Poisoned Pills: The Human Cost of Dangerous Foreign Drugs

Hearing before the United States Senate Committee on Aging
June 3rd, 2026

Testimony of Adam Clark-Joseph, Co-Founder and Chief Analytics Officer, Valisure

Chairman Scott, Ranking Member Gillibrand, and Members of the Committee, thank you for the honor of speaking before you today.

I have taken medicine for depression for most of my adult life. I first encountered a bad batch of medicine when I was 25; after a refill, I suddenly fell ill, and my doctor told me that sometimes you just get a bad batch. At 27, it happened again, and I became sick for months. Then at 29, after yet another incident, I used my chemistry background and some equipment in my home to test the pills myself. I found they were massively under-dosed.

That was the last straw. I reached out to my longtime friend, scientist David Light, and together we founded Valisure, America's first laboratory dedicated to independently testing and certifying on-market drug products.

We started Valisure to address drug quality problems, but we didn't initially realize the full scope and severity of those problems. Within a few years, our findings led to the recalls of more than 25 million pharmacy products,[1] worth over $9 billion.[2] We began testing the blockbuster drug Zantac when my infant daughter was prescribed the liquid form; our discovery of the drug's instability sparked its global withdrawal.[3] Our later work drove rolling recalls of sunscreens[4] and hand sanitizers,[5] as well as dozens of national recalls of multiple drugs[6] due to the presence of various carcinogenic contaminants.[7]

Why is the shocking problem of low-quality drugs in America so under-recognized? Bluntly, it's because for 40 years, the former FDA drug leadership has claimed to everyone that all approved drugs are equivalent in quality.[8] This demonstrably false narrative created a market

[1] Felton, Ryan. "Why Is FDA Going After Lab That Found Benzene in Sunscreen?" *Consumer Reports*. March 31, 2022.
[2] Edney, Anna. "FDA Lags Behind Lab That Found Benzene in Dry Shampoos, Sunscreen" *Bloomberg News*. November 9, 2022.
[3] Thomas Katie. "Zantac Products Should Not Be Sold or Used, F.D.A. Warns, Citing Cancer Danger" *The New York Times*. April 1, 2020
[4] Byron, Ellen. "Sunscreen Recall: What to Know as J&J Recalls Some Neutrogena Sprays Over Benzene" *The Wall Street Journal*. July 16, 2021
[5] Ducharme, Jamie. "Scientists Are Finding Out Just How Toxic Your Stuff Is" *TIME Magazine*. May 9, 2024
[6] Edney, Anna. "L'Oreal Recalls Acne Treatment Effaclar Duo in US on Cancer-Linked Benzene" *Bloomberg News*. March 10, 2025
[7] Erman, Michael; Mishra, Manas. "Online pharmacy Valisure says tests show carcinogen in diabetes drug metformin" March 2, 2020
[8] Cenziper, Debbie; Rose, Megan; Roberts, Brandon; Hwang, Irena. "The Secret Gamble at the FDA That Exposed Americans to Risky Drugs" *ProPublica*. June 17, 2025

that competes only on price,[9] which incentivizes cost-cutting, overseas manufacturing,[10] and products made just good enough to minimize regulatory scrutiny, all in the nearly complete absence of independent testing.

When you buy a car, do you just want the cheapest one in its class that claims to be legal to drive on the road? Of course not—yet this is essentially how we are forced to buy drugs.

Recently, the New England Journal of Medicine published an article titled "Substandard Generic Drugs — Threats to Patient Safety and National Security."[11] Its very first recommendation was that "the FDA should stop claiming that all generic drugs sold in the United States are equally safe and effective." Once we acknowledge that not all generics are created equal,[12] we can end the race to the bottom and begin fostering a race to the top.

The FDA currently has a "closer to zero" program for contaminants like lead in baby food.[13] Clearly the same should apply to medications. If one manufacturer's product contains far lower contaminant levels than another's, then shouldn't we prefer the objectively cleaner and safer product, even if neither are so bad they break the law?

In pursuit of exactly this end, the Military, via the Uniformed Services University, began a project with Valisure a few years ago to independently test essential medicines and assign quality-risk scores to classify suppliers as "red," "yellow," or "green".[14,15] By translating complex chemistry into simple "red/yellow/green" quality-risk designations, procurement decisions could easily favor objectively higher-quality manufacturers and avoid lower-quality ones.[16]

Incidentally, tacrolimus, which you just heard about from Mrs. Salberg, is on the Military's essential medicines list, and we found "red"-rated generics because the pills dissolved too quickly. In fact, the FDA received so many complaints that, after 11 years, the FDA completed a clinical study concluding lack of bioequivalence to the brand. Our independent chemical testing effectively reached the same conclusion in weeks instead of years, and identified the root cause mechanism.[17]

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[9] Teasdale, Ben; Light, David; Schulman, Kevin. "Price and Quality in the Generic Pharmaceutical Market" *Circulation*. Volume 145, No. 16. April 18, 2022

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

[11] Schulman, Kevin; Kellerman, Arthur. "Substandard Generic Drugs — Threats to Patient Safety and National Security" *The New England Journal of Medicine*. Volume 394, No. 17. March 18, 2026

[12] Noh, In Joon; Gray, John; et. al. "Are All Generic Drugs Created Equal? An Empirical Analysis of Generic Drug Manufacturing Location and Serious Drug Adverse Events" *Production and Operations Management*. February 6, 2025

[13] Food and Drug Administration. "Closer to Zero: Reducing Childhood Exposure to Contaminants from Foods" January 6, 2025.

[14] Edney, Anna; Griffin, Riley. "Cheap Generic Drugs May Not Be Safe for US Troops" *Bloomberg News*. December 4, 2023

[15] Valisure. "VALISURE SIGNS AGREEMENT WITH DEPARTMENT OF DEFENSE TO INDEPENDENTLY TEST & QUALITY SCORE DRUGS" August 8, 2023

[16] Fletcher, Lisa; Nejman, Andrea; Aaron, Nathan. "Bad drugs could threaten US troops: Inside lab doing groundbreaking tests to address it" *The National News Desk*. May 18, 2026

[17] Cenziper, Debbie; Rose, Megan."After His Kidney Transplant, He Took Tacrolimus From an FDA-Investigated Factory" *ProPublica.* June 23, 2025

More broadly, testing across 25 drugs and 359 suppliers has already shown that 72% of suppliers scored “green,” while 15% scored “red.” There was no correlation between price and quality. Also, on average, higher contaminant levels were found in certain drugs manufactured in India and China than in the same drugs made in the US. Simply buying “green” and avoiding “red” could be transformational[18] for incentivizing quality and American-made medicine. It could also save billions of dollars and thousands of lives.[19]

Kaiser Permanente, which, like both the military and the VA, represents several percent of the US pharmaceutical market, already requires independent testing of certain generic drugs it procures.[20] We know this works at scale.

Representatives Rich McCormick (R-GA-07) and Rosa DeLauro (D-CT-03) will be introducing the bipartisan “Transparency and Quality in Pharmaceuticals Act” to incorporate USU’s chemical quality metrics, and also *independently* derived manufacturing-location metrics, into Military drug procurement. We respectfully ask this Committee to support this legislation. It is our one, singular recommendation, because after over a decade of researching this problem, we strongly believe this is the most impactful solution available.

Thank you again for your engagement on this critical issue and for allowing me to share my story.

Attached to this testimony are the documents outlined below which reinforce many of the central themes and offer greater detail. One common concern that has been raised regarding efforts to reform drug procurement by avoiding lower quality manufacturers is that it could theoretically cause drug shortages and price hikes. This is a logically circular argument given that one of the primary reasons for drug shortages are quality problems, but this theoretical concern has been reviewed with real world data in the attached Circulation article titled "Price and Quality in the Generic Pharmaceutical Market.” This paper found no evidence of volume or price differences when angiotensin receptor blocker drugs (e.g. valsartan, losartan, irbesartan) where recalled due to carcinogenic contamination and ostensibly cleaner versions remained on the market.

- "Substandard Generic Drugs — Threats to Patient Safety and National Security"
- Military Drug Quality Risk Scoring Project Summary
- "Price and Quality in the Generic Pharmaceutical Market"
- "Estimation of Economic and Public Health Burden of Low-Quality Generic Drugs for Chronic Disease and Potential Solutions"

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[18] Tony Sardella, Testimony to Senate Committee on Aging. “Bad Medicine: Closing Loopholes that Kill American Patients” October 8, 2025

[19] Suarez, Victor; et. al. “Estimation of Economic and Public Health Burden of Low-Quality Generic Drugs for Chronic Disease and Potential Solutions” *SSRN*. May 27, 2026

[20] Edney, Anna; Griffin, Riley. “Drug Safety Fears Spur Pentagon Plan to Test Widely Used Medicines” *Bloomberg News*. June 7, 2023 (See “The Kaiser Model”)

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Perspective

Substandard Generic Drugs — Threats to Patient Safety and National Security

Kevin Schulman, M.D.,[1,2] and Arthur L. Kellermann, M.D., M.P.H.[3]

Generic drugs account for more than 90% of prescriptions filled in the United States. The first paragraph on the home page of the Office of Generic Drugs at the Food and Drug Administration (FDA) asserts that "FDA-approved generic drugs have the same high quality, strength, purity and stability as brand-name drugs." On the strength of this assurance, America's doctors, pharmacists, and patients assume that every version of a generic drug is equally safe. But this proposition is now being seriously challenged.

Back in 1984, the Hatch–Waxman Act established an "abbreviated new drug approval" process for generic drugs. This new pathway led to a sharp drop in drug prices. Between 2009 and 2019, the availability of generic medicines saved U.S. patients $2.2 trillion, according to the FDA.

Over time, intense price competition drove most production of generic drugs and ingredients offshore to countries with low labor costs and lax regulatory controls. Once that shift occurred, relentless pressure to minimize costs led some manufacturers to compromise on quality. Rapid globalization also outstripped the FDA's capacity to monitor manufacturers. In 2022, the Government Accountability Office reported that 61% of foreign plants had not been inspected by the FDA in the preceding 5 years.[1]

When FDA inspectors finally reach these plants, some find glaring problems. In 2023, inspectors in India reported that Intas Pharmaceuticals employees had poured acid over quality-assessment documents to keep them from being reviewed. In 2025, an FDA report noted that employees at a Hetero Pharmaceuticals plant destroyed manufacturing documents and stored drug ingredients in an unregistered warehouse where inspectors found birds, lizards, and cats.

More than 60% of generic-drug shortages are attributable to quality concerns, according to the FDA. Shortages are most likely to happen when production is concentrated in a few plants and problems with quality are found at one of them. For example, the Intas Pharmaceuticals plant that failed its 2023 inspection was one of only two suppliers of cisplatin, a vital cancer drug, to the United States. The failure triggered a months-long shortage.

In another instance, a private-

sector laboratory detected high levels of nitrosamines (known carcinogens) in drugs made by several FDA-approved manufacturers, prompting recalls of metformin, angiotensin-receptor blockers, angiotensin-converting–enzyme inhibitors, prazosin, and ranitidine. More recently, independent tests of generic methylphenidate found nitrosamine levels above the FDA's safety threshold in 7 of 15 immediate-release products.[2]

Low-quality drugs can harm patients. Although there was not much interest in this issue when generic drugs were assumed to be high quality, cases of organ failure have been linked to poor-quality immunosuppressive drugs.[3] Recently, a team of U.S. and South Korean researchers with access to FDA data determined that significantly more serious adverse event reports were linked to generic drugs manufactured in India than to equivalent drugs manufactured in the United States.[4]

The fragility of America's global supply chains complicates FDA enforcement. In 2008, a total of 238 deaths in the United States were linked to adulterated Chinese heparin. When the FDA toughened its approach to quality assessment of foreign manufacturers, shortages of more than 200 medications followed. This crisis prompted the FDA to prioritize minimizing drug shortages over ensuring safety. In some instances, overseas companies were allowed to ship shortage drugs to the United States from plants the agency had banned from exporting drugs to the United States. Congress, doctors, and patients were not informed, according to *ProPublica*.

There is a better way to assure the safety of generic drugs. In 1994, the European Medicines Agency (EMA), for example, established a proactive approach involving risk-based surveillance in addition to systematic planned and ad hoc testing of generic drugs both on the market and during routine inspections of manufacturers (in contrast, the FDA does not routinely test generic-drug products themselves, either on the market or during quality inspections of manufacturing plants). EMA testing relies on a network of official medicines control laboratories (OMCLs) that operate in accordance with International Organization for Standardization (ISO) accreditation standards for testing and calibration laboratories. At any point in a drug's life cycle, an OMCL can pull samples for product testing. If they couldn't do so, an OMCL brochure asserts, "patients and users of medicines in Europe could be exposed more often to defective (e.g., contaminated) or falsified and illegal products."

Five actions could leverage market forces to ensure drug safety in the United States. The first is acknowledging the problem. The FDA should stop claiming that all generic drugs sold in the United States are equally safe and effective. It cannot verify this claim without product testing. Moreover, recent budget and personnel cuts may make the agency's oversight of generic-drug quality even more challenging.

Second, to compensate, the FDA can encourage testing of generic-drug quality by independent, ISO-accredited laboratories. Recently, a group of pharmaceutical experts developed a scoring system that translates test results and past regulatory data into a readily interpretable rating scale.[5] Data from an ongoing evaluation of essential medicines for the U.S. Department of Defense illustrate the value of this approach (see table). The FDA could use test results to prioritize its factory inspections and strengthen oversight.

Third, federal agencies, including the Centers for Medicare and Medicaid Services, could purchase drugs on the basis of best value rather than lowest cost. High-quality generic drugs are often available at prices similar to those of low-quality products. Consistent use of only high-quality generic medications could reduce costs by preventing complications and improving outcomes.

Fourth, quality scores could be made transparent to consumers. Kaiser Permanente does not buy certain generic medicines unless they are independently certified by a laboratory of its choice. If drug-quality information were widely available, patients, health systems, and pharmacies would reward high-quality suppliers with contracts and market share. Structurally, transparency would drive the market toward higher quality more quickly and definitively than episodic FDA plant inspections can do.

And fifth, the U.S. government should oversee an effort to rebuild America's capacity to manufacture generic drugs, combining investment in private manufacturing with incentives for purchasing U.S.-made products under the Medicare and Medicaid programs. Currently, the United States is vulnerable to an embargo of essential drugs or the materials required to make them. A recent evaluation for the Department of Health and Human Services found that 87% of sites that make active pharmaceutical ingredients (APIs) and 63% of sites that produce finished dosage forms were located

Quality and Safety Scores of 13 Essential Medicines.*

Medication	Green	Yellow	Red	Total	Primary Concern
Vancomycin	20	0	1	21	Arsenic
Tacrolimus	4	4	4	12	Fast dissolution
Potassium chloride	15	3	4	22	Lead, thallium
Pantoprazole	17	0	4	21	Fast dissolution
Metronidazole	19	0	2	21	Lead, arsenic, lithium
Metoprolol	11	5	2	18	Slow dissolution
Metformin	20	7	3	30	Dimethylformamide
Magnesium sulfate	7	0	0	7	None
Lisinopril	8	0	2	10	Arsenic
Calcium gluconate	4	0	2	6	Lead
Bupropion	17	4	5	26	Fast dissolution
Atorvastatin	11	3	5	19	Lead, arsenic, lithium
Ampicillin	13	1	1	15	Lead
Total no. of products (%)	166 (72.8)	27 (11.8)	35 (15.4)	228 (100)	—

* Shown are results of quality testing of 13 generic medications that are included in the U.S. Department of Defense drug formulary; the tested products were purchased from pharmaceutical wholesalers. The numbers shown are the number of products tested that were assigned to each color category. Overall scores are based on three safety measures (absence of carcinogens, toxic elements, and endotoxins) and two effectiveness measures (proper dosage and rate of dissolution). An expert review panel assigned a quality score (from 0 to 100) to each version of the 13 tested drugs, with a categorical rating of "red" (major quality concerns), "yellow" (quality concerns), or "green" (no quality concerns). Test results for samples rated as red were confirmed by independent analytic laboratories (https://www.valisure.com/valisure-newsroom/ahrmm24-dod-led-pharmaceutical-quality-assessment).[5]

overseas. In 2021, a private holding company bought the only U.S. manufacturing plant licensed for the production of amoxicillin out of bankruptcy. Bringing generics manufacturing back to the United States is in our national interest. Advanced pharmaceutical manufacturing, pioneered by the Medicines for All Institute in Virginia, produces high-quality APIs at lower cost than traditional factory methods. CivicaRx, a not-for-profit generics company, supplies member hospitals by paying high-quality manufacturers a sustainable price under long-term contracts. We believe that both approaches should be more widely embraced.

Most generic drugs are safe, but a troubling minority are not. Testing finished drugs, signing "green" manufacturers to long-term contracts, and sharing quality scores with the public would help realign market forces to improve safety. The United States already tests a wide range of consumer products. We should also test our generic drugs.

Disclosure forms provided by the authors are available at NEJM.org.

[1] Division of Hospital Medicine, School of Medicine, Stanford University, Stanford, CA; [2] Operations, Information, and Technology, Graduate School of Business, Stanford University, Stanford, CA; [3] Department of Emergency Medicine, School of Medicine, Emory University, Atlanta.

This article was published on March 18, 2026, at NEJM.org.

1. Government Accountability Office. Drug safety: FDA should take additional steps to improve its foreign inspection program. January 7, 2022 (https://www.gao.gov/products/gao-22-103611).
2. Narayan A, Teasdale B, Hudspeth AJ, Light DY, Nailor JK, Schulman K. The price and quality of methylphenidate products. J Am Acad Child Adolesc Psychiatry 2025 May 15 (Epub ahead of print).
3. Cenziper D, Rose M. His kidney failed: he'll never know if a transplant drug from a banned factory was to blame. ProPublica. June 23, 2025 (https://www.propublica.org/article/fda-tacrolimus-kidney-transplant-patient).
4. Noh J, Gray J, Ball G, et al. Are all generic drugs created equal? An empirical analysis of generic drug manufacturing location and serious drug adverse events. Prod Ops Mgmt 2025; 34:2601-17 (https://journals.sagepub.com/doi/10.1177/10591478251319691).
5. Dabestani A, Grossman S, Nathan JP, et al. A data-driven quality-score system for rating drug products and its implications for the health care industry. J Am Pharm Assoc (2003) 2023;63:501-6.

DOI: 10.1056/NEJMp2518256

Drug Quality Scoring (PhaSQ) Project Summary of First 25 Essential Medicines

Prepared by Valisure, June 1, 2026

Key Points / BLUF

Independent testing of 359 suppliers of 25 essential medicines found that most are low-risk / "green"-rated (72%) while a minority are high-risk / "red"-rated (15%). Quality appears to correlate with location, and there appears to be no correlation between quality and price. Incorporating drug quality scores into federal purchasing could be transformative for incentivizing quality and American-made medicines without increasing costs or causing shortages.

Background Summary

Public health and national security are threatened by record numbers of drug shortages that are primarily caused by manufacturer quality problems, ~80% of US drugs originating from China or India, and growing evidence of problems with generic drug quality and safety. Estimates suggest that the lowest quality 10% of generic drugs lead to over $18 billion in avoidable public health costs annually. In 2012, FDA identified that the root cause of drug supply problems is "the inability of the [generic drug] market to observe and reward quality." Recent analyses and Congressional hearings have reached the same conclusion. Currently, large health systems like Kaiser Permanente are leading the way in finding solutions and are already using data from this project for millions of patients.

This project aims to serve as a model for the nation by attaching drug quality risk scores to national drug codes (NDCs) used by all U.S. drug purchasers and payors. This is not intended to measure clinical effectiveness or FDA / regulatory compliance, but instead to create transparency to objective quality metrics to guide purchasing. Initial data suggests that quality metrics correlate with the location of manufacturing for final dosage forms (FDF), active pharmaceutical ingredients (API), and key starting materials (KSM), with highest quality in the USA and lowest in India and China.

Analytical Summary of First 25 Drugs

A combination of "safety" (carcinogens, toxic elements, endotoxins) and "effectiveness" (dosage, dissolution) analytical tests were performed on products from all available suppliers of the listed drugs purchased from various private-market wholesalers. Samples with results suspected of a "red" designation were secondary tested at a network of commercial and analytical laboratories. The primary and secondary data was reviewed by the Expert Review Panel, and they established a scoring framework to assign "red," "yellow," or "green" designations based on the JAPhA paper "Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems" (the Panel members are all co-authors of this paper). Below are summary results from scoring the aggregate available 359 private-market suppliers of the initial 25 drugs (some overlap of suppliers exist between drugs, but each supplier of each drug is scored independently):

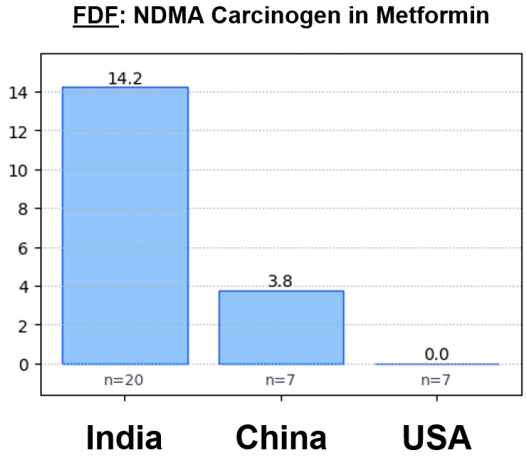
Drug	Green	Yellow	Red	Primary Reason for "Reds"
Metformin	17	8	6	Carcinogen: "DMF"
Lisinopril	8	0	2	Toxin: Arsenic
Potassium	15	3	4	Toxins: Lead, Thallium
Metoprolol	11	5	2	Slow Dissolution
Magnesium Sulfate	7	0	0	N/A
Tacrolimus	5	3	4	Fast Dissolution
Ampicillin	13	1	1	Toxin: Lead
Atorvastatin	11	3	5	Toxins: Lead, Arsenic, Lithium
Ca Gluconate	4	0	2	Toxin: Lead
Vancomycin	20	0	1	Toxin: Arsenic
Bupropion	17	4	5	Fast Dissolution
Metronidazole	19	0	2	Toxins: Lead, Arsenic, Lithium
Pantoprazole	17	0	4	Fast Dissolution

Drug	Green	Yellow	Red	Primary Reason for "Reds"
Dextrose	4	0	0	N/A
Norepinephrine	10	1	0	N/A
Atropine	8	1	0	N/A
Furosemide	17	7	3	Carcinogen: Nitrosamine, Slow Dissolution, Talc
Amlodipine	16	0	0	N/A
Duloxetine	1	2	5	Carcinogen: Nitrosamine, Fast Dissolution, Talc
Sodium Bicarbonate	5	0	2	Toxins: Arsenic, Particulates
Amiodarone	8	1	1	Fast Dissolution
Epinephrine	3	0	0	N/A
Sodium Phosphate	7	2	2	Toxins: Arsenic
Phenylephrine	10	1	3	Toxins: Arsenic
Trazodone	6	3	1	Fast Dissolution
TOTAL %	**72%**	**13%**	**15%**	

Valisure PI: David Light (david.light@valisure.com)

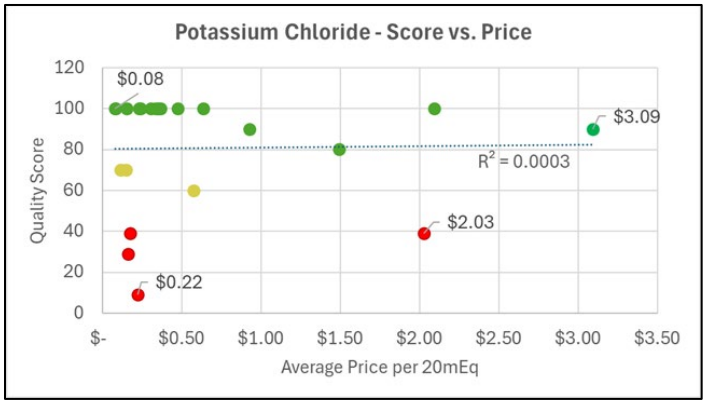
Manufacturing Location Correlates with Quality

To investigate any relationship between manufacturing location and quality metrics, researchers at Ohio State University have been collaborating with this project and merging the chemical quality data with their own data on manufacturing location. Key initial results from a detailed analysis on metformin data are summarized below:



No Correlation between Price & Quality

A comparison of Valisure's actual purchase price to the quality risk score for potassium chloride drugs was conducted and results shown below. In summary, there was no correlation between price and the quality risk scores – high quality drugs are available at low prices. This conclusion mirrors the results from 3 recent, peer-reviewed studies on the analysis of metformin, methylphenidate, and angiotensin receptor blockers, linked below.



Journal of the American Heart Association (2022): Price and Quality in the Generic Pharmaceutical Market

American Journal of Managed Care (2024): Safety vs Price in the Generic Drug Market: Metformin

Journal of the American Academy of Child & Adolescent Psychiatry (2025): The Price and Quality of Methylphenidate Products

Potential Utility Example

Based on the Military's 30mg lisinopril formulary, below is a model for potentially reforming purchasing of essential medicines according to "best value" practices instead of the current status quo of "lowest cost technically acceptable."

	Status Quo		"Best Value" Contracting				
Supplier	FDA-Approved	Price[c]	Quality Score	Manufacturer Location[a]	Independent Certification[b]	Final Score	Price[c]
Labeler 1	Yes	$6.57	100	USA	Yes (+10)	110	$6.57
Labeler 2	Yes	$6.24	100	USA	No	100	$6.24
Labeler 3	Yes	$6.90	100	India (-30)	No	70	$6.90
Labeler 4	Yes	$6.37	100	India (-30)	No	70	$6.37
Labeler 5	Yes	$6.77	90	China (-61)	No	29	$6.77
Labeler 6	Yes	$19.71	39	Taiwan	No	39	$19.71
Labeler 7	Yes	$6.04	39	China (-61)	No	-22	$6.04
Labeler 8	Yes	$7.10	39	China (-61)	No	-22	$7.10

Example Based on Current Data and DoD formulary for 30mg lisinopril

- **Best value:** save money, improve quality, buy American
- Potentially most purchased currently
- Cheapest

[a] *Currently based on manufacturer headquarters location and public records*

[b] *Labeler generally engages in independent certification*

[c] *Pricing model centered on private market average for 100-count bottle*

Valisure PI: David Light (david.light@valisure.com)

Circulation

PERSPECTIVE

Price and Quality in the Generic Pharmaceutical Market

Ben Teasdale, MPhil; David Light, BS; Kevin A. Schulman, MD

Branded medications dominated the prescription market in the 1980s, constituting 81% of fills in the United States. A majority lacked generic equivalents even after patent expiry. In 1984, the Hatch—Waxman Act eased the regulatory burdens of generic approval, radically changing the prescription landscape. Today, generic prescriptions account for 90% of new prescriptions and have saved patients an estimated $1.5 trillion.[1]

Although a significant economic advantage for consumers, generic medications are only a benefit to the extent that they provide the same quality product for patients as their branded counterparts. Currently, the market relies on Food and Drug Administration (FDA) review and inspections of manufacturers' quality management processes to assure drug quality. This approach has become increasingly strained during this period of rapid expansion of the generic market.

Concern about the quality of generics is a well-documented issue for cardiology. The sale of adulterated heparin in 2008 resulted in 149 deaths and many more severe adverse reactions, leading to large-scale recalls by Baxter. In 2010, the FDA determined that the majority of the 4 million nitroglycerin prescriptions dispensed the year before had not been approved for sale in the United States.

Recently, generic angiotensin II receptor blockers (ARBs) were found to contain carcinogenic N-nitrosamine impurities, which, beginning in 2018, led to a series of recalls of manufacturing lots of valsartan, losartan, and irbesartan. Unfortunately, concerns about manufacturing quality persist worldwide given the globalization of the supply chain. Health Canada led a new round of recalls in 2021 over elevated levels of mutagenic azido impurities in ARBs, and there were similar recalls in the United Kingdom and Europe.

The FDA estimated that 8000 people would have to be consistently exposed to the highest dose of contaminated valsartan for 4 years before any 1 person developed new cancer. The European Medicines Agency, taking a more conservative approach, estimated the ratio to be closer to 1 in 3000.[2] Since 2018, the FDA has reported recall of at least 12 million bottles of ARBs. Assuming each of these bottles was contaminated, this supply could have caused 31 to 83 cancers.

The cases of heparin, nitroglycerin, and ARBs represent the most publicized cases of quality control issues in the generic drug market. Fortunately, there is no indication that these events signal widespread concerns of substandard quality. Carcinogenic risk appears low relative to the known mortality benefits of these medications; however, these quality issues are preventable, and the truth is that we do not know how representative they are.

The generic medication market evolved to deliver low-cost products as its major focus. Despite the maturity of organizations within the supply chain, the issue of quality in the United States has been sidelined, delegated to the FDA alone, who focus their oversight on manufacturers. Beyond the manufacturer level, the distributors, wholesalers, retailers, and pharmacy benefit managers who profit off the sale of pharmaceuticals lack any corresponding accountability for the quality of the products they sell.

Manufacturers of generic drugs must demonstrate to the FDA that their products are bioequivalent to

Key Words: Food and Drug Administration ■ generic drugs ■ pharmaceutical industry ■ pharmaceutical economics ■ quality of health care

Correspondence to: Kevin A. Schulman, MD, Clinical Excellence Research Center, Center for Academic Medicine, 453 Quarry Rd., #117B, Palo Alto, CA 94304. Email kevin.schulman@stanford.edu

For Sources of Funding and Disclosures, see page 1186.

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the brand medication, that they meet certain labeling requirements, and that the manufacturers have certain manufacturing capabilities and quality processes. Once multiple generic manufacturers gain FDA approval, variation in medication quality becomes invisible to purchasers throughout the supply chain, and manufacturers compete to gain market share solely by offering lower prices. Manufacturers thus respond to a market where price, not quality, is the only observable characteristic of a product. The FDA has shared this perspective, testifying in 2019 on the maturity of quality management systems, "The market currently has no visibility into manufacturing facilities' quality."[3]

One of the factors straining the ability of the FDA to keep up with quality oversight of generic products has been the rapid globalization of the supply chain during the last 2 decades. By 2020, 74% of establishments manufacturing active ingredients were located oversees.[4] The FDA, a US government agency, must now oversee a global market where it does not have direct jurisdiction. This results in bureaucratic barriers to performing effective site visits. For example, inspection of foreign facilities requires visa applications and prior announcements of inspection dates, allowing these facilities to better prepare for inspections. The FDA relies on self-reported quality data from manufacturers, even in environments where veracity of data has been questioned. Further, the FDA does not perform routine testing at the product level. Although the FDA does investigate products when it has suspicion, there is currently no systematic exploration of product quality that would raise this suspicion.

The role of the FDA has been further complicated by the COVID-19 pandemic. Since March 2020, the FDA has been forced to limit itself to only "mission-critical" inspections of foreign manufacturers, with 3 inspections reported in the last 9 months of 2020.[4] The FDA now faces a backlog of surveillance inspections, and it was projected that 43% of foreign facilities would not have been inspected in 5 years by the end of 2021.

In essence, we have a market focused on price, with quality assurance relegated to the FDA's review of an initial application, manufacturer-provided data, and increasingly difficult site inspections, all in the absence of systematic quality surveillance by the purchasers of medication.

An open question is whether the presence of quality issues is an inherent tradeoff in a market that provides access to low-cost medications. To test this question, we examined the impact of product recalls on price and volume for ARBs (which were impacted by recalls) and angiotensin-converting enzyme (ACE) inhibitors (which were not impacted by recalls) for the period between the first quarter of 2018 through the first quarter of 2021 using prescription data from the Medicaid State Medication Utilization Database.[5] Overall, we found that recalls did not impact unit price or access for ARBs compared with ACE inhibitors, with prices increasing more for ACE inhibitors than ARBs during this period (13% and 7%, respectively). Meanwhile, the rate of use of ARBs increased relative to ACE inhibitors, with fills for ARBs increasing 156% and fills for ACE inhibitors increasing 64%.

Overall, these data suggest that we do not have to sacrifice quality for low costs, because prices did not increase disproportionately after removing poor-quality products from this market. If this is the case, why should we tolerate a generic drug market that looks solely at price and not at quality, given the quality concerns we reviewed in the cardiology market?

It's easy to imagine a market where quality factors into purchasing decisions. Just because the generic market is regulated does not mean that the supply chain should defer all quality assessments to FDA inspections and data reported from manufacturers testing their own product. Quality could also be monitored and assured from periodic testing of products independently sampled at later stages of the medication supply chain. Consumers could be protected by providing a transparent medication quality score that wholesalers, distributors, retailers, and consumers could check when making purchase decisions.

Ultimately, the healthcare system needs a supply chain that is accountable to quality. Our analysis suggests that higher-quality products are already available for the same price, but we lack a reliable mechanism for identifying these products. If we prescribe an ARB to help treat a patient with heart failure, it's not a clinical or economic advantage to use a $0.50 pill of poor quality when a better alternative is already available.

ARTICLE INFORMATION

Affiliations

Clinical Excellence Research Center, School of Medicine (B.T., K.A.S.), and Graduate School of Business (K.A.S.), Stanford University, Palo Alto, CA. Valisure, LLC, New Haven, CT (D.L.).

Sources of Funding

None.

Disclosures

David Light is Chief Executive Officer, board member, and equity holder in Valisure, a pharmaceutical testing firm. Dr Schulman has received grants from the National Basketball Association, Inc; and personal fees from HealthQuest, Motley Rice, Frazier Healthcare Partners, ISMIE Mutual Insurance Company, and all unrelated to this article. In addition, Dr Schulman is a board member and shareholder for Grid Therapeutics; managing director and shareholder in Faculty Connection, LLC; on the board of advisors for and shareholder in Prealize; a board member and shareholder in Reserve Therapeutics (Pharmaceutical Services Company); passive investor in Altitude Ventures Inc. and Excelerate Health Ventures; senior associate editor for Health Services Research; President of the Business School Alliance for Health Management (uncompensated),

an advisory board member for CivicaRx (uncompensated); and a board member for Catalysis (uncompensated), outside of the submitted work. B. Teasdale reports no conflicts.

REFERENCES

1. Thayer AM. 30 years of generics. *Chemical & Engineering News*. 2014;92(39). Accessed October 21, 2021. https://cen.acs.org/articles/92/i39/30-Years-Generics.html
2. Committee for Medicinal Products for Human Use. Assessment report: angiotensin-II-receptor antagonists (sartans) containing a tetrazole group. European Medicines Agency. Published February 14, 2019. Accessed October 11, 2021. https://www.ema.europa.eu/en/documents/variation-report/angiotensin-ii-receptor-antagonists-sartans-article-31-referral-chmp-assessment-report_en.pdf
3. Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program, Testimony Before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations (2019) (testimony of Janet Woodcock, MD, Director, Center for Drug Evaluation and Research). Accessed October 21, 2021. https://www.fda.gov/news-events/congressional-testimony/securing-us-drug-supply-chain-oversight-fdas-foreign-inspection-program-12102019
4. *Testimony before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, Committee on Appropriations, House of Representatives: Drug Safety: FDA's Future Inspection Plans Need to Address Issues Presented by COVID-19 Backlog* (2021) (statement of Mary Denigan-Macauley, Director, Health Care). GAO-21-409T. Accessed October 21, 2021. https://www.gao.gov/products/gao-21-409t
5. Medicaid. State Drug Utilization Data. Centers for Medicare & Medicaid Services. Accessed October 3, 2021. https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html

Estimation of Economic and Public Health Burden of Low-Quality Generic Drugs for Chronic Disease and Potential Solutions

Victor Suarez, MS, CMRP[1]; Carl W. Bazil, MD, PhD[2]; Christopher G. Bunick, MD, PhD[3]; Peter C. Butler, MD[4]; Adam Clark-Joseph, PhD[5]; Ryan C. Costantino, MS, PharmD, BCPS[6]; Steven Gong, BS, BA, BA[7], Joe Graedon, MS[8], John Gray, PhD, MBA[9]; Tracey Pérez Koehlmoos, PhD[1]; Harry Lever, MD[10], Xinyu Liang, PhD[11]; Robert Makuch, PhD[12]; Darin T. Okuda, MD[13,14]; Suzanne Robotti[15]; Lisa Salberg[16]; Jordan Shlain, MD[17]; C. Michael White, PharmD, FCP, FCCP, FASHP[18]; Kenny Yu, PharmD, MBA[19]; David Y. Light, BSc[12,20] Kevin A. Schulman, MD[6,21]

1 Uniformed Services University of the Health Sciences, Bethesda, Maryland
2 Columbia University Medical Center, New York City, NY
3 Department of Dermatology and Program in Translational Biomedicine, Yale School of Medicine, New Haven, CT
4 Larry L. Hillblom Islet Research Center, David Geffen School of Medicine at UCLA, LA, CA
5 Valisure, New Haven, CT
6 USA MEDCOM Pharmacy Service Line, Defense Health Agency, San Antonio, TX
7 Clinical Excellence Research Center, Department of Medicine, Stanford University, Stanford, California
8 People's Pharmacy, Durham, NC
9 Fisher College of Business, The Ohio State University, Columbus, OH
10 Hypertrophic Cardiomyopathy Center, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH
11 Technology and Operations Management, INSEAD, Singapore, Singapore
12 Department of Biostatistics, Yale School of Public Health, Yale School of Medicine, New Haven, CT
13 Department of Neurology, Neuroinnovation Program, Multiple Sclerosis & Neuroimmunology Imaging Program, The University of Texas Southwestern Medical Center, Dallas, TX
14 Peter O'Donnell Jr. Brain Institute, The University of Texas Southwestern Medical Center, Dallas, TX
15 MedShadow Foundation, New York, NY
16 Hypertrophic Cardiomyopathy Association, Denville, NJ
17 Private Medical, San Francisco, CA
18 University of Connecticut School of Pharmacy, Storrs, CT
19 Department of Pharmacy, Mount Sinai Health System, New York, NY
20 Long Island University Pharmacy, Brooklyn, NY
21 Graduate School of Business, Stanford University, Stanford, California

Abstract:

Objective

Conservatively quantify the public health and economic damages of low-quality generic drugs on chronic disease management in the United States based on available studies, and review health system solutions to avoid low-quality and incentivize high-quality generics.

Data Sources

Generic drug quality is an evolving but sparse field of research; therefore, the expertise of 21 experts with experience in the field were relied upon to identify meaningful areas of existing research within chronic disease, where medication issues are expected to be most pronounced due to longevity and persistence of treatment. Four diseases (epilepsy, multiple sclerosis, atherosclerosis, and hypertension) were chosen by the group due to the relative abundance of informative studies and the diversity of the diseases. A chronological review of published health system solutions was also performed.

Data Synthesis / Results

Extrapolating from studies in these four chronic diseases and focusing on the most directly observable 10% low-quality generic drugs, we conservatively estimate the 2024 economic burden of this low-quality subset of generic drugs at $18.4 billion growing to $238 billion over the next 10 years if not addressed, largely due to many thousands of avoidable serious adverse events like disease relapse and hospitalizations. Potential solutions are discussed that may enable a market correction to avoid the low-quality generic drugs and incentivize continuous product improvement.

Conclusion and Relevance

This novel review represents the first broad population analysis of the substantial economic and public health impact from low-quality generic drugs and synthesizes modern approaches to addressing this largely underappreciated issue. Real-world approaches are reviewed where pharmacy practice can be modified to help ensure only the highest-quality generics are dispensed to patients to improve outcomes and reduce waste.

Introduction:

Generic drugs are a critical component of healthcare delivery in the U.S., saving billions of dollars for the American public by offering lower-cost alternatives to innovator drug products [1]. Generic drugs are FDA-approved through an abbreviated new drug application, where the FDA reviews data provided by manufacturers to demonstrate bioequivalence. The FDA does not routinely test the actual generic drug products before approval or once they are on the market [2]. Over the last several years, there has been growing concern surrounding the chemical quality of a subset of these generic drugs and

the possibility of “low-quality generics” being less effective for, and potentially harmful to, patients [3] [4] [5] [6].

Since the passage of the Drug Price Competition and Patent Term Restoration Act in 1984, which created the generic drug industry, generic drugs grew from roughly 14% of all U.S. prescriptions to currently over 90%, [7] drug shortages in the U.S. have increased substantially over the last decade, with manufacturer quality problems being a major driver, [8] and roughly three drug recalls per day occur in the U.S., often related to carcinogenic impurities [9] or metrics of effectiveness [10].

While always a global industry, the manufacturing of these critical products and their ingredients has largely moved overseas, primarily to India and China [11] [12]. Since 2009, the Government Accountability Office has considered the FDA’s oversight of medical products as “high risk” [13] with increased concern due to COVID-19 complications [14] and continued challenges [15], especially with foreign inspections [16], even years after the pandemic [17]. Furthermore, new research has shown that such foreign manufactured generic drugs appear to be associated with significantly more serious adverse events compared to domestically manufactured versions of the same drug [18]. Together, the global nature of the generic drug supply chain and the concerns over poor product and supply chain quality are increasingly being considered serious concerns to both public health and national security [19] [20] [21].

Many misconceptions exist about the regulation of drugs in the U.S. which may have historically led to an underappreciation of the scope and impact of low-quality generic products [22]. Physicians’ misconceptions were illustrated in a national survey where 78% of respondents identified the role of the FDA was to “Remove a drug from market if unexpected risks are detected,” [23] a function that the FDA lacks due to not possessing mandatory recall power over drug products (FDA can only recommend voluntary product recalls [24]). In the same survey, 40% of physician respondents believed “testing drugs” constituted a substantive function of the FDA. However, since the 1960s, the FDA largely abandoned analytical testing of drugs in favor of a facility inspection program to review manufacturer compliance with Good Manufacturing Practices (GMP) and relying on the manufacturers’ self-reporting of their own analytical tests [25]. Currently, the FDA tests only a few dozen on-market drug products per year when they are flagged for specific cause [26]. Even when products were tested due to quality concerns, the FDA failed to identify some of the most significant chemical drug quality problems in recent years, including with ranitidine (Zantac), metformin, valsartan and losartan. It was only through independent testing by third parties that product contamination with potent carcinogens were identified leading to recalls and market withdrawals [25].

Generic drug quality problems are perpetuated and exacerbated by the structure of the supply chain serving the generic drug market that purchases only the lowest price products, with all product quality assumed to be equal given FDA oversight and review [27] [28]. In 2012, a senior FDA official co-authored a paper on drug shortages which concluded

“The fundamental problem we identify is the inability of the market to observe and reward quality [29].” Following the COVID-19 pandemic, the U.S. Administration for Strategic Preparedness and Response (ASPR) recommended in a 2022 report that the U.S. government should leverage its collective buying power to reform procurement protocols and revise purchasing models to increase emphasis on product quality and supply chain resilience, not simply lowest cost [30]. In a recent Senate Finance Committee hearing on drug shortages, Senator Mike Crapo summarized the expert witness testimonies by stating “Every one of you has made the point that one of the big problems here is that we don't compensate for quality, we compensate for price of product only” [31].

One issue omitted from this discussion, and from previous analyses of multi-billion-dollar failures in care delivery [32], is the clinical and economic harm from poor quality generic drugs. Given the lack of systematic assessment of product quality, it is difficult to quantify the downstream impact of low-quality products. However, recent research has begun to shed light on this issue. We review four case studies of the economic impact of low-quality generic drugs. Based on these studies, we begin to extrapolate the economic impact of low-quality generic drugs on the US healthcare system and their potential harm to patients.

Evidence Review:

We identified four disease categories that had extant literature on generic drug quality: epilepsy, multiple sclerosis (MS), atherosclerotic cardiovascular disease (ASCVD), and hypertension. For each of these conditions, we reviewed the available literature related to the economics of generic drug quality in the context of potential harm to public health.

For all these studies, the prevalence of poor-quality generic drugs in the market is unknown. However, reports exist in press and academic literature roughly estimating the prevalence of clearly identifiable, low-quality generic drugs at 10% [25] [33]. The Department of Defense has initiated a research program where all available generic drug products were procured, tested and quality risk scored. The results for the first thirteen essential medicines published in the New England Journal of Medicine found 15.4% of the 228 evaluated drug products received the lowest quality rating of a “red” [34]. For our analyses here, we make the conservative assumption of the lesser of the observed values of 10% objectively low-quality generics that can be focused on for our study. We also assume no disproportionately higher impact of the lowest quality 10% of generics for the overall additional burden from generics use and further assume that only this bottom 10% are most immediately addressable by corrective measures.

For epilepsy, there exists a particularly large body of epidemiological evidence supporting substantial economic and patient harm from low-quality generic drugs. Retrospective population studies have been conducted broadly on generic drug use in epilepsy [35] along with the use of specific generic drugs [36], on switching between brand to generics [37],

the switching between generic-to-generic manufacturer of the same drugs [38], and batch-to-batch variability in the same generic [39]. We were unable to identify any published studies on the chemical testing of different anti-epileptic drugs.

To enable an estimation on public health impact, the following approximate U.S. statistics were incorporated into the calculations outlined in Table 1: existence of 3,356,000 epileptic patients [40], 90% of which use medications [41] and 86% of which are generics [42]. Combined with the estimated rate of most identifiable, low-quality generics being 10% and a total additional cost burden for patients taking generics of $3,254 [37], the estimated annual economic burden of these 10% low-quality generics is $845 million, which is approximately 3.02% of the total economic burden of epilepsy [43]. Applying these assumptions to observed higher rates of healthcare utilization in generic epilepsy medication users versus brand users [35], the 10% low-quality generics lead to approximately 20,780 avoidable hospitalizations for epilepsy patients.

For MS, clear evidence exists demonstrating direct harm to a handful of individuals from their generic disease modifying therapies that were chemically tested to reveal evidence of low-quality in the form of subpotent dosage. Two studies by Okuda et al. examined patients who were switched as a result of directed treatment transitions by third-party administrators from brand to generic versions of either fingolimod or teriflunomide. The individuals described in these reports experienced incontrovertible evidence of a relapse of their otherwise well-controlled MS, and a high number of randomly selected samples of their generic medications were tested revealing dosage levels below the minimum regulatory standard of 90% content of the labelled ingredient in the majority of samples [44] [45]. Of the eight generic MS medications from eight different manufacturers tested across the two studies, three contained dosage levels below 90% and one was at risk of failure with an average dosage of 91% (standard deviation of 3%). Exposure to subpotent fingolimod was also associated with higher absolute lymphocyte counts, suggesting clear differences in the biological effect of the generic version. Furthermore, the resultant variable release of immune cells from lymphatic tissue may have placed patients with MS at greater risk for a relapse. Although these results suggest an approximate 38 – 50% prevalence of particularly low-quality generics in MS treatment, larger studies are needed to better understand a more exact estimate.

Relapse rates for MS can be difficult to quantify as the reporting of such events vary [46] and published studies reveal a broad range of annualized relapse rates with values of 5% [47] to 35-36% in individual studies [48] [49]. Conservatively assuming that 10% of generic disease modifying therapies for MS are of identifiably low quality, and approximately 44% of those induce a relapse due to subpotent dosage, then in combination with an approximate of 69% of MS patients using medications [50], and 90% of which are generic [7], the estimated relapse rate would be roughly 2.73%, or about 24,972 avoidable MS relapses annually. When further considering U.S. statistic on MS of 913,925 patients [51] and an average healthcare cost of an MS relapse to be $23,970 [52], then the estimated

conservative annual economic burden of these low-quality generics is $599 million, which is approximately 0.70% of the total economic burden of MS [53].

For ASCVD, there exists study of not only additional economic burden and poorer clinical outcomes with generic drug use versus brand, but furthermore different prevalence of these factors is observed for different generic manufacturers. A study by Liang et. al. investigates brand Lipitor versus generic atorvastatin use, the most prescribed statin and treatment for ASCVD, and finds that generics use is associated with higher healthcare costs and poorer clinical outcomes, specifically a significantly smaller reduction in LDL-cholesterol levels compared to brand-name drugs. These associations are more severe for standard generic manufacturers than for authorized generic manufacturers, which are licensed to replicate the proprietary formulation of the brand version [54]. Leveraging Liang et. al. study's conclusion of approximately $429 higher medical service costs for generic atorvastatin users and the U.S. statistics of 18,700,000 ASCVD patients, 47.8% taking the common statins of atorvastatin or rosuvastatin [55], 95% of which are generic (data from atorvastatin and assumed consistent for rosuvastatin) [54] together with assuming 10% identifiable, low-quality generics prevalence, then the estimated annual economic burden of these low-quality generics for treating ASCVD is $364 million or approximately 0.18% of the total economic burden of ASCVD in 2023 [56]. From a public health perspective, these 10% low-quality generics lead to approximately 200,403 avoidable outpatient visits for ASCVD patients.

For hypertension, striking examples exist of unambiguously low-quality generic versions of key medicines with the discovery of carcinogenic contaminants traced to manufacturing practices [57]. The FDA has estimated that the contamination in the angiotensin receptor blocker (ARB) valsartan may lead to one additional cancer case in 8000 exposed patients [58], and there is some epidemiological evidence of increased hepatic cancer risk from contaminated valsartan [59]. This serves as evidence of clear differences in manufacturing quality of generic drug products but is not quantified in our analysis of reduced clinical effectiveness of disease treatment and related adverse events. In hypertension drugs, there is evidence in other Western nations of higher rates of adverse events after multiple anti-hypertensive drugs went generic [60] [61], and higher rates of hospitalizations with the use of generic valsartan versus the brand [62]; however, no economic burden analyses are known to have been conducted nor direct testing of generic drugs for properties known to impact effectiveness.

Of use here are numerous studies in hypertension that have established a strong correlation of blood pressure to serious adverse events like stroke, cardiovascular disease, and heart attacks [63] [64], and furthermore the detrimental effect of high variability in blood pressure on these same outcomes [65]. There is clear evidence of variations in the manufacturing quality of hypertension medications. If the assumption is made that of the 10% of these generics that are identifiably the lowest quality have a similar rate as with MS (44%) of leading to the adverse clinical outcome of high variability in blood pressure which is correlated to a 0.500% higher rate of coronary heart disease,

0.046% higher rate of stroke and 0.056% higher rate of heart attack, then in combination with the U.S. statistics of a cost burden of $13,000, $35,000 [66] and $18,300 [67] per condition respectively, 119,900,000 hypertensive patients, 79% of which taking medications [68] that are 90% generic [7], the estimated annual economic burden of the 10% low-quality generics for treating hypertension is $344 million or approximately 0.16% of the total economic burden of hypertension in 2019 [68]. This is a similar value to that calculated for ASCVD where an estimate of total economic burden of generics was available. From an adverse event perspective, these calculations suggest that the 10% low-quality generics for the treatment of hypertension contribute to 2,111 heart attacks, 1,736 strokes, and 18,790 cases of coronary heart disease, all of which could be avoidable if these were replaced with high-quality generics.

National Impact:

To estimate the overall national burden of the estimated 10% low-quality generics that are most readily identifiable and potentially avoidable, a weighted average of the calculated effects across the four chronic diseases was used to produce an estimation on the impact broadly on chronic disease. This weighted average of 0.40% is applied to the estimated 2024 economic burden of total chronic disease in the U.S. of $4.54 trillion [69] [70], resulting in an estimate for the annual economic burden of these low-quality generics on chronic disease in the U.S. of approximately $18.4 billion. Assuming a 5.6% growth rate of healthcare costs [71] and a stable percentage of it being attributable to chronic disease, the cost of the roughly 10% lowest quality generic drugs in the U.S. over 10 years is approximately $238 billion. A summary of these calculations is provided in Table 1.

Poor quality generic drugs can have significant economic impact if they fail to provide the full therapeutic benefit of the product. This failure can have significant economic impact where treatment prevents hospitalizations or other clinical events. In a market where 90% of the products are generic products, a full economic analysis of the downstream impact of poor-quality products is difficult to estimate. Our analyses here, derived from specific studies across 4 disease classes, are likely conservative estimates of this clinical and economic impact.

Discussion:

There is increasingly clear evidence that serious problems exist in the pharmaceutical supply chain that harm public health. The evidence reviewed suggests avoiding the use of approximately 10% of generic drugs that are identifiably low-quality could lead to over $18 billion in annual savings and substantial improvement in public health and patient outcomes. However, it is also important to acknowledge that not all generics are poor-quality, nor should generics be abandoned in favor of branded medications. Instead, the intention is that by approximating the economic and public health costs of this subset of

low-quality drug products, the impetus to invest in solutions will accelerate and will ultimately bolster trust in generics overall, which appears to be eroding particularly with younger patients [72].

Addressing these quality issues can help create a market that rewards objectively higher-quality products and establishes an industry driven by continuous product improvement as opposed to manufacturing products just good enough to meet minimum standards, a particularly pervasive problem in drug manufacturing and regulated industries. Indeed, studies which have evaluated implementation of continuous improvement practices in manufacturing of medical devices [73] and pharmaceuticals [74] have concluded "continuous improvement can be problematic in the context of regulatory processes" and "a regulated environment can be a further barrier to CI [continuous improvement] deployment in an organization," respectively. Implementation of continuous improvement incentivized by health system purchasers recognizing and valuing quality could result in a generic drug industry that not only closes any gap between generic and brand quality, but could exceed it. In an evaluation of dimethylformamide carcinogen levels in valsartan drug products, the average of the generics showed a substantially higher level than the brand; however, of the seven companies tested, the consistently cleanest was a generic manufacturer, not the brand [75] [76]. Objective improvement in generic drug quality could eventually address not only the quality differences but also overcome any public negative perception or nocebo effect that may contribute to reduced outcomes [77].

This continuous improvement approach mirrors that taken by the Environmental Protection Agency (EPA) regarding toxins like the carcinogen benzene, which is a dangerous contaminant in the environment and has also been discovered at unacceptably high levels in a variety of drug products [78] [79]. The EPA, like the FDA, sets regulatory limits on benzene (e.g. 5 ppb in drinking water); however, uniquely, "EPA has set a goal of 0 ppb for benzene in drinking water … because benzene can cause leukemia" [80], a practice that can motivate industries to not only meet a regulatory requirement, but also strive to continuously reduce such a toxin for which epidemiological studies have concluded that "there is probably no safe level of exposure" [81]. Such a regulatory approach could bolster the effectiveness of solutions currently being attempted at a number of large health systems.

Health System Solutions:

Even without damages from low-quality generics well quantified, the clear problems with some generic manufacturers have led to increasing engagement to find solutions. Shortly after the passage of the Food and Drug Administration Safety and Innovation Act in 2012, the FDA started suggesting that quality metrics should be established to evaluate the suitability of drug manufacturers [82]. However, despite the efforts of multiple industry associations and FDA operated pilots [83] and workshops [84] for creating a 5-star Quality Management Maturity (QMM) rating system, neither a finalized scoring framework nor its

use in the supply chain has been achieved. In fact, shortly after the FDA announced pilots and workshops to accelerate progress on QMM development, many industry groups strongly opposed the QMM system and claimed manufacturers would likely not participate in the voluntary program [85] [86].

In theory, there are four primary definitions of "quality" that could be differentiated for drug products and their manufacturers: product (defined by its chemical attributes), resilience (defined by operational metrics), regulatory (defined by compliance information), and location (defined by the country where a product is manufactured). Table 2 evaluates the relative accessibility of the data and complexity of metrics inherent to these quality definitions. This comparison may help explain why QMM and other such systems which rely heavily on resilience and regulatory quality definitions that are often proprietary and hard to define, have been historically challenging to develop or implement; and why some health systems have recently chosen to rely on product quality to successfully establish solutions that are being actively utilized.

The first published example of a health system solution came from the Cleveland Clinic which maintains a "black list" of generic drug manufacturers that it does not buy from due to complaints by doctors that observed issues in their patients [87]. This approach is limited by the collection of anecdotal evidence from individual practitioners and its application may be too broad as it applies to all products from a manufacturer that may have multiple facilities and products with varying levels of quality; however, it was able to be implemented at the scale of a health system that services approximately 3 million individuals [88], enabling it to ostensibly avoid lower quality generics and preferentially purchase higher quality versions.

In recent years, large health systems have developed more sophisticated solutions that involve independently testing the chemical quality of generic drugs. University of Kentucky (UK) HealthCare, which provides 1.4 million outpatient visits annually [89], announced a drug testing program operated by their College of Pharmacy "to test UK HealthCare's incoming drugs for identity and quality in order to improve patient outcomes and to report adulterated drugs to the FDA [90]." This UK Healthcare process provides drug product specific data that is regularly updated by independent researchers; however, while both the Cleveland Clinic and UK HealthCare models potentially improve care for their own patients, they are challenging to scale to other systems – the former due to requiring high engagement from practitioners and the latter requiring the existence of, and high engagement from, internal analytical facilities.

Two of the largest health systems in the U.S. have started operating solutions involving independent chemical testing of generic drug products that have scalable application broadly in the national supply chain. In line with ASPR's recommendation to "reform procurement protocols" to increase emphasis on quality and not simply lowest cost [30], Kaiser Permanente, with 12.5 million individual members [91], has been employing a contracting program for certain generic drugs where manufacturers already selected for

being high quality are required as part of their supply contract to submit samples from each batch for independent testing and certification by an independent laboratory [92]. In addition to protecting its patients, Kaiser has effectively introduced into the marketplace a new contracting element that could be leveraged by any contracting entity or health system, as referenced by ASPR for government health systems like those of the Department of Defense (DoD) or Veterans Administration. Health system use of such quality requirements may also lead to voluntary adoption of independent certification programs by manufacturers [93] [94]. The visibility of such independent certifications may also lead to increased confidence in adopting and adhering to medications, especially new therapies like the COVID-19 vaccine that was independently tested in England through the European Union's network of independent laboratories [95]. Researchers found that "Trust in the vaccines … are supported through testing which is independent of the manufacturers." [96]

The DoD is also piloting a nationally scalable model for independently testing and differentiating the quality of drug products for the benefit of the Military Health System, which serves approximately 9.5 million members [97] and is often viewed as a model to the nation in terms of representative population and geographic variation [98]. In a multi-year study, the DoD is systematically evaluating each available manufacturer for each of 42 essential medicines [99] and through a series of objective chemical tests evaluated by an Expert Review Panel and scored through the Panel's published scoring framework [100] [101], assigning a red, yellow, or green quality risk score to all applicable National Drug Codes (NDCs) [102] [103]. Although not as direct and batch-level as the Kaiser program, the data from the DoD model applies broadly to most, if not all, manufacturers' products for the evaluated drug molecules and offers a simple and actionable process for utilization: strive to procure, or contract for, "green" rated drug products while avoiding "red" rated products. The fact that such quality risk scores are attached to NDCs enables any health system, group purchasing organization, distributor, pharmacy, insurance provider, or benefits manager to utilize the data since all purchasers and payors of drugs in the U.S. use these NDCs [104]. Currently, data from the DoD drug quality risk scoring project is being used by pharmacy procurement professionals to optimize quality drug sourcing at major health systems.

If we accept that drug quality issues exist and that actionable transparency to independent quality metrics is a valuable solution, concerns have been raised that implementation of such solutions, including the proposal of FDA's QMM, could give rise to drug shortages [105]. Indeed, the U.S. Pharmacopeia (USP), a private organization whose manufacturer-developed and registered testing methods are enforced by FDA law [106], stated that independent testing, like that which identified carcinogenic contamination in Zantac(ranitidine) drug products, "can cause harm and may even be life threatening" in addition to "leading to drug shortages [107]." This argument is countered by the fact that drug quality issues are a leading cause of drug shortages; and the example is ironic since the initial independent testing conclusion of ranitidine being unstable and forming carcinogens [108] was validated by the original manufacturer [109] [110] and the FDA

withdrew ranitidine from the U.S. market due to its instability and potential to be life threatening [111]; however, this theoretical matter has been reviewed with real-world data. The rolling national recalls of angiotensin receptor blockers (ARBs) valsartan, losartan, and irbesartan were evaluated for any impact on volume and price of these drugs in comparison to the similar therapeutic class of drug, the Angiotensin-Converting Enzyme (ACE) inhibitors. An evaluation of Medicaid data for the period during the recalls and a few years after "found that recalls did not impact unit price or access for ARBs compared with ACE inhibitors [112]." Although already partially addressed, this conclusion touches on another theoretical concern with an increased focus on quality transparency: price increase.

Although a real-world scenario where a subset of objectively low-quality, contaminated drug products was removed from the market in favor of leaving higher-quality, uncontaminated drug products did not result in increased prices beyond expected market inflation; it may still be of concern that improving quality of generic drugs may increase their purchase price. The relationship of price versus quality was further examined in the drug metformin, a frontline medication for the treatment of type II diabetes [113] and the second most prescribed drug in the U.S. in 2022 [114], which experienced numerous recalls due to carcinogenic contamination [115] after the unacceptably high presence of a carcinogen was identified by independent testing [116]. Dozens of bottles of metformin were acquired both by a university health system and an independent laboratory, and tested for the presence of carcinogens and the mapping of price versus carcinogen levels had no significant correlation [117]. This implies that high quality generic drugs are available at low prices in the current market and that adjusting the market to favor quality suppliers should not increase price. Recent research has also found that health system buyers would voluntarily pay incrementally more for higher quality drugs, if quality ratings were available [118] [119].

Additionally, the relative cost in healthcare of generic drugs is generally very low, and any additional costs for independent quality assurance are also reportedly low. For example, the total cost of an average prescription of metformin in 2022 is $70.33 [120], whereas most drug suppliers sell 90 tablets of metformin for less than $5.00, with many lower than $2.00 [117], and the cost of independently testing and certifying such medications for health systems is reported as 1 - 3% of the drug cost (approximately $0.02 - $0.15 for a metformin prescription) [103]. Restated in relative terms, this implies that for the average prescription of metformin, the acquisition cost of the generic drug itself is roughly 5% of the cost to a health system and requiring independent, batch-level testing would potentially add 0.1%.

Limitations

This study focuses on select therapeutic categories and key studies within them that enable the novel exercise of broadly quantifying the most direct harm from the most

identifiable low-quality generics. This approach is limited as it only provides insight on chronic disease and does not account for potential harm beyond complications with the disease being managed (e.g., cancer caused by carcinogenic contamination of a medicine). Given recent findings that "chronic disease is an overlooked risk factor for cancer, as important as five major lifestyle factors combined," [121] the chronic disease population might have elevated susceptibility to developing cancer from carcinogenic contaminants than the average population, among potentially other increased vulnerabilities. Further analysis is warranted to evaluate acute care medications and any damage separate from the treated disease. These assumptions permeate through the disease categories and may lead to substantial underestimation in our analysis of economic burden for the most identifiable, low-quality generic drugs. This study also does not consider the potential implications of counterfeit medications, a separate issue to authentic low-quality generics discussed here, and a problem that appears to primarily affect online pharmacies operating illegally [122].

Another limitation of this study is that it only evaluates research where the null hypothesis of all medications are made with equal quality, is false. There exist many statements [123], FDA-animated cartoons [124], and studies [125] [126] [127] that present the view that generics are of equally high quality to each other and to the brand product. Studies that support this null hypothesis are generally well-received by academia, industry, and regulators, whereas studies that identify problems in medication quality are often met with academic [128] [129] and industry criticisms [107] [130], regulatory actions [131] [132], and legal actions [133] – a common occurrence when financially adverse findings are identified in a large industry [134]. Given such potentially strong biases to avoid research identifying drug quality problems, it would not appear reasonable to compare the body of research of true versus false null hypotheses. Furthermore, the highly fragmented nature of the American drug supply where many different manufacturers of variable quality are regularly switched at pharmacies can make it particularly challenging to detect the presence of low-quality generics or directly correlate specific low-quality findings to a particular clinical harm [135].

Conclusion

The presence of some objectively low-quality generic drugs in the U.S. is a substantial blind spot for healthcare that could be costing many billions of dollars per year in preventable healthcare costs and causing severe adverse effects, especially in the treatment of chronic disease. Meaningfully addressing this issue, as is currently being started at leading public and private health systems, is expected to add de minimis cost for a likely major benefit of protecting patients, reducing healthcare costs, and improving incentives for quality and domestic manufacturing.

Patient Population				Estimation of Generic Drug Impact			Quantitation of Low-Quality Generics Cost			% of Total Disease Burden	
Epilepsy Patients in U.S.	% of Patients Taking Medications	% Generic	Observed Rate of Low-Quality Generics	Calculated through epidemiology research -->			**Increase total cost for generic users compared to brand**	Additional Economic Burden caused by generic use	Value of 10% improvement in generic drugs being closer to brand	Total Economic Burden of Epilepsy	% of cost due to low-quality generics
3,356,000	90%	86%	10%				**$3,254**	$ 8,452,408,176	$ 845,240,818	$ 28,000,000,000	3.02%
ASCVD Patients in U.S.	% on statins	% Generic	Observed Rate of Low-Quality Generics	Calculated through epidemiology research -->			**Increase total cost for generic users compared to brand**	Additional Economic Burden caused by generic use	Value of 10% improvement in generic drugs being closer to brand	Total Economic Burden of ASCVD	% of cost due to low-quality generics
18,700,000	47.8%	95%	10%				**$429**	$ 3,642,926,430	$ 364,292,643	$ 199,200,000,000	0.18%
Multiple Sclerosis Patients in U.S.	% of Patients Taking Medications	% Generic	Observed Rate of Low-Quality Generics	**Estimated rate of relapse from low-quality generics**	Estimate relapses from low-quality generics (%)	Adverse Outcome	Estimate relapses from low-quality generics (#)	Cost of MS relapse	Annual cost of 10% low-quality generics	Total Economic Burden of MS	% of cost due to low-quality generics
913,925	69%	90%	10%	**44%**	2.73%	MS Relapse	24,972	$ 23,970	$ 598,580,918	$ 85,400,000,000	0.70%
Hypertension Patients in U.S.	% of Patients Taking Medications	% Generic	Observed Rate of Low-Quality Generics	Estimated rate of higher blood pressure variability from low-quality generics	**Additional Adverse Event Rate due to High Variability**	Adverse Outcome	Estimated adverse outcomes from low-quality generics	Cost of adverse outcome	Annual cost of 10% low-quality generics	Total Economic Burden of Hypertension	% of cost due to low-quality generics
119,900,000	79%	90%	10%	44%	**0.5000%**	Cardiovascular Disease	18,790	$ 13,000	$ 244,272,600		
					0.0462%	Stroke	1,736	$ 35,000	$ 60,767,507		
					0.0562%	Heart Attack	2,111	$ 18,300	$ 38,622,429		
								Total:	$ 343,662,536	$ 219,000,000,000	0.16%
Total Chronic Disease									**Annual cost of 10% identifiably low-quality generics**	Total Economic Burden of Chronic Disease (2024 est)	Chronic Disease Weighted Average
									$18,360,534,398	$4,536,000,000,000	0.40%

Table 1: The various cited disease statistics and outcomes calculations discussed in this analysis are collected in this table by disease and for total chronic disease. The key cited academic research primarily driving the overall model is highlighted in bold, as is the result of the cost burden estimation of low-quality generics on total chronic disease.

[Image file shown here. A spreadsheet version available upon request.]

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Table 2: An overview of the four primary definitions of “quality” that could be differentiated for drug products and their manufacturers. The relative difficulty of creating metrics and accessing data for such definitions is ranked “red” for highest difficulty, “yellow” for medium difficulty, and “green" for lowest difficulty.

	Product	**Resilience**	**Regulatory**	**Location**
Examples of metrics	Heavy metals content, levels of carcinogens, dosage, dissolution rate difference percentage from brand	Additional inventory, multiple sources of critical inputs (e.g. API), level of quality management maturity (QMM)	Warning letter count and severity, import alerts, recalls	On-shore, near-shore, TAA-compliant
Metrics Complexity	Scientific and unambiguous (e.g. high toxin is bad; undetected toxin is good)	Stakeholder alignment difficult on metrics and meaning	Scientific but ambiguous as to its meaning (e.g. what constitutes a “severe” letter?)	Simple and unambiguous (e.g. U.S. site is good; non-TAA compliant site is bad)
Accessibility of Data	Available in public domain with acquisition of proper licenses	Largely proprietary and reliant on manufacturer voluntary engagement	Partial public domain, FOIA often required but can be redacted, difficult to link facility to drug products	Partial public domain, particularly problematic for API, raw materials
Relative Value	Highest overall value. Direct correlation to recalls, shortages, health outcomes	High value for preventing drug shortages	High value to industry, and likely correlated to shortages	High value to government, and to domestic pharmaceutical manufacturing

Disclosures:

Funding: This work was supported by the United States Department of Defense (DoD), Defense Health Agency under grant number HU00012420017. The sponsor had no role in the study design, collection, analysis, and interpretation of data, the writing of the report, nor in the decision to submit the article for publication.

Victor Suarez declares advisory board memberships at ScienceWerx, BioBuzz, and US Biologic. Principal at Blu Zone Bioscience Supply Chain Solutions, LLC, a consulting firm assisting biotechnology and life science supply chain organizations. Participation in the DoD grant.

David Light and Adam Clark-Joseph declare employment and stock ownership in Valisure, an independent testing laboratory. Participation in the DoD grant.

Kevin Schulman declares grant from Stanford Clinical Excellence Research Center, expert testimony for Motley Rice, LLC, and advisory board membership for Civica Rx SAB (unpaid).

Darin Okuda declares grants or contracts from Alexion, Biogen, Novartis, and National Multiple Sclerosis Society. Consulting fees from Biogen, Cortechs.AI, EMD Serono, Genentech, Genzyme/Sanofi, Immunic Therapeutics, Moderna, Pfizer, Zenas BioPharma, and expert witness testimony. Royalties for intellectual property licensed by The Board of Regents of The University of Texas System. Advisory board membership at the MS Foundation.

References

[1] Association for Accessible Medicines, "2023 Report: U.S. Generic and Biosimilar Medicines Savings Report," 2023. [Online]. Available: https://accessiblemeds.org/resources/blog/2023-savings-report/.
[2] A. Johnston, P. Stafylas and G. Stergiou, "Effectiveness, safety and cost of drug substitution in hypertension," British Journal of Clinical Pharmacology, vol. 70, no. 3, pp. 320-34, 2010.
[3] H. M. Lever, "A Physician's Perspective on Generic Drug Quality," Journal of Managed Care & Specialty Pharmacy, vol. 26, no. 5, pp. 592-593, 2020.
[4] S. B. E. Y. Anna Edney, "Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.," Bloomberg News, 12 September 2019. [Online]. Available: https://www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda. [Accessed 5 January 2025].
[5] F. Stockman, "Our Drug Supply Is Sick. How Can We Fix It?," New York Times, 18 September 2021. [Online]. Available: https://www.nytimes.com/2021/09/18/opinion/drug-market-prescription-generic.html. [Accessed 5 January 2025].
[6] R. G. A. L. Kellermann, "How To Ensure The Quality And Safety Of Our Generic Drugs," Health Affairs Forefront, 2023.

[7] Food and Drug Administration, "40th Anniversary of the Generic Drug Approval Pathway," Center for Drug Evaluation and Research, 23 September 2024. [Online]. Available: https://www.fda.gov/drugs/cder-conversations/40th-anniversary-generic-drug-approval-pathway. [Accessed 5 January 2025].
[8] Food and Drug Administration, "Report | Drug Shortages: Root Causes and Potential Solutions," 21 February 2020. [Online]. Available: https://www.fda.gov/media/131130/download?attachment. [Accessed 5 January 2025].
[9] Food and Drug Administration, "U.S. Food and Drug Administration Recall Information Search," 2020 - 2024. [Online]. Available: https://www.accessdata.fda.gov/scripts/ires/index.cfm#tabNav_advancedSearch. [Accessed 5 January 2025].
[10] J. Woodcock, M. Khan and L. X. Yu, "Withdrawal of Generic Budeprion for Nonbioequivalence," New England Journal of Medicine, vol. 367, no. 26, pp. 2463-2465, 2012.
[11] The API Innovation Center, "A BOLD GOAL: RESHORING 25% OF SMALL MOLECULE API TO THE U.S. IN 5 YEARS," 24 January 2024. [Online]. Available: https://apicenter.org/wp-content/uploads/2024/01/White-Paper_2024.pdf. [Accessed 5 January 2025].
[12] R. Gibson and J. P. Singh, China Rx: Exposing the Risks of America's Dependence on China for Medicines, Amherst, NY: Prometheus Books, 2018.
[13] Government Accountability Office, "GAO Adds Three Issues, Drops One Other, On 2009 "High Risk" List," 22 January 2009. [Online]. Available: https://www.gao.gov/press-release/gao-adds-three-issues%2C-drops-one-other%2C-2009-high-risk-list. [Accessed 22 January 2025].
[14] Government Accountability Office, "Drug Safety: FDA Has Faced Persistent Challenges Overseeing Foreign Drug Manufacturing," 6 Febuary 2024. [Online]. Available: https://www.gao.gov/products/gao-24-107359. [Accessed 5 January 2025].
[15] L. R. White and C. M. White, "Eye Drop Quality Issues: Can the FDA See This One Through?," The Annals of Pharmacotherapy, vol. 58, no. 11, pp. 1149-1152, 2024.
[16] C. M. White, "Generic Drugs Not as Safe as FDA Wants You to Believe," The Annals of Pharmacotherapy, vol. 54, no. 3, pp. 283-286, 2020.
[17] N. F. MATTHEW PERRONE, "FDA has massive backlog of factory inspections as staffers leave for private sector jobs," Associated Press, 4 September 2024. [Online]. Available: https://apnews.com/article/fda-inspections-drug-manufacturing-india-china-7b3a7e9b45bcc3aea86ce5bf781271f3. [Accessed 5 January 2025].
[18] I. J. Noh, J. Gray, G. Ball, Z. Wright and H. Park, "Are All Generic Drugs Created Equal? An Empirical Analysis of Generic Drug Manufacturing Location and Serious Drug Adverse Events," Production and Operations Management, no. https://journals.sagepub.com/doi/10.1177/10591478251319691, 2025.
[19] D. L. Victor Suarez, "A Quadruple Threat to Public Health and National Security — Understanding Drug Shortages and Ways to Help Prevent Them," Supply Chain Strategies & Solutions, American Hospital Association, no. Quarter 3, 2023.
[20] U.S. Senate Committee on Armed Services, "To receive testimony on the Department of Defense’s efforts to ensure servicemembers’ access to safe, high-quality

pharmaceuticals," Subcommittee on Personnel, 30 April 2024. [Online]. Available: https://www.armed-services.senate.gov/hearings/to-receive-testimony-on-the-department-of-defenses-efforts-to-ensure-servicemembers-access-to-safe-high-quality-pharmaceuticals.
[21] National Academies of Sciences, Engineering, and Medicine, "Building Resilience into the Nation's Medical Product Supply Chains," The National Academies Press, Washington, DC, 2022.
[22] C. M. White and L. R. White, "Believing FDA's Assurance of Quality Pharmaceutical Products Can Be Dangerous to Your Patients' Health," Annals of Pharmacotherapy, vol. 0, no. 0, 2025.
[23] Duke Margolis Institute for Health Policy, "FDA Convening: Understanding How the Public Perceives and Values Pharmaceutical Quality," Food and Drug Administration, 3 February 2020. [Online]. Available: https://healthpolicy.duke.edu/events/understanding-how-public-perceives-and-values-pharmaceutical-quality. [Accessed 5 January 2025].
[24] United States Representative Rosa DeLauro, "DeLauro Reiterates Call to Ban Ranitidine Sales, Reintroduces Bill to Giving FDA Mandatory Recall Authority Over Drugs," 10 January 2020. [Online]. Available: https://delauro.house.gov/media-center/press-releases/delauro-reiterates-call-ban-ranitidine-sales-reintroduces-bill-giving. [Accessed 5 January 2025].
[25] P. J. Almeter, J. T. Isaacs, A. N. Hunter and e. al., "FDA Approaches in Monitoring Drug Quality, Forces Impacting the Drug Quality, and Recent Alternative Strategies to Assess Quality in the US Drug Supply," Journal of Pharmaceutical Innovation, vol. 17, pp. 269-282, 2022.
[26] Food and Drug Administration, "Drug Quality Sampling and Testing Programs," 17 April 2024. [Online]. Available: https://www.fda.gov/drugs/science-and-research-drugs/drug-quality-sampling-and-testing-programs. [Accessed 5 January 2025].
[27] K. A. Schulman, "Challenges In Ensuring The Quality Of Generic Medicines," Health Affairs, vol. 39, no. https://doi.org/10.1377/hlthaff.2020.00321, 2020.
[28] L. Walker and D. Gorenstein, "The U.S. has relied on cheap, effective generic drugs for 40 years. Now that promise is under threat," STAT News, 24 September 2024. [Online]. Available: https://www.statnews.com/2024/09/24/generic-drugs-hatch-waxman-challenges-shortages-supply-chain-biosimilars/. [Accessed 5 January 2025].
[29] J. Woodcock and M. Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages," Clinical Pharmacology & Therapeutics, vol. 93, no. 2, p. 170–176, 2013.
[30] Administration for Strategic Preparedness and Response, "Essential Medicines Supply Chain and Manufacturing Resilience Assessment," Department of Health and Human Services, Washington DC, 2022.
[31] United States Senate Committee on Finance, "Drug Shortages: Examining Supply Challenges, Impacts, and Policy Solutions from a Federal Health Program Perspective," 5 December 2023. [Online]. Available: https://www.finance.senate.gov/hearings/drug-shortages-examining-supply-challenges-impacts-and-policy-solutions-from-a-federal-health-program-perspective. [Accessed 5 January 2025].

[32] D. M. Berwick and A. D. Hackbarth, "Eliminating waste in US health care," Journal of the American Medical Association, vol. 307, no. 14, pp. 1513-6, 2012.
[33] A. Edney, "A Tiny Lab Finds Danger on Drugstore Shelves While the FDA Lags Behind," Bloomberg News, 9 November 2022. [Online]. Available: https://www.bloomberg.com/news/features/2022-11-09/fda-lags-behind-lab-that-found-benzene-in-dry-shampoos-sunscreen. [Accessed 5 January 2025].
[34] K. Schulman and A. L. Kellermann, "Substandard Generic Drugs — Threats to Patient Safety and National Security," The New England Journal of Medicine, online ahead of print. DOI: 10.1056/NEJMp2518256, 2026.
[35] D. Labiner, P. Paradis, R. Manjunath, M. Duh, M.-H. Lafeuille, D. Latrémouille-Viau, P. Lefebvre and S. Helmers, "Generic antiepileptic drugs and associated medical resource utilization in the United States," Neurology, vol. 74, no. 20, pp. 1566-1574, 2010.
[36] J. LeLorier, M. S. Duh, P. E. Paradis, P. Lefebvre, J. Weiner, R. Manjunath and O. Sheehy, "Clinical consequences of generic substitution of lamotrigine for patients with epilepsy," Neurology, vol. 70, no. 22, pp. 2179-2186, 2008.
[37] S. L. Helmers, P. E. Paradis, R. Manjunath, M. S. Duh, M.-H. Lafeuille, D. Latrémouille-Viau, P. Lefebvre and D. M. Labiner, "Economic burden associated with the use of generic antiepileptic drugs in the United States," Epilepsy & Behavior, vol. 18, no. 4, pp. 437-444, 2010.
[38] M. S. Duh, P. E. Paradis, D. Latrémouille-Viau, P. E. Greenberg, S. P. Lee, M. B. Durkin, G. J. Wan, M. Rupnow and J. LeLorier, "The risks and costs of multiple-generic substitution of topiramate," Neurology, vol. 72, no. 24, pp. 2122-2129, 2009.
[39] J. J. Gagne, J. Avorn, W. H. Shrank and S. Schneeweiss, "Refilling and switching of antiepileptic drugs and seizure-related events," Clinical Pharmacology & Therapeutics:, vol. 88, no. 3, pp. 347-353, 2010.
[40] Centers for Disease Control and Prevention, "Epilepsy Facts and Stats," 2 February 2024. [Online]. Available: https://www.cdc.gov/epilepsy/data-research/facts-stats/index.html. [Accessed 5 January 2025].
[41] N. Tian, M. Boring, R. Kobau, M. M. Zack and J. B. Croft, "Active Epilepsy and Seizure Control in Adults — United States, 2013 and 2015," CDC Morbidity and Mortality Weekly Report, vol. 67, no. 15, pp. 437-442, 2018.
[42] S. W. Terman, C. C. Lin, W. T. Kerr, L. B. DeLott, B. C. Callaghan and J. F. Burke, "Changes in the Use of Brand Name and Generic Medications and Total Prescription Cost Among Medicare Beneficiaries With Epilepsy," Neurology, vol. 99, no. 8, pp. 751-761, 2022.
[43] UCB Inc, "Examining the Economic Impact and Implications of Epilepsy," American Journal of Managed Care, no. Clinical Brief, February 2020, 2020.
[44] D. T. Okuda, K. W. Burgess, T. M. Moog and M. A. Patel, "Underdosed generic specialty medications: A prescription for patient harm?," Multiple Sclerosis and Related Disorders, vol. 88, 2024.
[45] D. T. Okuda, L. M. Tardo, C. M. Wright, S. B. Munoz, T. G. Punnen, M. A. Patel, T. M. Moog and K. W. Burgess, "Clinical and radiological implications of subpotent generic fingolimod in multiple sclerosis: a case series," Therapeutic Advances in Neurological Disorders, vol. 17, pp. 1-11, 2024.

[46] T. A. Nazareth, A. R. Rava, J. L. Polyakov, E. N. Banfe, R. W. W. Ii, K. B. Zerkowski and L. B. Herbert, "Relapse prevalence, symptoms, and health care engagement: patient insights from the Multiple Sclerosis in America 2017 survey," Multiple Sclerosis and Related Disorders, vol. 26, pp. 219-234, 2018.
[47] A. Papathanasiou, A. Hibbert, E. Tallantyre, K. Harding, A. P. Selvam, M. Morgan, C. Quainton, M. Talaei, T. Arun, G. Ingram, G. R. Law and N. Evangelou, "Real-world annualized relapse rates from contemporary multiple sclerosis clinics in the UK: a retrospective multicentre cohort study," Neurological Sciences, vol. 44, no. 10, pp. 3629-3635, 2023.
[48] T. Derfuss, D. Ontaneda, J. Nicholas, X. Meng and K. Hawker, "Relapse rates in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of pooled data from three phase 3 trials," Multiple Sclerosis and Related Disorders, vol. 8, pp. 124-130, 2016.
[49] M. Duddy, M. Lee, O. Pearson, E. Nikfekr, A. Chaudhuri, F. Percival, M. Roberts and C. Whitlock, "The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies," Multiple Sclerosis and Related Disorders, vol. 3, no. 4, pp. 450-456, 2014.
[50] Statista, "Percentage of U.S. patients diagnosed with multiple sclerosis using selected treatments in 2016," 2016. [Online]. Available: https://www.statista.com/statistics/689877/treatments-used-by-ms-patients-in-the-us/. [Accessed 5 January 2025].
[51] US Multiple Sclerosis Prevalence Workgroup, "The prevalence of MS in the United States: A population-based estimate using health claims data," Neurology, vol. 92, no. 10, pp. 1029-1040, 2019.
[52] J. Nicholas, H. Zhou and C. Deshpande, "Annual Cost Burden by Level of Relapse Severity in Patients with Multiple Sclerosis," Advances in Therapy, vol. 38, no. 1, pp. 758-771, 2020.
[53] B. Bebo, I. Cintina, N. LaRocca, L. Ritter, B. Talente, D. Hartung, S. Ngorsuraches and M. Wallin, "The Economic Burden of Multiple Sclerosis in the United States," Neurology, vol. 98, no. 18, pp. 1810-1817, 2022.
[54] X. Liang, J. Li and R. Anupindi, "Brand-Name versus Generic Drugs: An Empirical Study on Health Outcomes of Generic Atorvastatin Usage," Social Science Research Network, 2024.
[55] C. J. Alanaeme, V. Bittner, T. M. Brown, L. D. Colantonio, N. Dhalwani, J. Jones, B. Kalich, J. Exter, E. A. Jackson, E. B. Levitan, B. Poudel, Z. Wang, M. Woodward, P. Muntner and R. S. Rosenson, "Estimated number and percentage of US adults with atherosclerotic cardiovascular disease recommended add-on lipid-lowering therapy by the 2018 AHA/ACC multi-society cholesterol guideline," American Heart Journal Plus, vol. 21, 2022.
[56] R. Khera, J. Valero-Elizondo and K. Nasir, "Financial Toxicity in Atherosclerotic Cardiovascular Disease in the United States: Current State and Future Directions," Journal of the American Heart Association, vol. 9, no. 19, 2020.
[57] L. K. Boerner, "NDMA, a contaminant found in multiple drugs, has industry seeking sources and solutions," Chemical & Engineering News, pp. Volume 98, Issue 15, 20 April 2020.

[58] S. Gottlieb, "FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues," Food and Drug Administration, 25 January 2019. [Online]. Available: https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps. [Accessed 5 January 2025].
[59] W. Gomm, C. Röthlein, K. Schüssel, G. Brückner, H. Schröder, S. Heß, R. Frötschl, K. Broich and B. Haenisch, "N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer," Deutsches Ärzteblatt International, vol. 118, no. 21, pp. 357-362, 2021.
[60] J. Leclerc, C. Blais, L. Rochette, D. Hamel, L. Guénette and P. Poirier, "Impact of the Commercialization of Three Generic Angiotensin II Receptor Blockers on Adverse Events in Quebec, Canada: A Population-Based Time Series Analysis," Circulation. Cardiovascular Quality and Outcomes, vol. 10, no. 10, p. e003891, 2017.
[61] J. Hellström and N. Rudholm, "Side Effects of Generic Competition?," The European Journal of Health Economics, vol. 5, no. 3, pp. 203-208, 2004.
[62] J. Leclerc, C. Blais, L. Rochette, D. Hamel, L. Guénette, C. Beaudoin and P. Poirier, "Public Health Outcomes May Differ After Switching from Brand-Name to Generic Angiotensin II Receptor Blockers," Drugs in R&D, vol. 20, no. 2, pp. 135-145, 2020.
[63] R. P. J. C. R. C. P. S. J. N. R. A. J. G. A. D. J. S. S MacMahon, "Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias," Lancet, vol. 335, no. 8692, pp. 765-74, 1990.
[64] R. P. S. M. P. H. N. H. F. K. A. E. J. G. N. Q. J. O. T. C. H. H. R Collins, "Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context," Lancet, vol. 335, no. 8693, pp. 827-38, 1990.
[65] S. L. Stevens, S. Wood, C. Koshiaris, K. Law, P. Glasziou, R. J. Stevens and R. J. McManus, "Blood pressure variability and cardiovascular disease: systematic review and meta-analysis," British Medical Journal, vol. i4098, p. 354, 2016.
[66] American Heart Association, "Forecasting the Economic Burden of Cardiovascular Disease and Stroke in the United States Through 2050: A Presidential Advisory From the American Heart Association," Circulation, vol. 150, no. 4, 2024.
[67] G. S. Tajeu, N. Ruiz-Negrón, A. E. Moran, Z. Zhang, P. Kolm, W. S. Weintraub, A. P. Bress and B. K. Bellows, "Cost of Cardiovascular Disease Event and Cardiovascular Disease Treatment–Related Complication Hospitalizations in the United States," Circulation: Cardiovascular Quality and Outcomes, vol. 17, no. 3, 2024.
[68] Centers for Disease Control and Prevention, "Health and Economic Benefits of High Blood Pressure Interventions," National Center for Chronic Disease Prevention and Health Promotion, 2024. [Online]. Available: https://www.cdc.gov/nccdphp/priorities/high-blood-pressure.html. [Accessed 5 January 2025].
[69] Centers for Disease Control and Prevention, "Fast Facts: Health and Economic Costs of Chronic Conditions," 12 July 2024. [Online]. Available: https://www.cdc.gov/chronic-disease/data-research/facts-stats/index.html. [Accessed 20 June 2025].

[70] Centers for Medicare & Medicaid Services, "National Health Expenditure Data - Projected," 10 September 2024 . [Online]. Available: https://www.cms.gov/data-research/statistics-trends-and-reports/national-health-expenditure-data/projected. [Accessed 6 June 2025].
[71] J. A. Fiore, A. J. Madison, J. A. Poisal, G. A. Cuckler, S. D. Smith, A. M. Sisko, S. P. Keehan, K. E. Rennie and A. C. Gross, "National Health Expenditure Projections, 2023–32: Payer Trends Diverge As Pandemic-Related Policies Fade," Health Affairs, vol. 43, no. 7, 2024.
[72] L. Leake, "Gen Z's expensive drug habit: More want brand-name meds that are 79% more expensive," Fortune Magazine, 14 February 2025. [Online]. Available: https://fortune.com/well/article/brand-name-vs-generic-drugs-prescription-over-the-counter-medications-cost-effectiveness/. [Accessed 16 February 2025].
[73] A. Brown, J. Eatock, D. Dixon, B. J. Meenan and J. Anderson, "Quality and continuous improvement in medical device manufacturing," Total Quality Management Journal, vol. 20, no. 6, pp. 541-555, 2008.
[74] O. McDermott, J. Antony, M. Sony and S. Daly, "Barriers and Enablers for Continuous Improvement Methodologies within the Irish Pharmaceutical Industry," Processes , vol. 10, no. 1, p. 73, 2022.
[75] D. Light and K. Kucera, "Valisure Citizen Petition," Valisure, 13 June 2019. [Online]. Available: https://www.regulations.gov/document/FDA-2019-P-2869-0001. [Accessed 8 June 2025].
[76] A. Edney, "Fourth Carcinogen Discovered in Heart Pills Used by Millions," Bloomberg News, 18 June 2019. [Online]. Available: https://www.bloomberg.com/news/articles/2019-06-18/fourth-carcinogen-discovered-in-heart-pills-used-by-millions. [Accessed 8 June 2025].
[77] K. MacKrill and K. J. Petrie, "What is associated with increased side effects and lower perceived efficacy following switching to a generic medicine? A New Zealand cross-sectional patient survey," British Medical Journal Open, vol. 8, no. 10, 2018.
[78] W. Nicole, "Skin Protection Dilemma: Testing Detects Benzene in Some Sun Care Products," Environmental Health Perspectives, vol. 130, no. 5, 2022.
[79] K. Kucera, N. Zenzola, A. Hudspeth, M. Dubnicka, W. Hinz, C. G. Bunick, A. Dabestani and D. Y. Light, "Benzoyl Peroxide Drug Products Form Benzene," Environmental Health Perspectives, vol. 132, no. 3, 2024.
[80] Agency for Toxic Substances and Disease Registry, "Toxicological Profile for Benzene," in PUBLIC HEALTH STATEMENT, Atlanta, GA, National Library of Medicine, 2007, p. https://www.ncbi.nlm.nih.gov/books/NBK591300/.
[81] M. T. Smith, "Advances in Understanding Benzene Health Effects and Susceptibility," Annual Review of Public Health, vol. 31, pp. 113-148, 2010.
[82] S. Schniepp, "An Update on the Quality Metrics Initiative," BioPharm International, vol. 28, no. 5, pp. 12-14, 2015.
[83] Food and Drug Administration, "Quality Management Maturity for Finished Dosage Forms Pilot Program for Domestic Drug Product Manufacturers; Program Announcement," DEPARTMENT OF HEALTH AND HUMAN SERVICES, 13 October 2020. [Online]. Available: https://public-inspection.federalregister.gov/2020-22976.pdf. [Accessed 5 January 2025].

[84] Food and Drug Administration, "Quality Management Maturity Workshop," 16 March 2023. [Online]. Available: https://www.fda.gov/drugs/news-events-human-drugs/quality-management-maturity-workshop-05242022. [Accessed 5 January 2025].
[85] J. S. Eglovitch, "Industry groups express misgivings on FDA's QMM program," Regulatory Focus, 15 December 2023. [Online]. Available: https://www.raps.org/News-and-Articles/News-Articles/2023/12/Industry-groups-express-misgivings-on-FDA%E2%80%99s-QMM-pr. [Accessed 5 January 2025].
[86] Premier Inc., "The Unintended Consequences of a Drug Quality Rating System," 3 March 2023. [Online]. Available: https://premierinc.com/newsroom/premier-in-the-news/industry-perspective-the-unintended-consequences-of-a-drug-quality-rating-system. [Accessed 5 January 2025].
[87] K. Eban, Bottle of Lies: The Inside Story of the Generic Drug Boom, New York: Harper Collins, 2019.
[88] Cleveland Clinic, "2023 Year-End Facts+Figures," 31 December 2023. [Online]. Available: https://my.clevelandclinic.org/-/scassets/files/org/about/who-we-are/cleveland-clinic-facts-and-figures-2023.pdf. [Accessed 5 January 2025].
[89] University of Kentucky HealthCare, "UK HealthCare Refreshed & Advancing 2023 Annual Report," 30 June 2023. [Online]. Available: https://ukhealthcare.uky.edu/sites/default/files/2024-05/Annual%20Report%20FY23.pdf. [Accessed 5 January 2025].
[90] E. Chapin and K. Willett, "UK Drug Quality Testing Leads to Petition to Recall Injectable Drug," University of Kentucky, 1 October 2020. [Online]. Available: https://uknow.uky.edu/research/uk-drug-quality-testing-leads-petition-recall-injectable-drug. [Accessed 5 January 2025].
[91] Kaiser Permanente, "Kaiser Permanente Fast Facts," 30 September 2024. [Online]. Available: https://about.kaiserpermanente.org/who-we-are/fast-facts. [Accessed 5 January 2025].
[92] A. Edney and R. Griffin, "US Military Is So Worried About Drug Safety It Wants to Test Widely Used Medicines," Bloomberg News, 7 June 2023. [Online]. Available: https://www.bloomberg.com/news/articles/2023-06-07/drug-safety-fears-spur-pentagon-plan-to-test-widely-used-meds. [Accessed 5 January 2025].
[93] American Pharmaceutical Review, "Valisure and Picket Pharmaceuticals Partner for Independent Certification of Injectable Drugs," 6 December 2024. [Online]. Available: https://www.americanpharmaceuticalreview.com/1315-News/616554-Valisure-and-Picket-Pharmaceuticals-Partner-for-Independent-Certification-of-Injectable-Drugs/. [Accessed 5 January 2025].
[94] L. M. Fisher, "Fixing Generic Drugs With Voluntary Privatized Regulation," Milken Institute Review, 14 March 2022. [Online]. Available: https://www.milkenreview.org/articles/fixing-generic-drugs-with-voluntary-privatized-regulation. [Accessed 5 January 2025].
[95] European Directorate for the Quality of Medicines & Healthcare, Council of Europe, "Brochure: The European Network of Official Medicines Control Laboratories (OMCLs)," 27 November 2024. [Online]. Available: https://www.edqm.eu/documents/52006/71923/brochure-omcl-double-page-

web.pdf/1b2e1f8a-17ce-49e4-5173-9390855c081b?t=1629096465234. [Accessed 16 February 2025].
[96] N. J. Rose, P. Stickings, S. Schepelmann, M. J. A. Bailey and C. Burns, "National control laboratory independent lot testing of COVID-19 vaccines: the UK experience," Nature Partner Journals Vaccines, vol. 100, no. 6, 2021.
[97] Military Health System, "Patient Numbers By State," U.S. Department of Defense, 23 September 2024. [Online]. Available: https://www.health.mil/Military-Health-Topics/MHS-Toolkits/Media-Resources/Media-Center/Patient-Population-Statistics/Patient-Numbers-By-State. [Accessed 5 January 2025].
[98] T. P. Koehlmoos, J. Korona-Bailey, M. L. Janvrin, C. Madsen and E. Schneider, "The collaborative research and service delivery partnership between the United States healthcare system and the U.S. Military Health System during the COVID-19 pandemic," Health Research Policy and Systems, vol. 20, no. 81, 2022.
[99] M. L. Janvrin, A. Kanagaratnam, V. A. Suarez, D. Y. Light, I. Lucki and T. P. Koehlmoos, "A Comparison of the Essential Medicines Lists of the U.S. Department of Health and Human Services, the U.S. Department of Defense, the U.S. Food and Drug Administration, and the World Health Organization," Journal of the American Pharmacist Association, no. Online ahead of print, 2025.
[100] A. Dabestani, S. Grossman, J. P. Nathan, C. W. Bazil, R. C. Costantino, E. R. Fox, J. Graedon, J. V. Gray, H. M. Lever, D. Y. Light, R. Makuch, K. A. Schulman, C. M. White and K. Yu, "A data-driven quality-score system for rating drug products and its implications for the health care industry," Journal of the American Pharmacist Association, vol. 63, no. 2, pp. 501-506, 2023.
[101] A. Narayan, B. Teasdale, A. J. Hudspeth, D. Y. Light, J. K. Nailor and K. Schulman, "The Price and Quality of Methylphenidate Products," Journal of the American Academy of Child and Adolescent Psychiatry, p. Online ahead of print, 2025.
[102] V. A. Suarez, "Statement of COL(Ret) Victor A. Suarez Before the U.S. SENATE COMMITTEE ON ARMED SERVICES SUBCOMMITTEE ON PERSONNEL," 17 April 2024. [Online]. Available: https://www.armed-services.senate.gov/imo/media/doc/suarez_statement.pdf. [Accessed 5 January 2025].
[103] V. Suarez and D. Light, "The Uniformed Services University Department of Pharmacology Seminar Series, DoD-led Pharmaceutical Quality Assessment: Pilot Study Preliminary Results and Applications for Health Systems," 8 December 2024. [Online]. Available: https://cdn.prod.website-files.com/6215052733f8bb8fea016220/67564b6c1c2c477352264d41_USU%20PHAQS_Presentation_16%20Oct%2024_v3p_updated_120824.pdf. [Accessed 5 January 2025].
[104] F. a. D. Administration, "National Drug Code Database Background Information," 20 March 2017. [Online]. Available: https://www.fda.gov/drugs/development-approval-process-drugs/national-drug-code-database-background-information. [Accessed 5 January 2025].
[105] C. V. ROSSI, "Economics and Risks Associated with FDA's QMM Rating Program," University of Maryland, 2022.
[106] P. Nithyanandan, "FDA-USP Collaboration and Partnership," in Pharmaceutical Quality Symposium, Held Online, 2023.

[107] USP, "Unvalidated methods for medicine quality testing lead to misleading results," 2023. [Online]. Available: https://www.usp.org/sites/default/files/usp-white-paper-unvalidated-methods-medicine-quality-testing-lead-misleading-results.pdf. [Accessed 5 January 2025].
[108] D. Light and K. Kucera, "Valisure Citizen Petition on Ranitidine," Valisure, 18 September 2019. [Online]. Available: https://downloads.regulations.gov/FDA-2019-P-4281-0001/attachment_1.pdf. [Accessed 5 January 2025].
[109] F. J. King, A. D. Searle and M. W. Urquhart, "Ranitidine—Investigations into the Root Cause for the Presence of N-Nitroso-N,N-dimethylamine in Ranitidine Hydrochloride Drug Substances and Associated Drug Products," Organic Process Research & Development, vol. 24, no. 12, 2020.
[110] A. Edney, S. Berfield and J. Feeley, "Zantac's Maker Kept Quiet About Cancer Risks for 40 Years," Bloomberg News, 15 February 2023. [Online]. Available: https://www.bloomberg.com/news/features/2023-02-15/zantac-cancer-risk-data-was-kept-quiet-by-manufacturer-glaxo-for-40-years. [Accessed 5 January 2025].
[111] Food and Drug Administration, "FDA Requests Removal of All Ranitidine Products (Zantac) from the Market," 1 April 2020. [Online]. Available: https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market. [Accessed 5 January 2025].
[112] B. Teasdale, D. Light and K. A. Schulman, "Price and Quality in the Generic Pharmaceutical Market," Circulation, vol. 145, no. 16, 2022.
[113] MedlinePlus, "Metformin," National Library of Medicine, 15 February 2024. [Online]. Available: https://medlineplus.gov/druginfo/meds/a696005.html. [Accessed 5 January 2025].
[114] ClinCalc DrugStats Database, "The Top 300 of 2022," Kane SP, 7 August 2024. [Online]. Available: https://clincalc.com/drugstats/Top300Drugs.aspx. [Accessed 5 January 2025].
[115] Food and Drug Administration, "FDA Updates and Press Announcements on NDMA in Metformin," 6 January 2021. [Online]. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin. [Accessed 5 January 2025].
[116] M. Mishra, M. Erman and A. D'Silva, "Online pharmacy Valisure says tests show carcinogen in diabetes drug metformin," Reuters, 2 March 2020. [Online]. Available: https://www.reuters.com/article/business/healthcare-pharmaceuticals/online-pharmacy-valisure-says-tests-show-carcinogen-in-diabetes-drug-metformin-idUSKBN20P2TW/. [Accessed 5 January 2025].
[117] B. Teasdale, A. Hudspeth, K. Kucera, D. Light, J. Nailor, S. Williams, A. Milstein and K. Schulman, "Safety vs Price in the Generic Drug Market: Metformin," The American Journal of Managed Care, vol. 30, no. 4, pp. 161-168, 2023.
[118] American Society of Healthsystem Pharmacists , "SEVERITY AND IMPACT OF CURRENT DRUG SHOTAGES," 1 July 2023. [Online]. Available: https://www.ashp.org/-/media/assets/drug-shortages/docs/ASHP-2023-Drug-Shortages-Survey-Report.pdf. [Accessed 20 July 2025].

[119] S. Villa, G. Urrea, G. Ball, J. Gray and M. Ganio, "Generic Drug Transparency: Testing a Regulatory Policy Proposal," Social Science Research Network, 2025.
[120] ClinCalc DrugStats Database, "Metformin Drug Usage Statistics, United States, 2013 - 2022," Kane SP, 7 August 2024. [Online]. Available: https://clincalc.com/drugstats/Drugs/Metformin. [Accessed 5 January 2025].
[121] H. Tu, C. P. Wen, S. P. Tsai, W.-H. Chow, C. Wen, Y. Ye, H. Zhao, M. K. Tsai, M. Huang, C. P. Dinney, C. K. Tsao and X. Wu, "Cancer risk associated with chronic diseases and disease markers: prospective cohort study," British Medical Journal, vol. 360, no. k134, 2018.
[122] Centers for Disease Control and Prevention, "Potential public health risk among individuals ordering counterfeit prescription medications from online pharmacies," CDC Newsroom, 2 October 2024. [Online]. Available: https://www.cdc.gov/media/releases/2024/s1002-counterfit-prescription-online-pharmacies.html. [Accessed 16 February 2025].
[123] Association for Accessible Medicines, "Experts Agree: Generics Offer Same Safety and Effectiveness," 2025. [Online]. Available: https://accessiblemeds.org/about/generic-medicines/. [Accessed 5 January 2025].
[124] Food and Drug Administration, "Generic Drugs Stakeholder Toolkit," 23 December 2020. [Online]. Available: https://www.fda.gov/drugs/generic-drugs/generic-drugs-stakeholder-toolkit. [Accessed 5 January 2025].
[125] B. M. Davit, P. E. Nwakama, G. J. Buehler, D. P. Conner, S. H. Haidar, D. T. Patel, Y. Yang, L. X. Yu and J. Woodcock, "Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration," The Annals of Pharmacotherapy, vol. 43, no. 10, pp. 1583-97, 2009.
[126] B. Zhao, J. Wu, C. Lu and X. L. Feng, "Generic substitution of amlodipine is not associated with increased risk of mortality or adverse cardiovascular events: An observational cohort study," Clinical and Translational Science, vol. 17, no. 4, p. e13779, 2024.
[127] T. Y. Ting, W. Jiang, R. Lionberger, J. Wong, J. W. Jones, M. A. Kane, A. Krumholz, R. Temple and J. E. Polli, "Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard," Epilepsia, vol. 56, no. 9, pp. 1415-24, 2015.
[128] N. K. Sethi, "Letter to the Editor Re: Generic antiepileptic drugs and associated medical resource utilization in the United States," Neurology, 2010.
[129] R. Luhana, "Lawmakers Seek More Action on Ranitidine, While JAMA Withholds New Study," Legal Examiner, 22 January 2020. [Online]. Available: https://newyork.legalexaminer.com/health/lawmakers-seek-more-action-on-ranitidine-while-jama-withholds-new-study/. [Accessed 5 January 2025].
[130] Personal Care Product Council, "Comment from Personal Care Products Council," 10 November 2022. [Online]. Available: https://www.regulations.gov/comment/FDA-2021-P-1193-0005. [Accessed 5 January 2025].
[131] R. Felton, "A Tiny Lab Found Benzene in Sunscreen and Hand Sanitizer. Why Did the FDA Go After It?," Consumer Reports, 31 March 2022. [Online]. Available:

https://www.consumerreports.org/product-safety/valisure-found-benzene-in-products-fda-inspected-lab-a7872407447/. [Accessed 5 January 2025].
[132] B. Cox, "Why The US FDA Did Not Appreciate Valisure's Extra Measure Of Protection From Poor Quality Drugs," Pink Sheet, 4 January 2023. [Online]. Available: https://insights.citeline.com/PS147514/Why-The-US-FDA-Did-Not-Appreciate-Valisures-Extra-Measure-Of-Protection-From-Poor-Quality-Drugs/. [Accessed 5 January 2025].
[133] C. Bolado, "Drugmakers Won't Get Discovery From Valisure In Zantac MDL," Law 360, 28 January 2022. [Online]. Available: https://www.law360.com/healthcare-authority/articles/1459744/drugmakers-won-t-get-discovery-from-valisure-in-zantac-mdl. [Accessed 5 January 2025].
[134] G. Reed, Y. Hendlin, A. Desikan, T. MacKinney, E. Berman and G. T. Goldman, "The disinformation playbook: how industry manipulates the science-policy process—and how to restore scientific integrity," Journal of Public Health Policy, vol. 42, pp. 622-634, 2021.
[135] N. Z. A. H. M. D. W. H. C. G. B. M. G. A. D. D. Y. L. K. Kucera, "Evaluation of Benzene Presence and Formation in Benzoyl Peroxide Drug Products," Journal of Investigative Dermatology, vol. 24, pp. 02115-9, 2024.