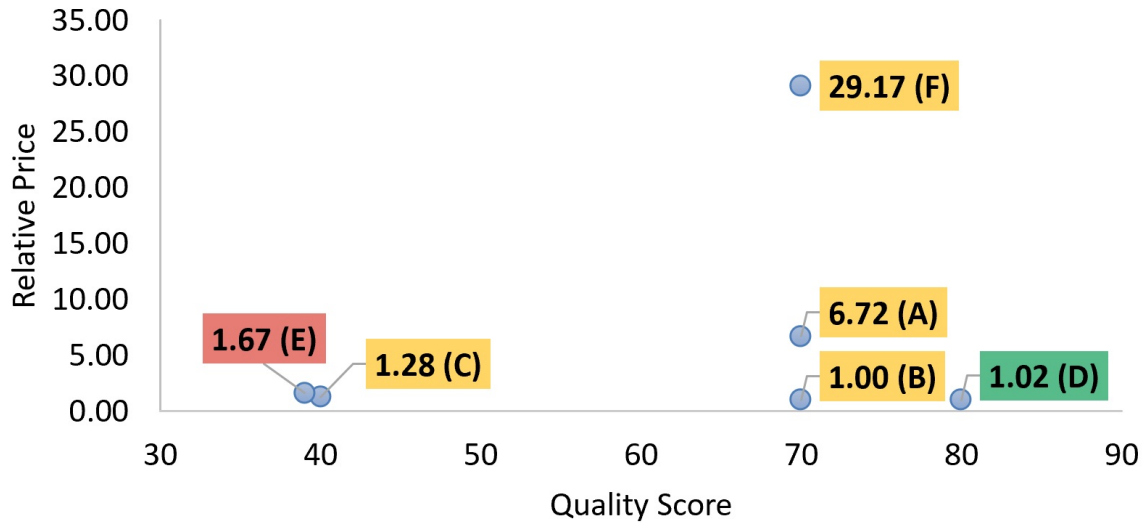


Figure 2. Relative pricing of drug products from companies A – F (denoted in parenthesis) plotted against their quality scores and given their respective red/yellow/green designation.

Although the decision tree in Figure 1 proposes the option of paying more for a higher scoring drug product, the pricing comparison illustrated above suggests that higher quality drug products do not necessarily cost more. Despite continued quality issues with valsartan, the least expensive option had the second-highest quality score, the highest quality score option was only 2% more expensive and the lowest scoring option was 67% more expensive.

Discussion and Conclusion

When originally conceived, generic drug products were assumed to be equal in quality to each other and to the innovator product so the only differentiating feature would be the price paid. This has led to automatic generic substitution laws across the country where patients receive the generic selected by the pharmacy and this could change several times over the patient's course of therapy. The premise that every innovator and generic product is of equal quality is demonstrably false.⁸

With the changing market dynamics that drove pharmaceutical manufacturing offshore and made it very difficult to warrant acceptable quality, a new strategy is needed to ensure patient safety. The use of drugs that are improperly dosed as well as products that don't dissolve properly can put patients at risk of clinical failure or adverse events. The use of products with bacterial contamination, unacceptably high amounts of carcinogens or heavy metals may lead to unintended health problems as a result.²⁴

²⁴ Mathes, RW., et. al. (2008) Relationship between histamine2-receptor antagonist medications and risk of invasive breast cancer. *Cancer Epidemiology Biomarkers & Prevention*, a publication of the

We hope this will be a useful overview and baseline proposal for the use of quality scores for drug products. This is critical for adding much-needed transparency into the American drug supply chain and enabling health system purchasers and payers of medications to avoid low-quality drug products. As the data demonstrates with valsartan, high quality drug products do not necessarily cost more. Thus, even if a health system is unable or uninterested to add any additional purchasing cost or add any potential drug shortage burden, it is highly likely that the use of the proposed quality score system will provide a significant benefit in avoiding low-quality drug products.

Such action taken by established healthcare systems could help protect them from recalls and drug shortages while serving as a significant market driver to incentivize the manufacturing industry to produce quality products. Furthermore, the proposed quality score system could provide regulatory agencies with transparent and rational metrics with which to reward high-scoring manufacturers (e.g. faster ANDA approvals) and/or penalize low-scoring manufacturers (e.g. slower and more scrutinized drug approvals).

Overall, drug quality scores have the potential to improve public health; therefore, their continued development and implementation is highly encouraged.

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- ³ *Statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, F.D.A., Before the Subcommittee on Health Committee on Energy And Commerce, U.S. House of Representatives, Safeguarding Pharmaceutical Supply Chains in a Global Economy 2* (Oct. 30, 2019), available at <https://bit.ly/2SYjqyy>.
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- ¹⁷ Your Medication May Not Be Dissolving Properly (2018). *The Valisure Notebook*. <http://bit.ly/38XVDNm> (accessed March 15, 2020)
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