

Drug Quality & Safety Issues in the US and Health- System Strategies to Address Them

- **Background**
 - Status quo
 - Independent Testing
- **Drug Quality Scoring**
 - Mechanics
 - Initial Data
- **Implementation**
 - DoD & Kaiser Models
 - Fixing a broken market & drug shortages



Born out of a Real World Need



Adam Clark-Joseph



David Light

Adam suffered serious complications with his anti-convulsant meds due to batch variability. He called up tech-development friend, David Light, to help solve the problem.

Adam is Not Alone..

Ever refilled a prescription and then noticed a difference in how you felt or how effective the medication was?

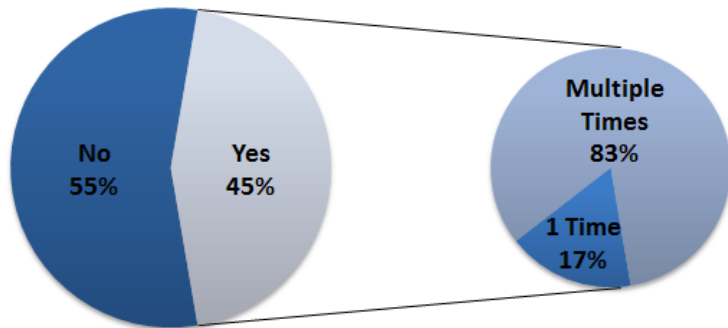
How many times has it happened?

Waynik Group Patient Survey

65 in-person respondents

Noticed a difference

Number of times

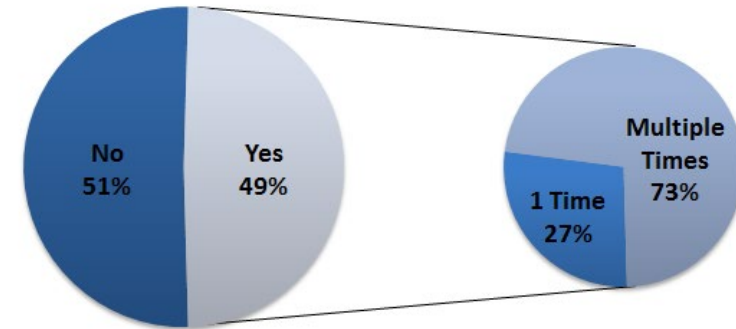


Google Consumer Survey

511 respondents on meds

Noticed a difference

Number of times

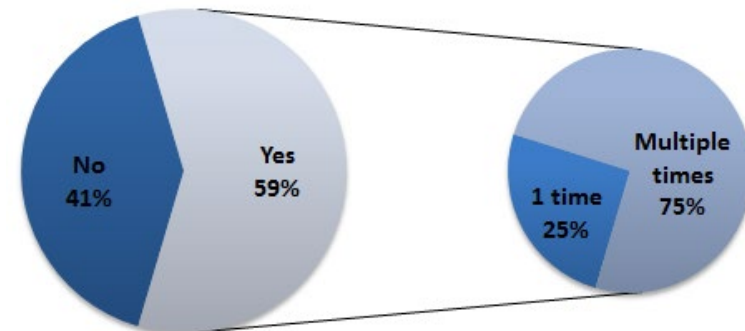


Pollfish Consumer Survey

720 respondents on meds

Noticed a difference

Number of times



Many Case Studies Reported by Doctors

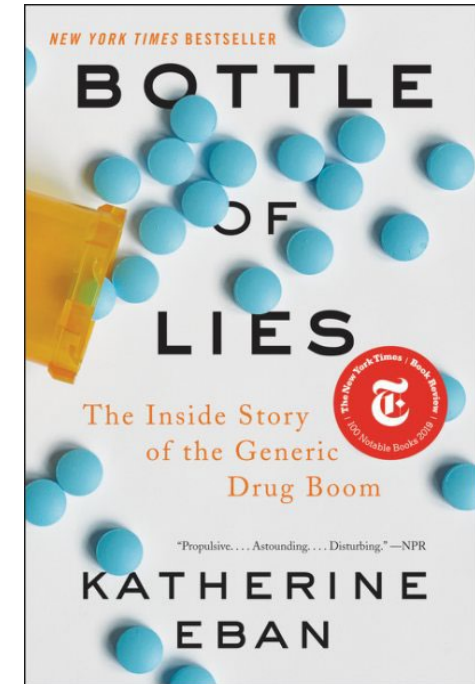
HEALTH AFFAIRS

Challenges In Ensuring The Quality Of Generic Medicines

A refill of a generic attention deficit hyperactivity disorder prescription leads to new side effects and raises questions about the quality of generic drugs.

BY KEVIN A. SCHULMAN

[Link ▶](#)



2019 NYT Bestseller

[Link ▶](#)



Medscape

'Sheriff' Cardiologist Sounds the Alarm on Ineffective Generics

[Link ▶](#)

FDA Regulatory Oversight is Highly Dependent on Manufacturers

“FDA is only as good as the data that manufacturers submit to it,” David Kessler, the FDA commissioner for most of the 1990s, said in an interview. “Yes, the agency can audit data, it can do inspections, but it’s not going to catch everything.”

Bloomberg

By Jef Feeley

February 1, 2019 at 5:00 AM EST

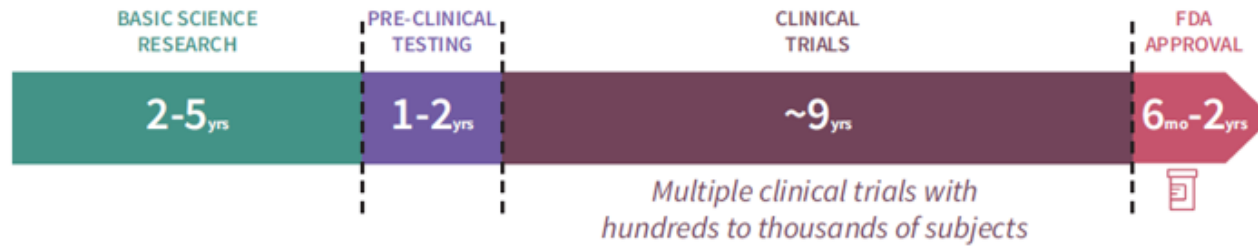
Regulation is Based on Honor System

The FDA does **NOT** routinely test drug products

FDA APPROVAL RIGOR \neq

QUALITY & SAFETY MONITORING

NEW DRUG APPROVAL



GENERIC DRUG APPROVAL



MANUFACTURER

~80% in India and China



HONOR SYSTEM
Self-reported data

TESTING DATA

FACILITY INSPECTIONS

CONCERNING BACKLOG

In 2022, 61% of high-risk facilities were not inspected in 5 years

[Link](#) ▶



A “Novel” Approach: **Independently Test & Certify Drugs**

Just like:

Electronics by industry demand



Food by consumer demand



EU has Network of Independent Testing Labs

The European Network of Official Medicines Control Laboratories (OMCLs)

WORKING TOGETHER TO PROTECT PUBLIC HEALTH IN EUROPE EVERY DAY



WHAT ARE THE EUROPEAN OMCLs?

Independent public laboratories with unique expertise to test medicines.

The Official Medicines Control Laboratories (OMCLs) are public institutions helping national competent authorities to control the quality of medicines.

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

What is Independent Testing?

Independent testing aims to answer *fundamental question*:

IS THIS A QUALITY PRODUCT?

“ISO” Screening vs “GMP” Product Validation

- **GMP/Regulatory:** 1,000s of methods for 1 product
- **ISO/Independent:** 1 method for 1,000s of products



*Speaking on Independent Testing
at June 2020 Senate Hearing*

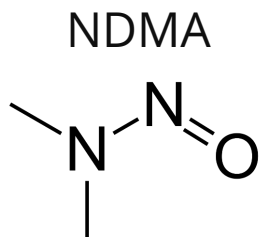
UNITED STATES SENATE
COMMITTEE ON FINANCE



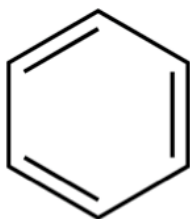
C-SPAN: Valisure Opening Remarks

[Link ▶](#)

Results from ~2 Years of Testing for Contaminants



Benzene



Drug Product	FDA For-Cause Testing	Independent Testing	Outcomes
VALSARTAN, LOSARTAN, IRBESARTAN	2013: 3 losartan tested - All tests passed 2015: 3 valsartan tested - All tests passed 2017: 3 losartan, 2 irbesartan tested - All tests passed	Novartis 2018: Tests on valsartan API ordered from Zhejiang Huahai reveal high level of impurity – further independent testing detected carcinogen NDMA . Subsequent investigations determine losartan and irbesartan also contaminated. Valisure 2019: 34 valsartan tested - Detected carcinogen DMF	- Recalls of over 1,000 drug lots in the US - Valisure filed FDA Citizen Petition on DMF in valsartan, 6/13/19
ZANTAC / RANITIDINE	2014: 1 product tested. - All tests passed , tested due to impurities complaint	Valisure 2019: 10 products tested. - Detected carcinogen NDMA and determined drug degrades into NDMA	- Recalls - Market withdrawal - Clinical and in vitro studies conducted by FDA
NIZATIDINE	2014: 1 product tested. - All tests passed , tested due to impurities complaint	Valisure 2019: 1 product tested. - Detected carcinogen NDMA and determined drug degrades into NDMA	- Recalls - Drug discontinued by multiple companies.
METFORMIN	2015-16: 19 products tested. - All tests passed Feb 2020: 16 products tested for NDMA - All tests passed	Valisure 2020: 38 products tested. - Detected carcinogens NDMA and DMF	- Recalls for NDMA, latest recall: 6/11/21 - DMF still not addressed by FDA
HAND SANITIZERS	2020-21: 200+ FDA alerts for detecting methanol, no benzene testing	Valisure 2021: 260 products tested. - Detected carcinogen benzene , in addition to methanol and other impurities	- First recall due to benzene on 4/28/21 - FDA alert for ArtNaturals products 10/4/21
SUNSCREEN	No product quality testing	Valisure 2021: 294 products tested. - Detected carcinogen benzene	- Recalls due to benzene of multiple major brands
ANTIPERSPIRANTS	No product quality testing	Valisure 2021: 108 products tested. - Detected carcinogen benzene	- Recalls due to benzene of multiple major brands

Turning Data into Actionable “Quality Scores”



Journal of the
American Pharmacists
Association

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

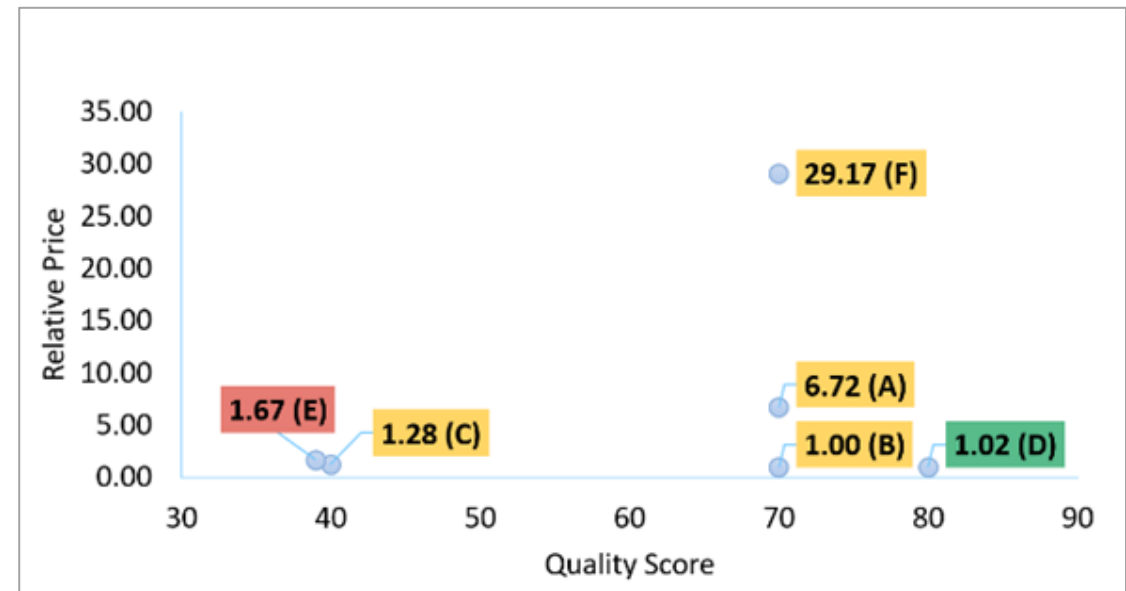
Long Island University School of Pharmacy, Cleveland Clinic, Columbia University Medical Center, Defense Health Agency, NYU Langone Medical Center, Ohio State University, People’s Pharmacy, Stanford University, University of Connecticut School of Pharmacy, University of Utah Health Care, Valisure, Yale School of Medicine

<https://www.sciencedirect.com/science/article/abs/pii/S1544319122003272>

October 10, 2022

SCORE	DESCRIPTION
RED	High risk <i>of containing chemical quality issues</i>
YELLOW	Medium risk
GREEN	Low risk

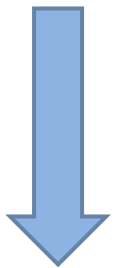
Valsartan: Price vs Quality Score



Scoring Mechanics

Scoring Rubric / “Cut-offs” for “Red / Yellow / Green” set by Expert Review Panel

Independent
chemical
testing data



Scoring
Rubric
& Final Score

	<i>Effectiveness</i>				<i>Safety</i>			
	Dosage (% of label)	Dissolution ("Difference" to brand)	Contaminant (ppb lead)	Contaminant (ppm impurity-X)	Carcinogen (ppb NDMA)	Carcinogen (ppm DMF)	Cross- Contamination (# of APIs)	Cross- Contamination (# of total hits)
Manufacturer A	98%	2	0.3	1.2	0	0.2	3	33
Manufacturer B	101%	10	0	1.6	0	0	0	26
Manufacturer C	103%	8	0.4	1.1	0	98	1	72
Manufacturer D	99%	5	2.1	1.5	0	0.5	0	19
Manufacturer E	96%	12	0	7.7	0	7	4	88

	Dosage (% of label)	Dissolution ("Difference" to brand)	Contaminant (ppb lead)	Contaminant (ppm impurity-X)	Carcinogen (ppb NDMA)	Carcinogen (ppm DMF)	Cross- Contamination (# of APIs)	Cross- Contamination (# of total hits)	SCORE
Manufacturer A	--	--	--	--	--	--	--	--	100
Manufacturer B	--	-30	--	--	--	--	--	--	70
Manufacturer C	--	-10	--	--	--	-61	--	-10	19
Manufacturer D	--	--	-10	--	--	--	--	--	90
Manufacturer E	--	-61	--	-10	--	--	-10	-10	9

Quality Scores Implementation

New Column
NDC-specific scores



Supplier	NDC	PRICE	SCORE
Manufacturer A	12345-678-90	3.45	GRN
Manufacturer B	54321-987-90	3.21	YLW
Manufacturer C	12345-876-90	5.78	RED
Manufacturer D	33333-888-90	3.25	GRN
Manufacturer E	22222-778-90	3.94	RED

SELECT

Initial Data on Tacrolimus

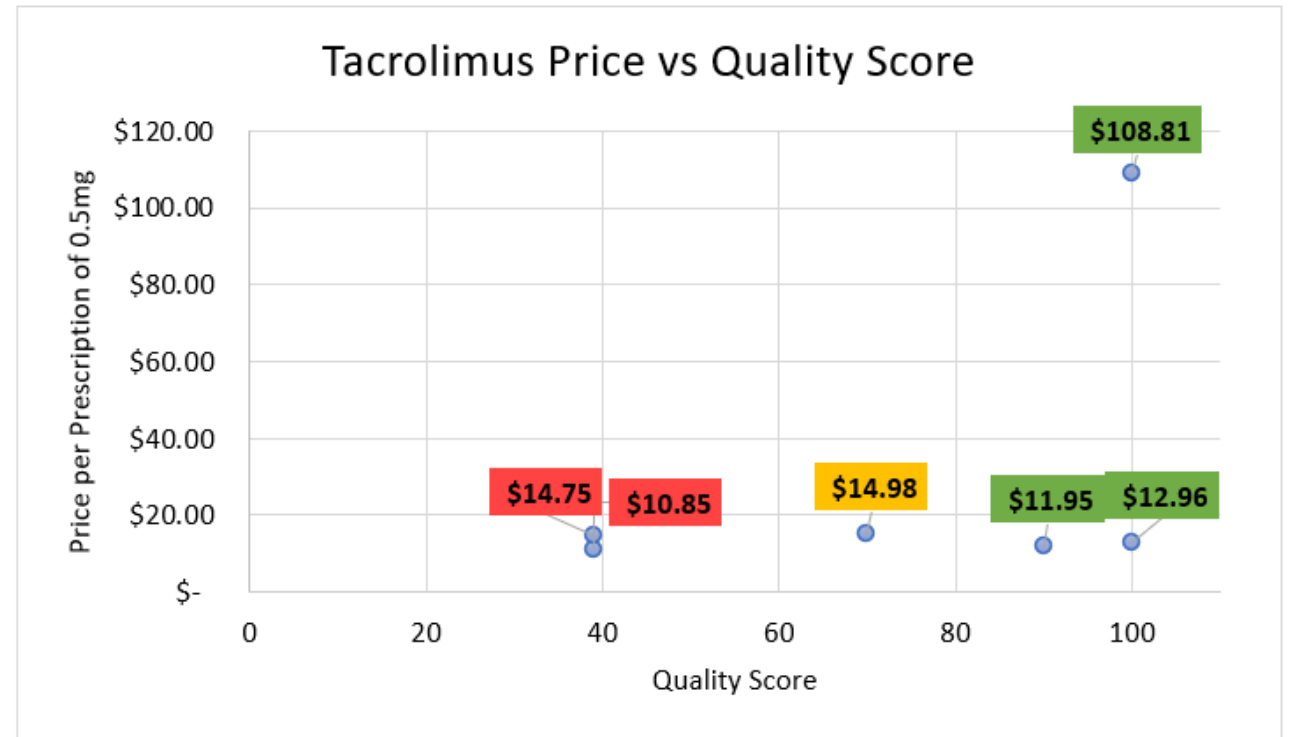
Used to prevent organ rejection after transplant of skin (for combat burn victims), kidney, liver, lung or heart.

	Initial Score	Dosage (Score Impact)	Carcinogens (Score Impact)	Toxic Elements (Score Impact)	Notes
Manufacturer A (Generic)	39	-61	--	--	After concerns first raised in 2012, FDA reclassified bioequivalence status on 9/18/23
Manufacturer B (Brand)	100	--	--	--	
Manufacturer C (Generic)	100	--	--	--	
Manufacturer D (Generic)	90	-10	--	--	
Manufacturer E (Generic)	39	-61	--	--	
Manufacturer F (Generic)	70	-30	--	--	

Price vs Quality Score (Tacrolimus)

Pricing from prime vendor pulled for each tested product and compared to the quality score

	Score	Price
Manufacturer A (Generic)	39	\$10.85
Manufacturer B (Brand)	100	\$108.81
Manufacturer C (Generic)	100	\$12.96
Manufacturer D (Generic)	90	\$11.95
Manufacturer E (Generic)	39	\$14.75
Manufacturer F (Generic)	70	\$14.98



Initial Data on Furosemide

Used to treat edema and swelling caused by congestive heart failure, liver disease, kidney disease, etc.

	Initial Score	Dosage	Dissolution	Carcinogens	Toxic Elements
Manufacturer A (Generic)	90	--	--	-10	--
Manufacturer B (Generic)	60	--	--	-10	-30
Manufacturer C (Generic)	100	--	--	--	--
Manufacturer D (Generic)	100	--	--	--	--
Manufacturer E (Generic)	100	--	--	--	--
Manufacturer F (Generic)	100	--	--	--	--
Manufacturer G (Generic)	100	--	--	--	--
Manufacturer H (Generic)	90	-10	--	--	--
Manufacturer I (Generic)	90	--	--	-10	--
Manufacturer J (Generic)	70	--	--	-30	--
Manufacturer K (Generic)	70	-30	--	--	--
Manufacturer L (Generic)	100	--	--	--	--
Manufacturer M (Generic)	100	--	--	--	--
Manufacturer N (Generic)	100	--	--	--	--
Manufacturer O (Generic)	90	--	--	-10	--
Manufacturer P (Generic)	100	--	--	--	--
Manufacturer Q (Generic)	100	--	--	--	--
Manufacturer R (Generic)	80	-10	--	-10	--
Manufacturer S (Generic)	100	--	--	--	--
Manufacturer T (Brand)	70	--	--	--	-30
Manufacturer U (Generic)	100	--	--	-10	--

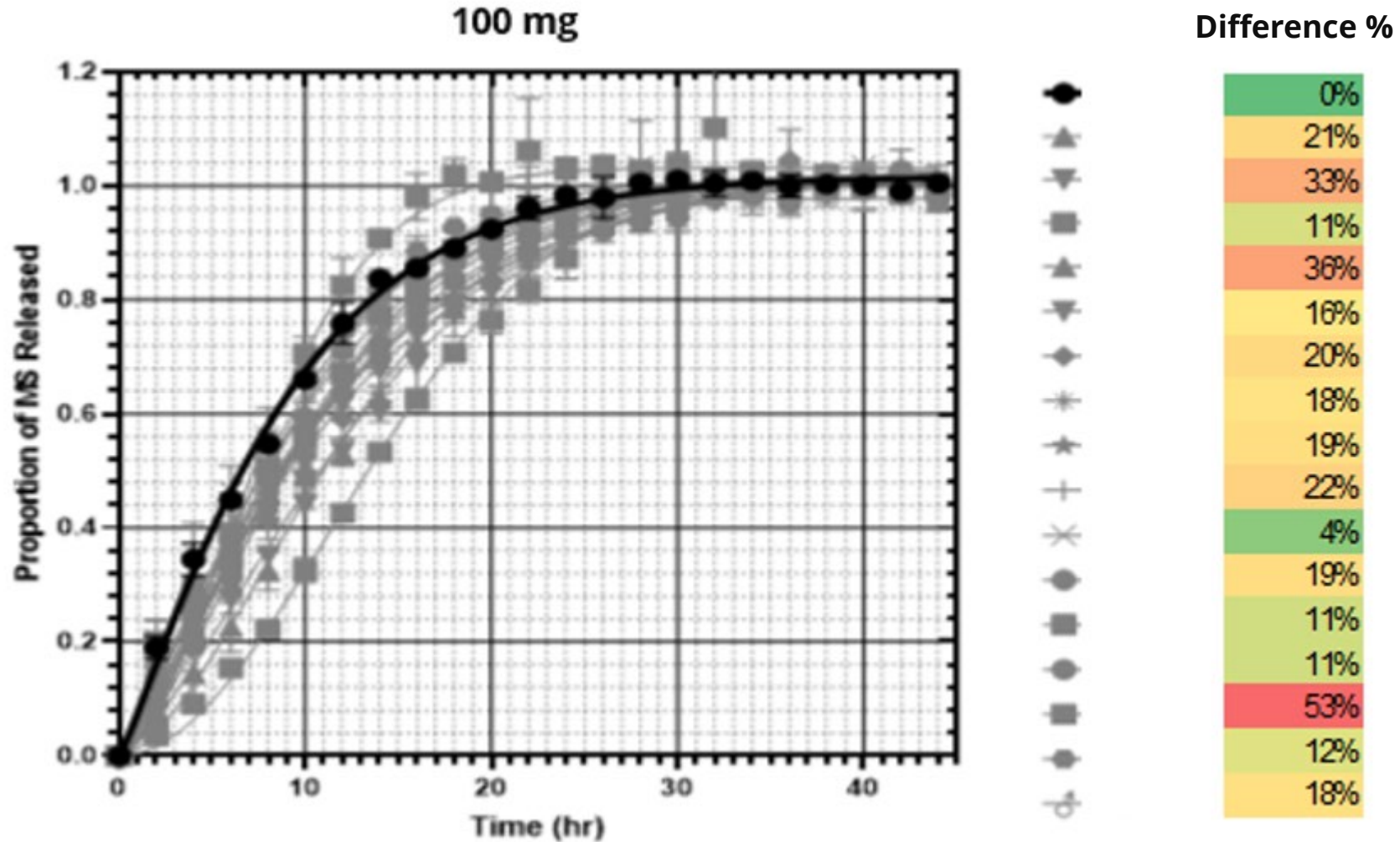
Initial Data on Metoprolol

Used to treat chest pain (angina), heart failure, and high blood pressure.

	Initial Score	Dissolution	Carcinogens	Toxic Elements
Manufacturer A (Brand)	100	--	--	--
Manufacturer B (Generic)	70	-30	--	--
Manufacturer C (Generic)	40	-30	--	-30
Manufacturer D (Generic)	90	-10	--	--
Manufacturer E (Generic)	70	-30	--	--
Manufacturer F (Generic)	70	-30	--	--
Manufacturer G (Generic)	90	-10	--	--
Manufacturer H (Generic)	60	-30	--	-10
Manufacturer I (Generic)	90	-10	--	--
Manufacturer J (Generic)	90	-10	--	--
Manufacturer K (Generic)	90	-10	--	--
Manufacturer L (Generic)	70	-30	--	--
Manufacturer M (Generic)	90	-10	--	--
Manufacturer N (Generic)	70	-30	--	--
Manufacturer O (Generic)	9	-61	--	-30
Manufacturer P (Generic)	100	--	--	--
Manufacturer Q (Generic)	39	-61	--	--

Metoprolol Dissolution Highly Variable

“Similar” products expected to be **less than 15% difference**



Many Studies Link Generic Drug Variability and Adverse Events

Generic antiepileptic drugs and associated medical resource utilization in the United States [Link >](#)

Impact of the Commercialization of Three Generic Angiotensin II Receptor Blockers on Adverse Events in Quebec, Canada

A Population-Based Time Series Analysis [Link >](#)

Hemorrhagic and Thrombotic Events Associated with Generic Substitution of Warfarin in Patients with Atrial Fibrillation: A Retrospective Analysis [Link >](#)

The risks and costs of multiple-generic substitution of topiramate [Link >](#)

Results: Compared to brand use, multiple-generic use was associated with higher utilization of other prescription drugs, **higher hospitalization rates** and longer hospital stays, but the effect was less pronounced in single-generic use. The risk of **head injury or fracture was nearly three times higher** following a generic-to-generic switch compared to brand use.



2023 Drug Shortages Skyrocket, #1 Cause: Quality Issues

**THE
WALL STREET
JOURNAL**

Drug Shortages Stem From Quality Problems in Indian Factories

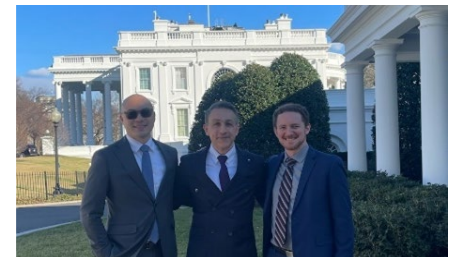
Eye drops, chemotherapy drugs raise concerns about generic products



Oversight and Investigations Subcommittee
Hearing: “Examining the Root Causes of Drug Shortages: Challenges in Pharmaceutical Drug Supply Chains”

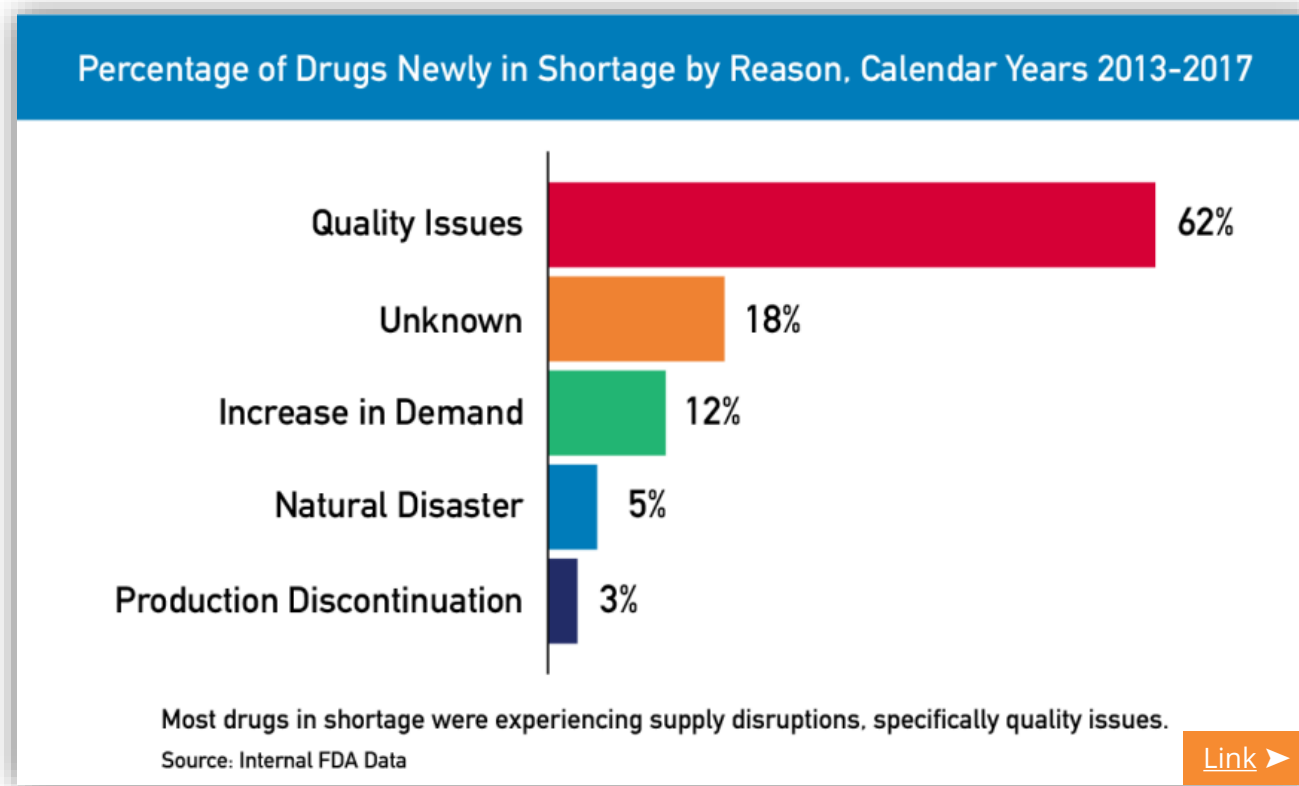
Bloomberg

White House Assembles Secret Team to Tackle Drug Shortages, Quality Woes



2023 Drug Shortages Skyrocket, #1 Cause: Quality Issues

FDA Data:

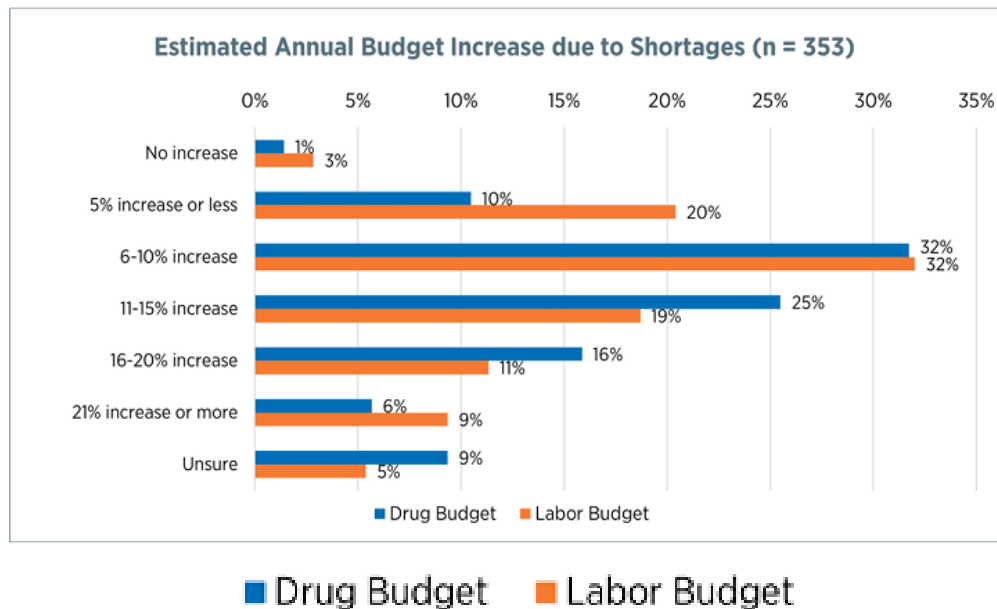


76% of *known* reasons for drug shortages:
Quality Issues

Drug Shortages: 2023 ASHP Nationwide Survey



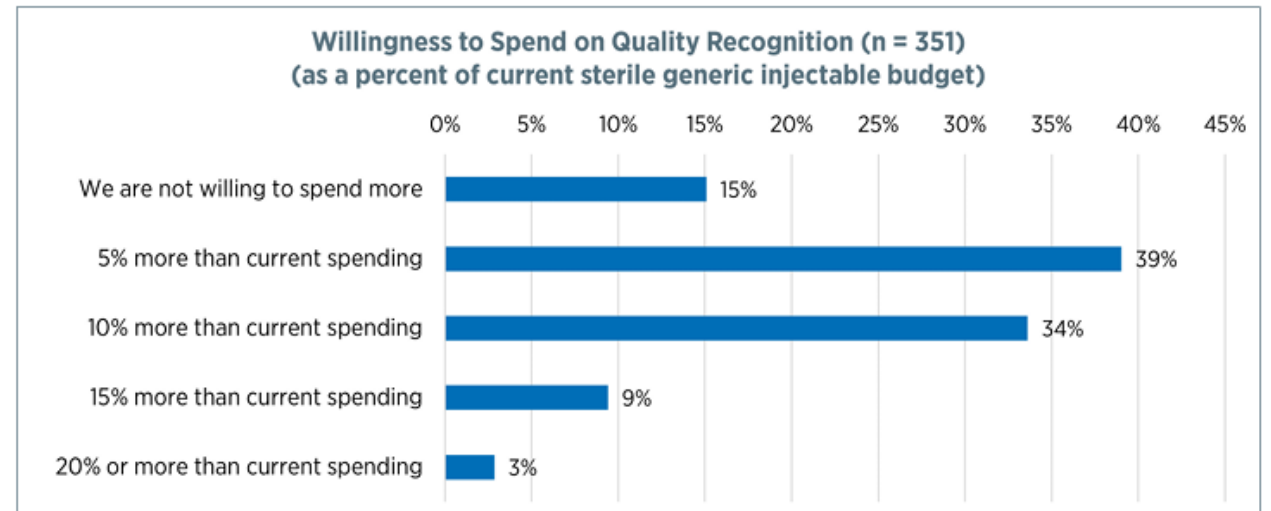
Shortages are costly



Health systems *want* quality recognition programs

Quality Recognition Programs

The 354 survey respondents who said they participate in drug budgeting were also asked if they are willing to spend more on drug products from manufacturers that achieve quality recognition. In all, 85% were willing to spend more on such products. Most respondents were willing to spend 5% more (39%) or 10% more (34%).



Root Causes of Problem

Journal of
Pharmaceutical Innovation

FDA Approaches in Monitoring Drug Quality, Forces Impacting the Drug Quality, and Recent Alternative Strategies to Assess Quality in the US Drug Supply

[Link](#) ▶

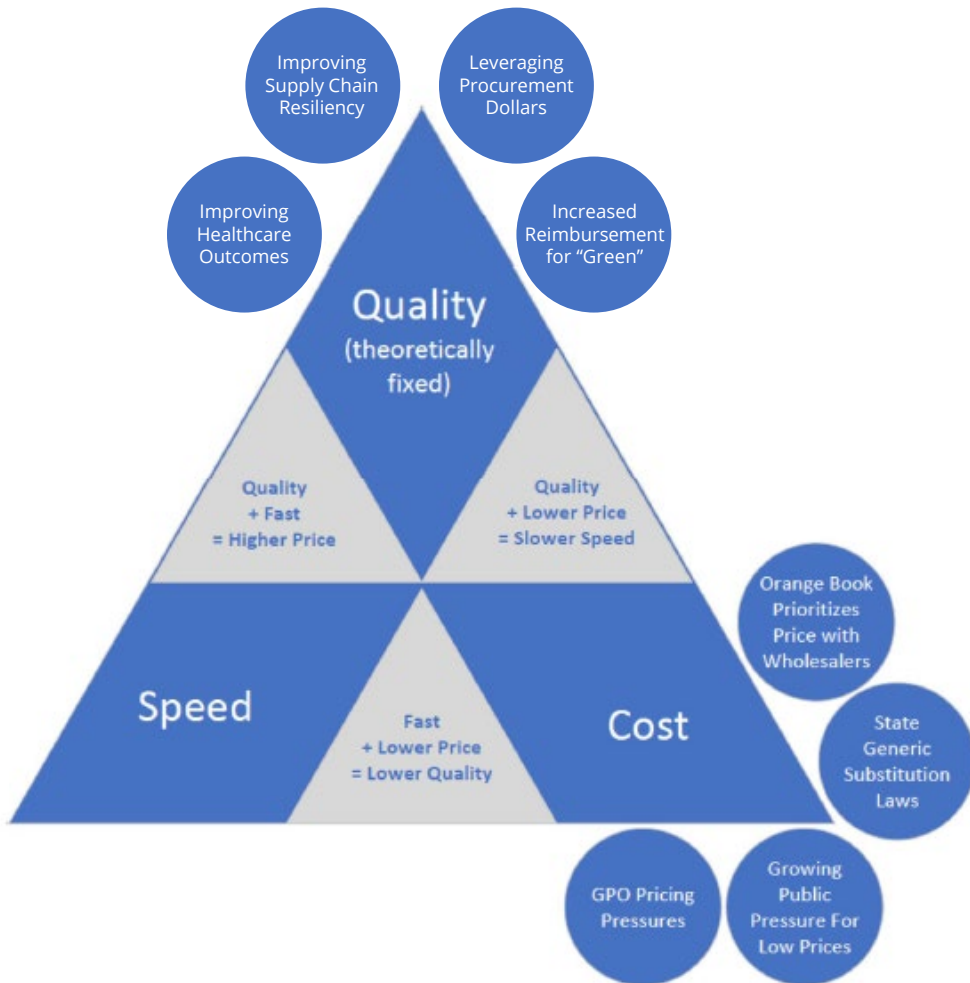


40+ years of market focused solely on PRICE

QUALITY is assumed based on singular FDA approval and limited facility surveillance

No transparency to product quality

Incentivizing **Quality** Fixes Broken Marketplace



UNITED STATES SENATE COMMITTEE ON FINANCE

Full Committee Hearing

Drug Shortages: Examining Supply Challenges, Impacts, and Policy Solutions from a Federal Health Program Perspective

Date: Tuesday, December 5, 2023

[Link](#) ▶



Senator Mike Crapo:

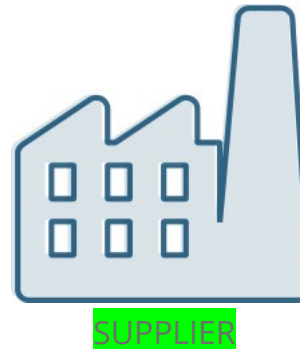
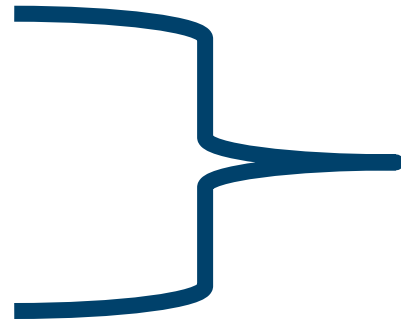
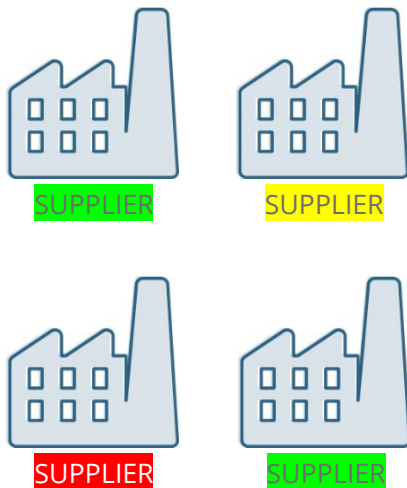
"Let me tell you the issue that I'm focused on. Every one of you has made the point that one of the big problems here is that we don't compensate for quality, we compensate for price of product only. And I get that. What I am trying to figure out, given that we are talking about Federal Government administrated payment systems, is who's going to decide, if we get a solution here, who decides which products are worth more compensation?"

Quality Scores + Contracting Programs

Data for selecting “green” supplier and ongoing certification requirement to ensure product remains green



**KAISER
PERMANENTE®**



PURCHASER

Improve the System to Improve Quality for Patients



Internal Testing Program



External Testing Program



Contract Requirements



Drug Quality Scores



Outcomes Research



www.fda.gov

Thank You

David.Light@Valisure.com