

# Safety vs Price in the Generic Drug Market: Metformin

Ben Teasdale, MPhil; Amber Hudspeth, MS; Kaury Kucera, PhD; David Light, BS; Jill Nailor, RPh; Shannon Williams, BS; Arnold Milstein, MD; and Kevin A. Schulman, MD

**M**etformin, a first-line drug used in the treatment of type 2 diabetes, was prescribed 85 million times in the US in 2019.<sup>1</sup> In early 2020, independent testing of marketed generic metformin extended-release (ER) tablets in the US revealed the presence of the known carcinogen *N*-nitrosodimethylamine (NDMA).<sup>2,3</sup> Regulation of NDMA is based on evidence of DNA mutagenicity in animal models, and NDMA is estimated to cause cancers in 1 in 100,000 patients with continued exposure above acceptable limits.<sup>4,5</sup> Recalls began in June 2020 with all-lot recalls from Apotex Inc and Amneal Pharmaceuticals Inc, and subsequent detection of NDMA has since led to recalls of products from 13 different labelers.<sup>2</sup> This process is global<sup>6</sup> and ongoing; Viona Pharmaceuticals Inc issued a recall of metformin ER products due to detection of NDMA as recently as January 7, 2022.<sup>7</sup> NDMA is hypothesized to be introduced to the metformin supply via contamination of active pharmaceutical ingredients (APIs) with NDMA precursors or factors related to film coating.<sup>8-10</sup>

This problem is not unique to metformin; NDMA contamination has also led to extensive recalls of other drug products, including ranitidine,<sup>11-13</sup> angiotensin-converting enzyme inhibitors,<sup>14</sup> and angiotensin II receptor blockers.<sup>15-17</sup> Nor is the problem of drug contamination exclusive to NDMA; *N,N*-dimethylformamide (DMF), a common solvent used in drug manufacturing, has been detected in high levels in various finished drug products.<sup>18,19</sup> DMF, classified as a group 2A probable carcinogen by the World Health Organization (WHO) due to animal-model evidence, is both inherently toxic and a precursor to NDMA production.<sup>19</sup>

In the context of an increasingly globalized drug supply chain—and the significant delays in regular foreign site inspections caused by COVID-19–related travel restrictions—product-level recalls provide an increasingly important complement to the FDA's quality surveillance program, which traditionally relies heavily on inspection at the manufacturer level.<sup>20-23</sup> Although product-level surveys of drug quality have been published abroad,<sup>24</sup> there has been no public-facing analysis of metformin recalls in the US. Literature on nitrosamine contamination tends to focus on either (1) analytic methods for detection of impurities or strategies for reducing their

## ABSTRACT

**OBJECTIVES:** Generic medications represent 90% of prescriptions in the US market and provide a tremendous financial benefit for patients. Recently, multiple generic drugs have been recalled due to the presence of carcinogens, predominantly *N*-nitrosodimethylamine (NDMA), including an extensive recall of extended-release (ER) metformin products in 2020.

**STUDY DESIGN:** Primary pharmaceutical quality testing and database analysis.

**METHODS:** We tested marketed metformin immediate-release (IR) and ER tablets from a wide sample of generic manufacturers for the presence of carcinogenic impurities NDMA and *N,N*-dimethylformamide (DMF). We examined the association of level of impurity with drug price and the impact of the 2020 FDA recalls on unit price and prescription fill rate.

**RESULTS:** Postrecall NDMA levels were significantly lower in metformin ER samples (standardized mean difference =  $-2.0$ ;  $P = .01$ ); however, we found continued presence of carcinogens above the FDA threshold in 2 of 30 IR samples (6.67%). Overall, the presence of contaminant levels was not significantly associated with price for either IR (NDMA:  $R^2 = 0.142$ ;  $P = .981$ ; DMF:  $R^2 = 0.382$ ;  $P = .436$ ) or ER (NDMA:  $R^2 = 0.124$ ;  $P = .142$ ; DMF:  $R^2 = 0.199$ ;  $P = .073$ ) samples. Despite recalls, metformin ER prescription fills increased by 8.9% while unit price decreased by 19.61% ( $P < .05$ ).

**CONCLUSIONS:** Recalls of metformin ER medications were effective in lowering NDMA levels below the FDA threshold; however, some samples of generic metformin still contained carcinogens even after FDA-announced recalls. The absence of any correlation with price indicates that potentially safer products are available on the market for the same price as poorer-quality products.

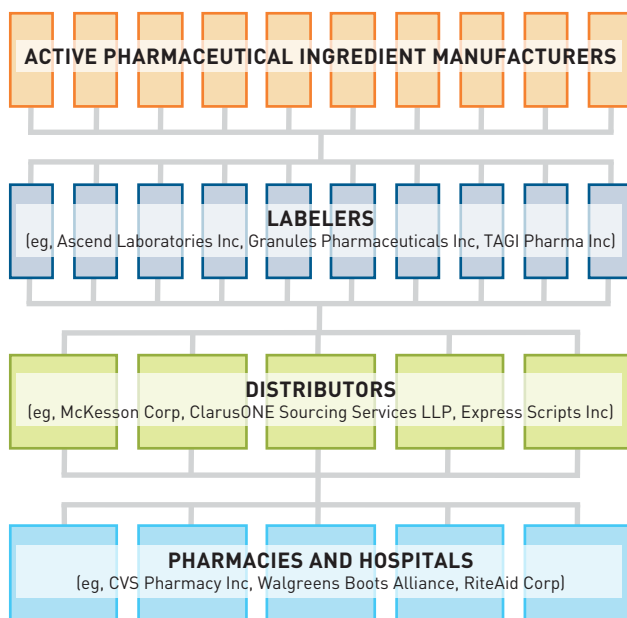
*Am J Manag Care.* 2024;30(4):161-168. doi:10.37765/ajmc.2024.89450

## TAKEAWAY POINTS

Generic medications represent 90% of prescriptions in the US market, but the market focuses extensively on price. Recently, however, multiple generic metformin drugs have been recalled due to poor drug quality, including the presence of carcinogens.

- ▶ We examined the price and quality after recalls of metformin and found better-quality drugs on the market at the same or lower cost.
- ▶ Making the supply chain accountable for quality will not increase the price of medications or affect access to generic drugs.

FIGURE 1. Supply Chain of Pharmaceutical Production\*



\*Generic medication production begins with synthesis of active pharmaceutical ingredients. Labelers are intermediaries in the pharmaceutical supply chain that generally purchase these active pharmaceutical ingredients and combine them with other ingredients (such as fillers) to create the final medication form (eg, tablets, capsules). Medical distributors then purchase generic medication from many labelers and ship these products to patient-facing organizations (ie, hospital systems and retail pharmacies).

generation during drug manufacturing or (2) qualitative reviews of the regulatory issues in drug quality.<sup>8,13,25-27</sup>

To our knowledge, no paper has attempted to quantify how metformin recalls affected the market for generic products both pharmacologically (in enduring measures of quality past the recall period) and economically (in terms of drug access and pricing). The voluntary recalls in the metformin market provide a natural experiment to test the following questions: First, did the recalls improve the quality of generic medications on the market, using NDMA and DMF contamination as a proxy for product quality? Second, did the removal of medications with higher contaminant levels from the market have an impact on price or access for consumers?

## METHODS

## Generic Market: Relevant Background

Generic medication production begins with synthesis of an API (Figure 1). Labelers are intermediaries in the pharmaceutical supply chain that generally purchase APIs and combine them with other ingredients (such as fillers) to create the final medication form (eg, tablets, capsules). Generally, a labeler will use a single quantity of an API from a supplier to produce

a batch of medications. For example, a single barrel of an API may be used to produce a batch size of 500,000 tablets. Each batch is then used to create pills that are characterized as lots based on the dosage form. In other words, a single batch can produce several lots of medications. Labelers, however, may switch API suppliers between batches of medications, creating the possibility of batch-to-batch variation in product quality within the same labeler.

Medical distributors then purchase generic medication from many labelers and ship these products to health care systems and retail pharmacies.<sup>28</sup> Red Oak Sourcing LLC, McKesson Corp, ClarusONE Sourcing Services LLP, and Express Scripts Inc are the dominant medical distributors in the US, controlling 91% of the market.<sup>29</sup> Due to this production, labeling, and distribution pattern, generic products utilized by the same hospital system or the same retail pharmacy may vary over time in a manner largely opaque to both health care providers and their patients. Products within the same lot and same batch are generally considered to have the same quality; however, quality may vary within a single labeler over time because of changes to API sourcing, and quality may vary within a single distributor over time given the presence of multiple labelers.

## Sampling Strategy

In October 2021, generic metformin was purchased by both Stanford Health Care and Valisure, LLC, in an attempt to capture products from a varied set of labelers. One bottle of generic metformin immediate release (IR) or ER was purchased from each available labeler for each available dosage. Products from all labelers may not be available at all times due to stocking decisions by distributors. Purchase price was recorded and normalized to a 90-tablet prescription for ease of comparison. All samples were shipped to a central facility (Valisure) for quality analysis. Valisure is an analytic pharmacy accredited by the International Organization for Standardization to perform quality testing, and several authors of this study are current employees.

## Quality Assessment

In this study, quality testing assessed for the presence of the carcinogenic compounds NDMA and DMF using liquid chromatography mass spectroscopy methods previously described in literature.<sup>30</sup> (See eAppendix A [eAppendices available at [ajmc.com](https://www.ajmc.com)] for a complete discussion of drug quality testing protocols.) Four metformin tablets

were selected from each bottle and analyzed separately for each round of quality testing. Upper levels of acceptability were 96 ng per maximum daily dose for NDMA and 8800 µg per maximum daily dose for DMF. Cutoffs for NDMA were based on FDA guidance for acceptable daily intake based on a 1 in 100,000 cancer risk over a 70-year period.<sup>4,31</sup> DMF is recognized as both a group 2A carcinogen by the WHO and a potential precursor to NDMA, and the cutoff used was based on current FDA recommendations.<sup>4,19</sup>

To determine the efficacy of product recall on improving medication quality, NDMA and DMF contaminant levels for metformin IR and metformin ER samples collected during our study in October 2021 were compared with existing data generated from metformin purchased in 2019 and previously published by Valisure.<sup>3,18</sup> Comparisons of contaminant levels pre- and post recall were quantified using the standardized mean difference (SMD).

### Cost and Quality of Generic Metformin: Product-Level Associations

The association between levels of carcinogenic contaminants and drug price was assessed by examining samples purchased in October 2021 using separate ordinary least squares linear regression models for each NDMA and DMF and plotted on correlation plots. Pricing data were defined as the purchase price obtained by each purchaser (Stanford or Valisure), normalized to a 90-pill prescription. Variations in carcinogenic contaminant level were normalized to that expected if taking the prescription at maximum daily dose (2500 mg) to account for variation in dosages. The potential for bias from autocorrelation between initial product dosage and level of carcinogen was examined using the collinearity diagnostics function in Stata (ie, the collin command). Finally, the regression model separately controlled for purchaser, which may confound price in a product-agnostic way.

### Cost and Quality of Generic Metformin: Market-Level Trends

To determine the impact of product recall on drug access and price at the market level, we used the Medicaid State Drug Utilization Data to examine metformin ER product sales quantity and unit prices before and after the recalls.<sup>32</sup> This data set reports all prescriptions filled through Medicaid drug programs in all 50 states at the National Drug Code level by fiscal quarter. Importantly, this data set reports the number of prescriptions filled by labeler and product codes within each quarter, allowing the differentiation between recalled and unrecalled products when examining time trends. The data set also reports total reimbursement in US\$, which can be used to calculate unit price. FDA-announced recalls of metformin ER began on June 11, 2020.<sup>2</sup> This included all-lot recalls of products from the labelers Amneal, Apotex, and Lupin Pharmaceuticals, Inc, and partial-lot recalls of products from 3 other labelers (Marksans Pharma Ltd, Lupin, and Teva Pharmaceuticals USA, Inc). Our study examined data from quarter 1 through quarter 4 of 2020 and compared products from recalled and unrecalled labelers. Labelers

were considered recalled only if subject to all-lot recalls, as lot-level data are not available in this data set.

### Statistical Analysis

All statistical analyses mentioned here and the creation of the resultant figures were completed using Stata 16 (StataCorp LLC).

## RESULTS

### Product Sampling

In October 2021, we obtained metformin IR products from 9 of 21 labelers in the Medicaid database, representing 63.9% of claims filled under the Medicaid program during 2021, and we obtained metformin ER products from 9 of 21 labelers in the Medicaid database, representing 98.2% of claims filled under the Medicaid program during 2021 (**Table 1**). Acquisition of samples from other labelers was limited by availability from distributors contracted with Stanford and Valisure.

### Quality Assessment

In general, contaminant levels between replicates of the same sample were highly congruent, with SD averaging 7 ng for NDMA and 2.5 µg for DMF levels. For metformin IR in 2021, mean NDMA levels were 15 ng (95% CI, 4-32 ng) and mean DMF levels were 19.9 µg (95% CI, 11.9-27.9 µg) (**Table 2**). For metformin ER in 2021, mean NDMA levels were 8.6 ng (95% CI, 1-16 ng) and mean DMF levels were 14.6 µg (95% CI, 4.4-24.8 µg). In total, 2 of 30 (6.67%) metformin IR products and 0 of 26 (0.00%) metformin ER products contained NDMA levels above the FDA acceptable daily intake limit of 96 ng/day. Labelers with samples with NDMA levels above this limit comprised 10.6% of metformin IR claims filled under the Medicaid drug programs in 2021. No samples tested contained DMF levels above the current standard.

For metformin IR products purchased prior to the FDA-announced recalls, mean NDMA levels were 15 ng (95% CI, 5-25 ng) and mean DMF levels were 64.5 µg (95% CI, 8.8-120.0 µg). Changes in levels of carcinogens before and after recall were not significant for NDMA (SMD=0.02; *P*=.92) but were significant for DMF (SMD=-14.0; *P*=.03). For metformin ER products purchased prior to the FDA-announced recalls, mean NDMA levels were 264 ng (95% CI, 50-477 ng) and mean DMF levels were 63.3 µg (95% CI, 21.3-105.2 µg). Changes in levels of carcinogens before and after recall were significant for NDMA (SMD=-2.0; *P*=.01) but not significant for DMF (SMD=-1.92; *P*=.07) (**Table 2**).

### Cost and Quality of Generic Metformin: Product-Level Associations

Metformin IR contaminant levels were not significantly associated with 90-tablet prescription price (**Figure 2**; for regression results see **Appendix Table 1**). This lack of association held true for both NDMA ( $R^2=0.142$ ; *P*=.981) and DMF ( $R^2=0.382$ ; *P*=.436). Similarly, metformin ER contaminant levels were not significantly associated

**TABLE 1.** Number of Metformin Samples Tested Before and After Product Recalls<sup>a</sup>

	Immediate release		Extended release	
	2019	2021	2019	2021
Unique samples, n	16	30	22	26
Unique labelers, n	8	9	14	9
By labeler, n (%)				
ACI Pharmaceuticals	3 (18.75)	0 (0.00)	0 (0.00)	0 (0.00)
Actavis Generics	0 (0.00)	0 (0.00)	2 (9.09)	0 (0.00)
AiPing Pharmaceutical Inc	0 (0.00)	0 (0.00)	2 (9.09)	0 (0.00)
American Pharmaceutical Co	1 (6.25)	0 (0.00)	0 (0.00)	0 (0.00)
Amneal Pharmaceuticals Inc	1 (6.25)	0 (0.00)	4 (18.18)	0 (0.00)
Apotex Inc	0 (0.00)	0 (0.00)	2 (9.09)	0 (0.00)
Ascend Laboratories LLC	3 (18.75)	5 (16.67)	0 (0.00)	6 (23.08)
Aurobindo Pharma Ltd	2 (12.50)	5 (16.67)	0 (0.00)	0 (0.00)
Bayshore Pharmaceuticals	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.85)
Epic Pharma LLC	0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
Granules Pharmaceuticals Inc	0 (0.00)	6 (20.00)	1 (4.55)	3 (11.54)
Heritage Pharmaceuticals Inc	3 (18.75)	0 (0.00)	0 (0.00)	0 (0.00)
Ingenus Pharmaceuticals LLC	0 (0.00)	0 (0.00)	1 (4.55)	1 (3.85)
Laurus Labs	0 (0.00)	1 (3.33)	0 (0.00)	0 (0.00)
Lupin Pharmaceuticals Inc	0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
Megalith Pharmaceuticals Inc	1 (6.25)	0 (0.00)	0 (0.00)	0 (0.00)
Mylan Pharmaceuticals Inc	0 (0.00)	2 (6.66)	1 (4.55)	0 (0.00)
Nivagen Pharmaceuticals Inc	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.85)
Nostrum Laboratories Inc	0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
Oceanside Pharmaceuticals	0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
ScieGen Pharmaceuticals Inc	0 (0.00)	3 (10.00)	0 (0.00)	0 (0.00)
Sun Pharmaceutical Industries Inc	0 (0.00)	0 (0.00)	2 (9.09)	3 (11.54)
TAGI Pharma Inc	0 (0.00)	1 (3.33)	2 (9.09)	7 (26.92)
TIME Pharmaceuticals	0 (0.00)	0 (0.00)	1 (4.55)	3 (11.54)
Viona Pharmaceuticals Inc	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.85)
Westminster Pharmaceuticals LLC	2 (12.50)	3 (10.00)	0 (0.00)	0 (0.00)
Zyodus Pharmaceuticals (USA) Inc	0 (0.00)	4 (13.33)	0 (0.00)	0 (0.00)

<sup>a</sup>Metformin samples were purchased before (2019) and after (2021) product recalls. Metformin was ordered from labelers available to 2 different buyers, Stanford Health Care and Valisure LLC. Both immediate-release and extended-release metformin were ordered with varying strengths and package sizes (ie, quantity per bottle).

with 90-tablet prescription price for either NDMA ( $R^2=0.124$ ;  $P=.142$ ) or DMF ( $R^2=0.199$ ;  $P=.073$ ). Initial sample dosage was confirmed not to be collinear with other examined variables, including contaminant levels and price.

### Cost and Quality of Generic Metformin: Market-Level Trends

In quarter 1 of 2020, Amneal Pharmaceuticals and Apotex produced 12.2% of examined metformin ER prescriptions filled under Medicaid drug programs (Figure 3). By quarter 4 of 2020, after the FDA-announced recalls, utilization of metformin ER for those labelers decreased to 0.3%. During this same period, fills from other labelers increased by 24.1% and total metformin ER prescription

fills increased by 8.9%. Further, unit price for nonrecalled metformin ER products decreased by 19.61%, from \$13.05 per 90-pill prescription to \$10.49.

## DISCUSSION

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, created a new pathway for generic versions of branded medications to receive FDA approval.<sup>33</sup> This effort was so successful that generic medications, then only 19% of the US market, came to represent 90% of US prescriptions by 2020.<sup>34</sup> Generic medications provide significant savings for patients when compared with branded alternatives: One industry estimate suggests that generic medications saved \$313 billion in 2019 alone.<sup>34</sup>

Cost savings have been the generic drug market’s primary benefit, with generic manufacturers entering the market by offering a lower price than their competitors,<sup>35,36</sup> while quality has traditionally been treated as a binary: approved or not approved.

The FDA is the primary regulatory body overseeing quality of drugs sold in the US market. Over the past several decades, the US Government Accountability Office has documented how globalization of the generic medication supply chain has created novel challenges for the federal agency; 70% of active ingredients sold in the US are now manufactured abroad.<sup>20-23</sup> A central component of the FDA’s quality assurance of drug manufacturers is site inspections. Tools key to effective oversight—unannounced quality inspections, for example—become untenable when inspectors must communicate with these foreign

establishments to apply for visas or coordinate interpreters.<sup>37,38</sup> Further, COVID-19 travel restrictions have constrained the number of foreign inspections, which had already been in documented decline for several years prior.<sup>17</sup>

In this context, together with frequent news reports of product recalls, concerns have developed about the quality of the generic medication supply in the US market.<sup>37-39</sup> Beliefs about the lack of integrity of generic medications are echoed by health care professionals.<sup>40,41</sup> A 2009 survey showed that up to one-fourth of physicians expressed negative views of generic medications or avoided prescribing them as first-line therapies,<sup>42</sup> and many pharmacists may avoid filling generic medications they deem ineffective or unsafe.<sup>43</sup> Although more recent data, published in 2016, showed

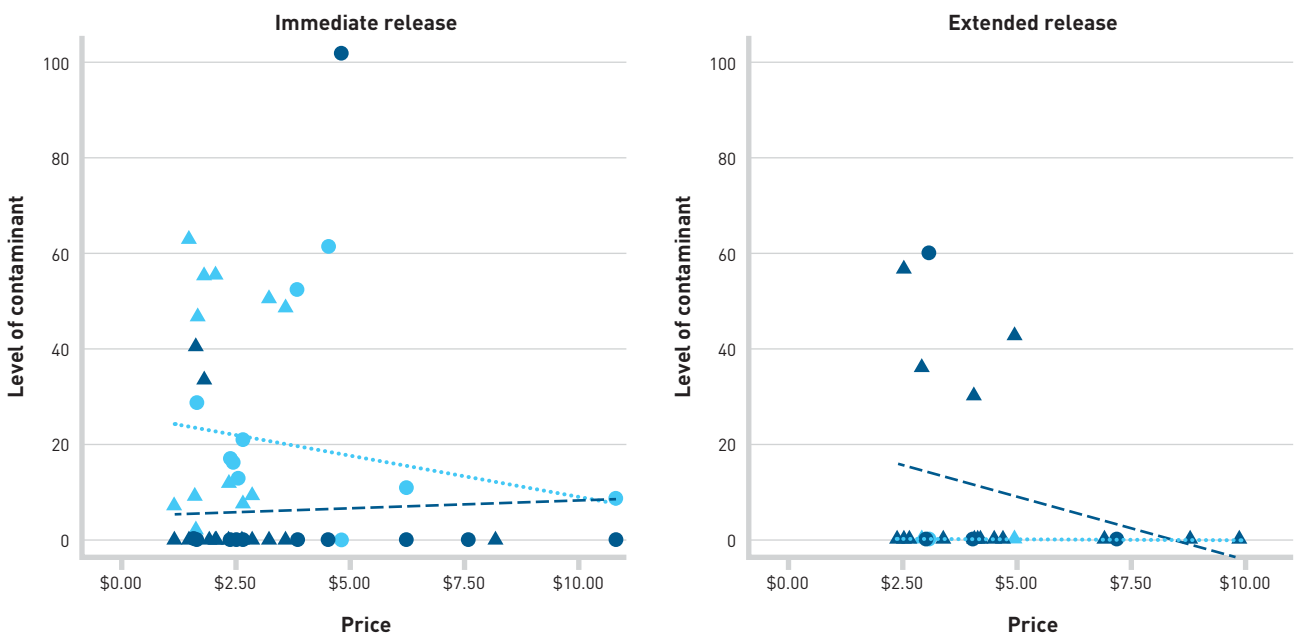
**TABLE 2.** Summary of Drug Quality Results<sup>a</sup>

	Immediate release				Extended release			
	2019	2021	SMD	P	2019	2021	SMD	P
NDMA (ng), mean (SD)	15 (20)	15 (48)	0.02	.92	264 (471)	8.6 (114)	-2.0	.01
DMF (µg), mean (SD)	64.5 (113.6)	19.9 (21.8)	-14.0	.03	63.3 (92.5)	14.6 (92.5)	-1.92	.07
Price in US\$, mean (SD)	—	5.94 (4.44)	—	—	—	9.14 (8.06)	—	—
Above threshold, %	0/16 (0.0%)	2/30 (6.7%)	—	—	8/22 (36.4%)	0/26 (0.0%)	—	—

DMF, *N,N*-dimethylformamide; NDMA, *N*-nitrosodimethylamine; SMD, standardized mean difference.

<sup>a</sup>Each sample was tested for the contaminants NDMA and DMF. Cost of sample acquisition is reported by labeler as the price per 90-pill prescription. Each unique sample, determined by lot number, was tested in quadruplicate. The number of samples detected above threshold was determined using the FDA standard for NDMA (92 ng/maximum daily dose); no FDA standard for DMF currently exists.

**FIGURE 2.** Relationship Between Drug Quality and Price for Immediate-Release and Extended-Release Metformin<sup>a</sup>



DMF, *N,N*-dimethylformamide; NDMA, *N*-nitrosodimethylamine.

<sup>a</sup>Mean contaminant levels of NDMA (dark blue marker symbols, in ng) and DMF (light blue marker symbols, in µg) were plotted against drug price per 90-pill prescription using data collected from samples obtained in 2021. Prescriptions were ordered from Stanford Health Care (triangle marker symbols) and Valisure LLC (circle marker symbols). Contaminant levels for products with different pill quantities or doses were adjusted to fit those expected in a maximum daily dose of metformin (ie, 2000 mg). Linear fit models for each contaminant were constructed using ordinary least squares regression shown alongside individual data points (dashed). Level of contaminant was not significantly associated ( $\alpha=0.05$ ) with prescription price for NDMA or DMF or for immediate-release or extended-release metformin formulations (see eAppendix Table 1 for a summary of regression results).

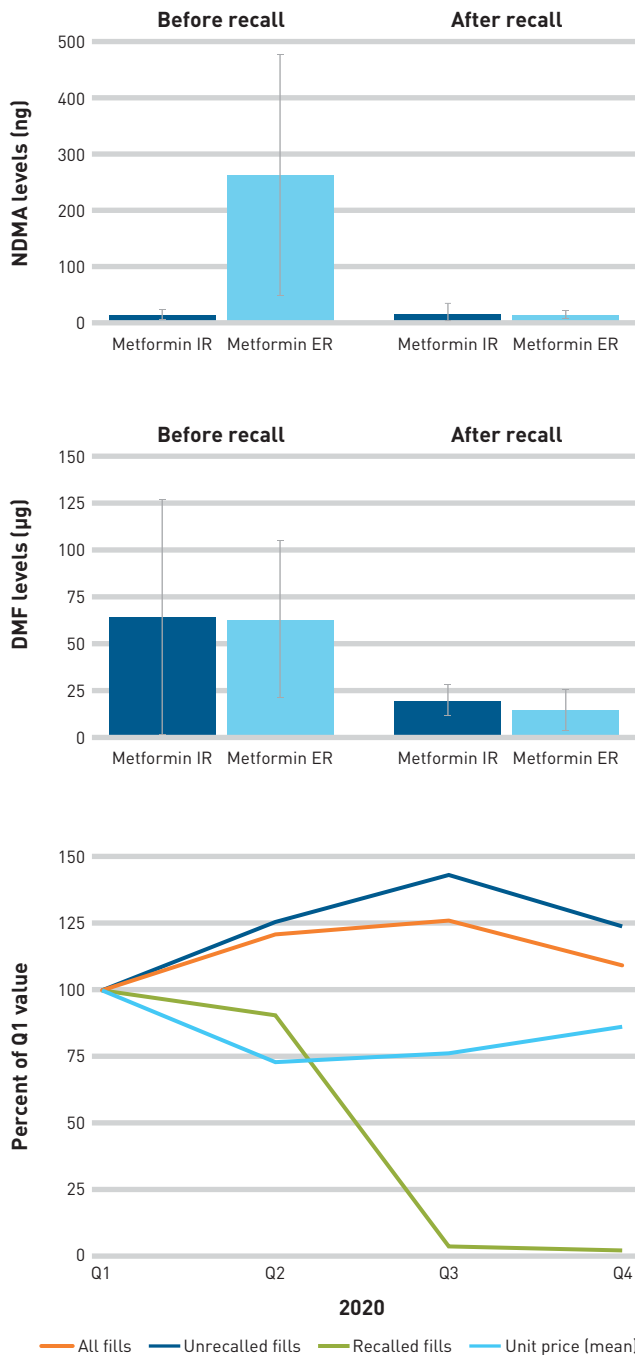
physician trust to be improving,<sup>44</sup> a key factor in continuing this trend will be assuring the public that there are robust systems in place to ensure product quality.<sup>45</sup>

Two findings are notable from our study in this regard. First, we found that FDA-announced manufacturer recalls were effective in reducing the levels of carcinogenic impurities in the generic metformin drug supply. NDMA levels in examined metformin ER products were significantly less than those identified prior to the recalls in 2020. Second, there was no evidence from a population level that these recalls significantly limited metformin prescription

fills or increased unit price; the recall of products from certain labelers was offset by an increase in fills of other products. This latter finding is consistent with that of a prior study of metoprolol utilization within the FDA's Sentinel System database, which found that a large portion of users switched from generic to branded or authorized generic formulations after FDA-announced recalls.<sup>46</sup>

Nonetheless, by sampling and retesting the metformin IR and ER supply, we discovered that products remain on the market with NDMA levels above the FDA acceptable daily intake. Further, we broadly detected the presence of the carcinogen DMF, which the

**FIGURE 3.** Effect of Extended-Release Metformin Recalls on NDMA and DMF Carcinogen Levels, Fill Rate, and Unit Price<sup>16,27,a</sup>



DMF, *N,N*-dimethylformamide; ER, extended release; IR, immediate release; NDMA, *N*-nitrosodimethylamine; Q, quarter.

<sup>a</sup>Top: NDMA levels for IR and ER metformin products before and after FDA-announced drug recalls. Middle: DMF levels for metformin IR and metformin ER before and after FDA drug recalls. Bottom: Metformin ER fill rate and unit price response to FDA recalls. Fill and pricing data are from the Medicaid State Drug Utilization Data.<sup>27</sup> All-lot recalls were announced for Amneal Pharmaceuticals LLC, Apotex Inc, and Lupin Pharmaceuticals Inc in June 2020 (Q3).<sup>16</sup> Alternatives include all metformin ER labelers not listed as having all-lot recalls during this time period.

WHO and International Agency for Research on Cancer classified as a group 2A probable human carcinogen in 2018. Since this decision, the FDA has not reevaluated regulation of DMF. Further, the initial recall of metformin ER was prompted by a petition based on independent quality analysis of drug products rather than ongoing quality screening by the FDA or industry,<sup>2,18</sup> suggesting the need for more systematic and comprehensive drug quality testing protocols by the FDA<sup>38</sup> and across the market.<sup>39</sup> Further, there have been reports of NDMA accumulation over time in stored metformin products, with 12 weeks being an important inflection point, suggesting that some products with undetectable levels at one time point may accumulate contaminants at a later time point.<sup>47</sup>

Our analysis provides evidence that increasing drug quality can be accomplished without significantly increasing generic medication cost or limiting medication access. First, our regression analyses demonstrated that levels of carcinogenic impurities were not significantly associated with acquisition cost, suggesting that high-quality products may be obtained at low cost if a reliable mechanism exists for identifying them and incentivizing their purchase. Second, examination of time trends for medication utilization and price found that dispensing volumes of total metformin products did not significantly decrease following recalls of contaminated products (ie, a net increase of metformin ER fills was observed over the study period), nor did costs of metformin increase in the Medicaid program over this period (ie, a net decrease of unit price of metformin ER was observed). Although these aggregate trends do not account for epidemiological shifts in metformin demand or other time-associated confounders unrelated to FDA-announced recall, these data suggest that drug shortages or price inflation may not have been significant consequences of the metformin recalls, even when a substantial portion of the initial market share was recalled.

**Limitations**

Our study was not sufficiently powered to examine variation in quality within each labeler over time. Generic medication production begins with synthesis of APIs. Labelers generally outsource production of APIs, and they may switch ingredient suppliers between batches of medications. Therefore, medication quality from a given labeler may vary significantly from batch to batch, which was not investigated. Results for NDMA and DMF levels are means of 4 dosage units from each lot, and SDs represent variability within manufacturing batches and a snapshot of quality across companies for the product sampling period.

Second, modeling health risks of NDMA and DMF is based on incomplete understanding of toxicological risk. Regulatory bodies agree that there exists no safe exposure to genotoxic compounds, even if acceptable daily intake thresholds may be practical.<sup>31,48</sup> Regulatory decisions regarding NDMA and DMF are based on evidence from in vitro or animal studies demonstrating their potential to cause metastatic tumors in multiple organ sites<sup>49</sup> as well as epidemiological evidence of the carcinogenicity of NDMA

and DMF in humans based on cohort studies and meta-analyses of case control studies.<sup>50-52</sup> Thus, although it is clear that NDMA and DMF pose a risk to human health, how best to quantify the impact of various levels of contaminants is uncertain. Further, patients who have diabetes and take metformin may have taken multiple other medications with NDMA contamination (ranitidine, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors<sup>53</sup>).

Last, our ecological study of metformin ER drug utilization and price was limited to data available in the Medicaid State Drug Utilization Data.<sup>26</sup> Although this database is extensive, it may not detect all medication shortages. Similarly, it is difficult to distinguish impacts of medication shortages from changes in demand due to evolving epidemiological need for metformin products.

## CONCLUSIONS

The rate of the carcinogenic contaminant NDMA in the metformin prescription drug supply appears to be significantly reduced after recall of contaminated products; however, medications currently on the market may still vary widely in quality. Meanwhile, product price set by labelers is not a significant determinant of quality, so the market cannot continue to compete on price and assume quality is equivalent.<sup>54</sup> Finally, there is no evidence to say that prior recalls resulted in either shortages or price inflation, suggesting that safer products may be available on the market for the same price as poor-quality products. ■

**Author Affiliations:** Clinical Excellence Research Center, School of Medicine, Stanford University (BT, AM, KAS), Stanford, CA; Valisure, LLC (AH, KK, DL, JN, SW), New Haven, CT; Graduate School of Business, Stanford University (KAS), Stanford, CA.

**Source of Funding:** None.

**Author Disclosures:** Ms Hudspeth, Dr Kucera, Mr Light, and Ms Williams are employees of Valisure, LLC, an independent testing laboratory. Mr Light and Ms Nailor are stockholders in Valisure, and Mr Light is also a board member of Valisure and has received a speaker honorarium from Stanford University Medicine grand rounds. Dr Schulman is an unpaid member of the Civica Rx Scientific Advisory Board. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

**Authorship Information:** Concept and design (BT, KK, DL, AM, KAS); acquisition of data (BT, AH, JN, SW, AM, KAS); analysis and interpretation of data (BT, AH, DL, JN, SW); drafting of the manuscript (BT, DL, JN, SW); critical revision of the manuscript for important intellectual content (BT, AH, DL, SW); statistical analysis (BT, AH); provision of patients or study materials (BT); obtaining funding (AM); administrative, technical, or logistic support (AH, KK, AM, KAS); and supervision (KK).

**Address Correspondence to:** Kevin A. Schulman, MD, Clinical Excellence Research Center, School of Medicine, Stanford University, 453 Quarry Rd #117B, CAM Building, Palo Alto, CA 94304. Email: kevin.schulman@stanford.edu.

## REFERENCES

- Mikulich M. Number of metformin prescriptions in the U.S. from 2004 to 2020 (in millions). Statista. October 17, 2022. Accessed February 4, 2022. <https://www.statista.com/statistics/780332/metformin-hydrochloride-prescriptions-number-in-the-us/>
- FDA updates and press announcements on NDMA in metformin. FDA. Updated January 6, 2021. Accessed October 3, 2021. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin>
- Citizen petition from Valisure, LLC. Regulations.gov. March 3, 2020. Accessed February 7, 2022. <https://www.regulations.gov/document/FDA-2020-P-0978-0001>
- Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry. HHS, FDA, Center for Drug Evaluation and Research; February 2021. Accessed January 15, 2022. <https://www.fda.gov/media/141720/download>
- Li K, Ricker K, Tsai FC, et al. Estimated cancer risks associated with nitrosamine contamination in commonly used medications. *Int J Environ Res Public Health*. 2021;18(18):9465. doi:10.3390/ijerph18189465

- Zmystowski A, Książek I, Sztzerk A. *N*-nitrosodimethylamine contamination in the metformin finished products. *Molecules*. 2020;25(22):5304. doi:10.3390/molecules2525304
- Viona Pharmaceuticals Inc., issues voluntary nationwide recall of metformin HCl extended-release tablets, USP 750 mg, due to the detection of *N*-nitrosodimethylamine (NDMA) impurity. News release. Viona Pharmaceuticals Inc. January 12, 2022. Accessed February 7, 2022. [https://vionausa.com/wp-content/uploads/2022/01/Viona-Metformin-HCl-ER-Tablets-USP-750-mg-Recall-Press-Release\\_01-07-2022.pdf](https://vionausa.com/wp-content/uploads/2022/01/Viona-Metformin-HCl-ER-Tablets-USP-750-mg-Recall-Press-Release_01-07-2022.pdf)
- Jirés J, Kaláček S, Gibala P, et al. Insight into the formation of *N*-nitrosodimethylamine in metformin products. *J Pharm Biomed Anal*. 2021;195:113877. doi:10.1016/j.jpba.2020.113877
- Fritzsche M, Blom G, Keitel J, et al. NDMA analytics in metformin products: comparison of methods and pitfalls. *Eur J Pharm Sci*. 2022;168:106026. doi:10.1016/j.ejps.2021.106026
- Liao X, Shen L, Jiang Z, et al. NDMA formation during ozonation of metformin: roles of ozone and hydroxyl radicals. *Sci Total Environ*. 2021;796:149010. doi:10.1016/j.scitotenv.2021.149010
- FDA requests removal of all ranitidine products (Zantac) from the market. News release. FDA. April 1, 2020. Accessed October 3, 2021. <https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market>
- Aldawsari FS, Alshehry YM, Alghamdi TS. *N*-nitrosodimethylamine (NDMA) contamination of ranitidine products: a review of recent findings. *J Food Drug Anal*. 2021;29(1):39-45. doi:10.38212/2224-6614.1133
- Shaik KM, Sarmah B, Wadekar GS, Kumar P. Regulatory updates and analytical methodologies for nitrosamine impurities detection in sartans, ranitidine, nizatidine, and metformin along with sample preparation techniques. *Crit Rev Anal Chem*. 2022;52(1):53-71. doi:10.1080/10408347.2020.1788375
- Pfizer voluntary nationwide recall of lots of Accuretic (quinapril HCl/hydrochlorothiazide), quinapril and hydrochlorothiazide tablets, and quinapril HCl/hydrochlorothiazide tablets due to *N*-nitroso-quinapril content. News release. Pfizer Inc. March 21, 2022. Accessed October 5, 2022. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntary-nationwide-recall-lots-accuretic>
- Committee for Medicinal Products for Human Use. *Assessment Report: Angiotensin-II Receptor Antagonists (Sartans) Containing a Tetrazole Group*. European Medicines Agency; 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](https://www.ema.europa.eu/en/documents/variation-report/angiotensin-ii-receptor-antagonists-sartans-article-31-referral-chmp-assessment-report_en.pdf)
- FDA updates and press announcements on angiotensin II receptor blocker (ARB) recalls (valsartan, losartan, and irbesartan). FDA. Updated March 1, 2023. Accessed October 11, 2021. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan>
- Teasdale B, Light D, Schulman KA. Price and quality in the generic pharmaceutical market. *Circulation*. 2022;145(16):1185-1187. doi:10.1161/CIRCULATIONAHA.121.057727
- Citizen petition from Valisure, LLC. Regulations.gov. June 13, 2019. Accessed October 4, 2022. <https://www.regulations.gov/document/FDA-2019-P-2869-0001>
- ICH. *Q3C Impurities: Guidance for Industry*. FDA; July 2017. Accessed October 5, 2022. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ich-q3c-maintenance-procedures-guidance-industry-q3c-impurities-residual-solvents>
- COVID-19 Complicates Already Challenged FDA Foreign Inspection Program, Testimony Before the Committee on Finance, 116th Cong. 2nd Sess (2020) [statement of Mary Denigan-Macauley, director, Health Care, US Government Accountability Office]. Accessed October 3, 2021. <https://www.gao.gov/assets/710/707372.pdf>
- FDA's Future Inspection Plans Need to Address Issues Presented by COVID-19 Backlog, Testimony Before Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, Committee on Appropriations, 117th Cong. 1st Sess (2021) [statement of Mary Denigan-Macauley, director, Health Care, US Government Accountability Office]. Accessed October 21, 2021. <https://www.gao.gov/assets/720/712959.pdf>
- Preliminary Findings Indicate Persistent Challenges With FDA Foreign Inspections, Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, 116th Cong. 1st Sess (2019) [statement of Mary Denigan-Macauley, director, Health Care, US Government Accountability Office]. Accessed January 13, 2022. <https://www.gao.gov/assets/710/705865.pdf>
- Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program. US Government Accountability Office; September 22, 2008. Report No. GAO-08-970. Accessed January 13, 2022. <https://www.gao.gov/assets/gao-08-970.pdf>
- Ndichu E, Ohiri K, Sekoni O, Makinde O, Schulman K. Evaluating the quality of antihypertensive drugs in Lagos State, Nigeria. *PLoS One*. 2019;14(2):e0211567. doi:10.1371/journal.pone.0211567
- Schmidtsdorff S, Neumann J, Schmidt AH, Parr MK. Prevalence of nitrosamine contaminants in drug samples: has the crisis been overcome? *Arch Pharm (Weinheim)*. 2023;356(2):e2200484. doi:10.1002/ardp.202200484
- Ruepp R, Frötschl R, Bream R, et al. The EU response to the presence of nitrosamine impurities in medicines. *Front Med (Lausanne)*. 2021;8:782536. doi:10.3389/fmed.2021.782536
- Bharate SS. Critical analysis of drug product recalls due to nitrosamine impurities. *J Med Chem*. 2021;64(6):2923-2936. doi:10.1021/acs.jmedchem.0c02120
- Dabora MC, Turaga N, Schulman KA. Financing and distribution of pharmaceuticals in the United States. *JAMA*. 2017;318(1):21-22. doi:10.1001/jama.2017.5607
- Fein AJ. The big three generic drug mega-buyers drove double-digit deflation in 2018: stability ahead? Drug Channels. January 8, 2019. Accessed January 17, 2022. <https://www.drugchannels.net/2019/01/the-big-three-generic-drug-mega-buyers.html>
- Wu Q, Kvitko E, Zenzola N, Kucera K, Light D. A broadly accessible liquid chromatography method for quantification of six nitrosamine compounds and *N,N*-dimethylformamide in metformin drug products using high resolution mass spectrometry. *ChemRxiv*. Preprint posted online November 9, 2020. doi:10.26434/chemrxiv.13202849.v1
- M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk: Guidance for Industry. HHS, FDA, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; March 2018. Accessed October 5, 2022. <https://www.fda.gov/media/85885/download>
- State drug utilization data. Medicaid.gov. Updated December 19, 2022. Accessed October 3, 2021. <https://www.medicare.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html>
- Boehm G, Yao L, Han L, Zheng O. Development of the generic drug industry in the US after the Hatch-Waxman Act of 1984. *Acta Pharm Sin B*. 2013;3(5):297-311. doi:10.1016/j.apbsb.2013.07.004
- 2020 Generic Drug and Biosimilars Access and Savings in the U.S. Report. Association for Accessible Medicines; 2020. Accessed October 4, 2021. <https://accessiblemeds.org/sites/default/files/2020-09/AAM-2020-Generics-Biosimilars-Access-Savings-Report-US-Web.pdf>
- Wiske CP, Ogbechie OA, Schulman KA. Options to promote competitive generics markets in the United States. *JAMA*. 2015;314(20):2129-2130. doi:10.1001/jama.2015.13498

36. Generic competition and drug prices. FDA. Updated September 12, 2022. Accessed October 5, 2022. <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices>
37. Lambert J. 'Bottle of Lies' exposes the dark side of the generic-drug boom. NPR. May 12, 2019. Accessed October 10, 2021. <https://www.npr.org/sections/health-shots/2019/05/12/72216512/bottle-of-lies-exposes-the-dark-side-of-the-generic-drug-boom>
38. Edney A, Berfield S, Yu E. Carcinogens have infiltrated the generic drug supply in the U.S. Bloomberg. September 12, 2019. Accessed October 10, 2021. <https://www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda>
39. Stockman F. Our drug supply is sick: how can we fix it? *New York Times*. September 18, 2021. Accessed October 3, 2021. <https://www.nytimes.com/2021/09/18/opinion/drug-market-prescription-generic.html>
40. Kesselheim AS, Gagne JJ, Eddings W, et al. Prevalence and predictors of generic drug skepticism among physicians: results of a national survey. *JAMA Intern Med*. 2016;176(6):845-847. doi:10.1001/jamainternmed.2016.1688
41. Schulman KA. Challenges in ensuring the quality of generic medicines. *Health Aff (Millwood)*. 2020;39(9):1643-1646. doi:10.1377/hlthaff.2020.00321
42. Shrank WH, Liberman JN, Fischer MA, Girdish C, Brennan TA, Choudhry NK. Physician perceptions about generic drugs. *Ann Pharmacother*. 2011;45(1):31-38. doi:10.1345/aph.1P389
43. Sarpatwari A, Lee MP, Gagne JJ, et al. Generic versions of narrow therapeutic index drugs: a national survey of pharmacists' substitution beliefs and practices. *Clin Pharmacol Ther*. 2018;103(6):1093-1099. doi:10.1002/cpt.884
44. Kesselheim AS, Eddings W, Raj T, et al. Physicians' trust in the FDA's use of product-specific pathways for generic drug approval. *PLoS One*. 2016;11(10):e0163339. doi:10.1371/journal.pone.0163339
45. Drug quality sampling and testing programs. FDA. Updated May 2, 2023. Accessed February 7, 2022. <https://www.fda.gov/drugs/science-and-research-drugs/drug-quality-sampling-and-testing-programs>
46. Gagne JJ, Popovic JR, Nguyen M, et al. Evaluation of switching patterns in FDA's Sentinel System: a new tool to assess generic drugs. *Drug Saf*. 2018;41(12):1313-1323. doi:10.1007/s40264-018-0709-4
47. Dharani S, Mohamed EM, Khuroo T, et al. In-use stability assessment of FDA approved metformin immediate release and extended release products for *N*-nitrosodimethylamine and dissolution quality attributes. *Int J Pharm*. 2022;623:121923. doi:10.1016/j.ijpharm.2022.121923
48. Nohmi T. Thresholds of genotoxic and non-genotoxic carcinogens. *Toxicol Res*. 2018;34(4):281-290. doi:10.5487/TR.2018.34.4.281
49. Anderson LM, Souliotis VL, Chhabra SK, Moskal TJ, Harbaugh SD, Kyrtopoulos SA. *N*-nitrosodimethylamine-derived *O*<sup>6</sup>-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol. *Int J Cancer*. 1996;66(1):130-134. doi:10.1002/(SICI)1097-0215(19960328)66:1<130::AID-IJC22>3.0.CO;2-G
50. Yoon JH, Yoo CI, Ahn YS. *N,N*-dimethylformamide: evidence of carcinogenicity from national representative cohort study in South Korea. *Scand J Work Environ Health*. 2019;45(4):396-401. doi:10.5271/sjweh.3802
51. Song P, Wu L, Guan W. Dietary nitrates, nitrites, and nitrosamines intake and the risk of gastric cancer: a meta-analysis. *Nutrients*. 2015;7(12):9872-9895. doi:10.3390/nu7125505
52. Jakszyn P, Gonzalez CA. Nitrosamine and related food intake and gastric and oesophageal cancer risk: a systematic review of the epidemiological evidence. *World J Gastroenterol*. 2006;12(27):4296-4303. doi:10.3748/wjg.v12.i27.4296
53. Teasdale B, Light D, Schulman KA. Price and quality in the generic pharmaceutical market. *Circulation*. 2022;145(16):1185-1187. doi:10.1161/CIRCULATIONAHA.121.057727
54. Schulman KA, Kumar W, Adashi E. Ensuring access to generic medications in the US. *Health Affairs Forefront*. September 12, 2023. Accessed September 15, 2023. <https://www.healthaffairs.org/content/forefront/ensuring-access-generic-medications-us>

Visit [ajmc.com/link/89450](https://ajmc.com/link/89450) to download PDF and eAppendix



## **eAppendix A. Analytic Methods**

### **Chemicals and Reagents**

Reference standards of NDMA, DMF, and isotope labeled DMF standard D<sub>7</sub>-DMF were purchased from Sigma-Aldrich (St. Louis, MO). Isotopically labeled NDMA standard <sup>13</sup>C<sub>2</sub>-D<sub>6</sub>-NDMA was purchased from Cambridge Isotope Laboratories (Tewksbury, MA). Formic acid (LC-MS grade) was purchased from Millipore Sigma (Burlington, MA). Methanol (LC-MS grade) was purchased from Honeywell (Charlotte, NC). Milli-Q water (18.2 MΩ) was generated from a Milli-Q IQ Element system from Millipore Sigma.

### **Sample Preparation**

A description of these methods has been previously published and validated.<sup>23</sup> A single metformin tablet is transferred to a 15-mL polypropylene (PP) tube and accurately weighed. Methanol is added to the 15-mL PP tube to dilute the tablet sample to approximately 100 mg active pharmaceutical ingredient (API) per mL of methanol, and the mass of methanol is accurately recorded. The tablet sample in methanol is blended with a Pro2000 blender by Pro Scientific (Oxford, CT). Between samples, the probe of the blender is rinsed by performing blending action in a series of two 50-mL PP tubes with Milli-Q water and two 50-mL PP tubes with methanol. At the end of sample preparation of each batch, the last tube of rinsing methanol is analyzed along with the metformin samples as the laboratory reagent blank (LRB). The sample methanol extract is centrifuged at 13,000 rpm for one minute, and 250 μL of the supernatant is transferred and diluted with 750 μL of Milli-Q water, followed by vortex mixing. After filtering by 0.2 μm nylon filter, 480 μL of the sample extract is pipette-transferred to an amber LC vial, and 20 μL of isotopic internal standard mixture containing 666 ng of <sup>13</sup>C<sub>2</sub>-D<sub>6</sub>-NDMA and 333 ng of D<sub>7</sub>-DMF is spiked into the sample extract. The final sample extract contains 26 ng/mL <sup>13</sup>C<sub>2</sub>-D<sub>6</sub>-NDMA and 13 μg/mL D<sub>7</sub>-DMF, respectively. The vial is capped and vortexed prior to LC-HRMS analysis.

### **Instrumental Analysis**

SCIEX ExionLC AD (LC) coupled with SCIEX X500R quadrupole time-of-flight high resolution mass spectrometry (QToF HRMS) was purchased from SCIEX (Framingham, MA). Ten (10)  $\mu\text{L}$  of sample extract is injected and the separation of NDMA and DMF is performed on an InfinityLab Poroshell 120 EC-C18,  $4.6 \times 100$  mm,  $2.7 \mu\text{m}$  analytical column (Agilent Technology, Santa Clara, CA) at  $30^\circ\text{C}$ . LC mobile phase is 0.1% (v/v) formic acid in water (A) and 0.1% (v/v) formic acid in methanol (B). The flow rate is 0.6 mL/min with a ramp from A to 98% B from 3.5 to 9.5 minutes and hold for 1.4 minutes.

Determination of target analytes is performed by SCIEX X500R QToF HRMS operated in positive atmospheric pressure ionization (APCI+) mode. Mass resolution for TOF MS scan was greater than 34,000 for amino-dPEG 4-acid calibrant mass of 266.15981, and mass resolution for TOF MS/MS scan was greater than 31,000 for mass 176.09134 fragment of reserpine calibrant. The mass spectrometry method was "MRMHR", which has similar action compared to triple quadrupole mass spectrometry that allows the HRMS to detect precursor and product ions of target molecules, but with extremely high mass resolution detection. Exact masses for MRMHR mass transitions and other mass spectrometry parameters, including qualifier (Q) ions, are listed in Methods Supplementary Table 1 below. Mass accuracy for quantification was set at 5 ppm for all analytes. The total run time is 15 minutes for each sample. Metformin API is diverted to waste in the first 3 minutes of the LC gradient.

### **Quality Assurance and Quality Control (QA & QC)**

All calibration and QC samples are prepared in 25:75 (v/v) methanol:water. A ten-point standard calibration ranged from 0.1 ng/mL to 100 ng/mL for six nitrosamines, and 1 ng/mL to 1000 ng/mL for DMF and DEF is analyzed on LC-QToF HRMS. Isotopic dilution calibration method is used for NDMA and DMF quantification with quadratic regression and  $1/x$  weighting, while external calibration method is used for rest of the analytes with linear regression and  $1/x$  weighting, and  $R^2$  for all calibrations need to be greater than 0.99. A calibration standard is acceptable if the calculated concentration is within  $\pm 20\%$  of its theoretical concentration, except for the lowest acceptable concentration which is  $\pm 30\%$ . Limit of quantification (LOQ) is

acceptable for the lowest calibration standard that meets all three criteria 1) signal to noise ratio not less than 10; 2) the calculated concentration is within  $\pm 30\%$  of its theoretical concentration; 3) the calculated concentration is not less than three times higher than the concentration in the laboratory reagent blank (LRB) if the LRB has a detectable concentration. For NDMA, LOQ is less than 0.5 ng/mL and for DMF, LOQ is less than 25 ng/mL. Low, medium, and high QC samples are prepared following the same procedure of sample preparation, and a QC is acceptable if the calculated concentration is within  $\pm 20\%$  of its theoretical concentration. Mean and medium of results for four dosage units per lot are reported as well as single dosage unit measurements determined for lots of medications purchased prior to the FDA-announced recalls of metformin products beginning on June 11, 2020 (see Supplementary Table 5).

In addition to NDMA and DMF levels, a screen for Metformin Related Compound A (1-Cyanoguanidine), Compound B (1-Methylbiguanide hydrochloride), and Compound C (N,N-Dimethyl-[1,3,5]triazine-2,4,6-triamine) (reference powders of 99% purity (A) or labelled for qualitative use only (B, C) purchased from U.S. Pharmacopeia) was performed using high resolution LC-MS methods similar to those described here. These three synthetic impurities are included in metformin specific standards published by the U.S. Pharmacopeia and only Compound B was putatively detected in one sample (data not shown).

**Methods eAppendix Table 1.** SCIEX X500R QToF HRMS parameters for determination of six nitrosamines and DMF in the present study.

<b>Source and Gas Parameters</b>			
Ion source gas 1	45 psi	Curtain gas	25 psi
Temperature	325 °C	CAD gas	8
<b>Experiment Parameters</b>			
Polarity	Positive	Nebulizer current	5 µA
<b>TOF MS</b>		Accumulation time	0.1 s
TOF start mass	50 Da	TOF stop mass	450 Da
Declustering potential/spread	40/0 V	Collision energy/spread	10/0 V
<b>TOF MS/MS</b>		Accumulation time	0.05 s for NDMA 0.025 s for DMF
<b>Compound</b>	<b>Precursor (Da)</b>	<b>Product (Da)</b>	<b>DP/CE (V)</b>
NDMA	75.06	75.0553	80/5
NDMA(Q)	75.06	43.0291	80/22
<sup>13</sup> C <sub>2</sub> D <sub>6</sub> -NDMA	83.1	83.0997	80/5
<sup>13</sup> C <sub>2</sub> D <sub>6</sub> -NDMA(Q)	83.1	47.0513	80/22
DMF	74.06	74.0600	100/5
D <sub>7</sub> -DMF	81.10	81.1040	100/5

## eAppendix B. Supplementary Results Tables:

**eAppendix Table 1. Regression results for drug quality on price**

		<b>Coef.</b>	<b>95% CI</b>	<b>p-value</b>	<b>R-squared</b>	<b>N</b>
<b>Immediate Release</b>	<b>NDMA (ng)</b>	0.13	(-11.21 – 11.47)	0.981	0.142	30
	<b>DMF (µg)</b>	-1.61	(-5.81 – 2.59)	0.436	0.382	30
<b>Extended Release</b>	<b>NDMA (ng)</b>	-2.84	(-6.71 – 1.04)	0.142	0.124	26
	<b>DMF (µg)</b>	0.00	(0.00 – 0.01)	0.073	0.199	26

Summary of contaminant levels of DMF (µg) and NDMA (ng) were regressed as continuous variables on price per 90-pill prescription using OLS linear regression. Regressions were performed separately for metformin immediate-release and metformin extended-release formulations. The model controlled for dose strength (i.e. 500 mg, 750 mg, 850 mg, and 1000 mg), package size (i.e. 100 pills, 500 pills, 1000 pills) and ordering company (i.e. Stanford vs. Valisure). Coefficients are reported as the expected change in NDMA (ng) or DMF (µg) level associated with a \$1.00 increase in prescription price. Given the testing methods used, significant changes in NDMA levels are detectable at differences of 10 ng and significant changes in DMF levels are detectable at differences of 10 µg.

**eAppendix Table 2. Summary of drug quality results by labeler post-2020 recalls**

<b>A. Summary of Post-Recall Data</b>						
<b>Formulation</b>	<b>NDMA (mean, ng)</b>		<b>DMF (mean, µg)</b>		<b>Price (mean)</b>	
	<b>Q1 – Q3</b>	<b>Q1 – Q3</b>	<b>Q1 – Q3</b>	<b>Q1 – Q3</b>	<b>Q1 – Q3</b>	<b>Q1 – Q3</b>
Immediate Release	15	(0 – 0)	19.9	(0.0 – 46.7)	\$3.14	(1.65 – 3.57)
Extended Release	8.6	(0 – 0)	14.6	(0.0 – 24.6)	\$7.73	(3.09 – 7.16)
<b>B. Immediate Release</b>						
<b>Labeler</b>	<b>NDMA (median, ng)</b>		<b>DMF (median, µg)</b>		<b>Price (median)</b>	
	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>
Ascend	0	(0 – 11)	49.0	(12.9 – 61.4)	\$3.05	(1.65 – 4.92)
Aurobindo	0	(0 – 8)	10.1	(8.7 – 11.8)	\$4.52	(1.59 – 10.80)
Granules	1	(0 – 33)	39.6	(17.0 – 63.0)	\$2.08	(1.46 – 3.21)
Laurus	41	(41 – 41)	2.2	(2.2 – 2.2)	\$1.61	(1.61 – 1.61)
Mylan	4	(0 – 8)	34.3	(16.1 – 52.4)	\$3.12	(2.42 – 3.82)
ScieGen	0	(0 – 0)	0.0	(0.0 – 7.5)	\$2.07	(1.90 – 2.64)
TAGI	0	(0 – 0)	7.1	(7.1 – 7.1)	\$1.14	(1.14 – 1.14)
Westminster	0	(0 – 0)	0.0	(0.0 – 0.9)	\$2.03	(1.53 – 2.60)
Zydus	11	(3 – 263)	0.0	(0.0 – 0.2)	\$6.81	(0.72 – 8.15)
<b>C. Extended Release</b>						
<b>Labeler</b>	<b>NDMA (median, ng)</b>		<b>DMF (median, µg)</b>		<b>Price (median)</b>	
	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>	<b>(min-max)</b>
Ascend	18	(0 – 43)	0	(0.0 – 69.1)	\$4.21	(3.02 – 5.88)
Bayshore	18	(18 – 18)	0.2	(0.2 – 0.2)	\$9.87	(9.87 – 9.87)
Granules	57	(7 – 60)	30.8	(24.6 – 54.7)	\$2.66	(2.55 – 3.09)
Ingenus	6	(6 – 6)	5.1	(5.1 – 5.1)	\$72.48	(72.48 – 72.48)
Nivagen	16	(16 – 16)	51.6	(51.6 – 51.6)	\$2.55	(2.55 – 2.55)
Sun	0	(0 – 12)	0.0	(0.0 – 0.3)	\$7.20	(6.92 – 8.78)
TAGI	0	(0 – 5)	0.7	(0.0 – 10.2)	\$4.10	(2.40 – 9.86)
TIME	30	(24 – 36)	0.0	(0.0 – 0.0)	\$4.07	(2.93 – 4.16)
Viona	19	(19 – 19)	100.7	(100.7 – 100.7)	\$13.15	(13.15 – 13.15)

Labeler was recorded for samples of metformin immediate release and metformin extended release. Each sample was tested for the contaminants DMF and NDMA. Cost of sample acquisition is reported by labeler as the price in USD per 90-pill prescription. Each unique sample, determined by lot number, was tested in quadruplicate.

**eAppendix Table 3. Summary of drug quality results of metformin product sampling prior to 2020 recalls**

<b>A. Summary of Pre-Recall Data</b>				
<b>Formulation</b>	<b>NDMA (mean, ng)</b>	<b>Q1 – Q3</b>	<b>DMF (mean, µg)</b>	<b>Q1 – Q3</b>
Immediate-Release	15	(0 – 27)	64.5	(0.5 – 67.2)
Extended-Release	264	(0 – 277)	63.3	(0.0 – 175.1)
<b>B. Immediate-Release</b>				
<b>Labeler</b>	<b>NDMA (median, ng)</b>	<b>(min-max)</b>	<b>DMF (median, µg)</b>	<b>(min-max)</b>
ACI	0	(0 – 0)	0.6	(0.4 – 3.0)
American	27	(27 – 27)	0.9	(0.9 – 0.9)
Amneal	27	(27 – 27)	113.6	(113.6 – 113.6)
Ascend	15	(14 – 30)	16.7	(16.0 – 204.0)
Aurobindo	3	(0 – 6)	13.2	(9.8 – 16.7)
Heritage	31	(6 – 78)	215.5	(20.9 – 413.3)
Megalith	0	(0 – 0)	0.0	(0.0 – 0.0)
Westminster	0	(0 – 0)	0.0	(0.0 – 0.0)
<b>C. Extended-Release</b>				
<b>Labeler</b>	<b>NDMA (median, ng)</b>	<b>(min-max)</b>	<b>DMF (median, µg)</b>	<b>(min-max)</b>
Actavis	245	(213 – 277)	237.5	(232.9 – 242.1)
AiPing	7	(0 – 14)	0.8	(0.4 – 1.3)
Amneal	1,389	(329 – 1,460)	196.0	(175.1 – 230.0)
Apotex	76	(0 – 152)	0.9	(0.0 – 1.7)
EPIC	27	(27 – 27)	4.0	(4.0 – 4.0)
Granules	8	(8 – 8)	34.5	(34.5 – 34.5)
Ingenus	17	(17 – 17)	16.6	(16.6 – 16.6)
Lupin	69	(69 – 69)	16.2	(16.2 – 16.2)
Mylan	39	(39 – 39)	27.5	(27.5 – 27.5)
Nostrum	1	(1 – 1)	10.2	(10.2 – 10.2)
Oceanside	24	(24 – 24)	0.0	(0.0 – 0.0)
Sun	0	(0 – 0)	0.0	(0.0 – 0.0)
TAGI	0	(0 – 0)	3.5	(0.0 – 7.0)
TIME	397	(397 – 397)	0.0	(0.0 – 0.0)

Labeler was recorded for samples of metformin immediate release and metformin extended release. Each sample was tested for the contaminants DMF and NDMA. Pricing data is not available for pre-recall samples. Each unique sample, determined by lot number, was tested once.

**eAppendix Table 4. Post-recall levels of contaminants for immediate-release and extended-release metformin by lot number**

Labeler	Lot Number	Formulation	Dose	NDMA (ng)	DMF (µg)
Ascend	4200094A	IR	1000	0	48.6
Ascend	4990023A	IR	850	8	55.5
Ascend	4980129A	IR	500	0	12.9
Ascend	4980096A	IR	500	11	46.7
Ascend	4990031A	IR	850	0	61.4
Aurobindo	MTSC20075-A	IR	1000	0	8.7
Aurobindo	MTSB20015-B	IR	850	0	11.8
Aurobindo	MTSC20080-A	IR	1000	0	9.2
Aurobindo	MTSA20035-A	IR	500	8	10.9
Aurobindo	MTSA20045-A	IR	500	0	9.2
Granules	4390173A	IR	1000	0	21.0
Granules	4370071A	IR	500	2	63.0
Granules	4370144A	IR	500	11	28.7
Granules	4380013A	IR	850	0	17.0
Granules	4380017A	IR	850	33	55.4
Granules	4390166A	IR	1000	0	50.5
Laurus	19051811	IR	1000	41	2.2
Mylan	4630352A	IR	1000	8	52.4
Mylan	4610245A	IR	500	0	16.2
ScieGen	F107066A	IR	1000	0	7.5
ScieGen	E106010B	IR	850	0	0.0
ScieGen	E105038B	IR	500	0	0.0
TAGI	4402012090	IR	500	0	7.1
Westminster	D105020A	IR	500	0	0.0
Westminster	E107082C	IR	1000	0	0.9
Westminster	D106010A	IR	850	0	0.0
Zydus	M002462	IR	500	102	0.0
Zydus	M014576	IR	1000	3	0.2
Zydus	M002463	IR	500	263	0.0
Zydus	M013623	IR	850	11	0.0
Ascend	3120231	ER	500	4	69.1
Ascend	21121783	ER	500	18	0.0
Ascend	21122550	ER	750	43	0.0
Ascend	21122139	ER	500	0	0.0
Ascend	3120117	ER	500	25	28.8
Ascend	20122689	ER	750	16	0.0
Bayshore	20942	ER	750	18	0.2



Granules	4910391A	ER	500	57	54.6
Granules	4910320AA	ER	500	60	30.8
Granules	4910206A	ER	500	7	24.6
Ingenus	20388014	ER	1000	6	5.1
Nivagen	NIV20216	ER	500	16	51.6
Sun	JKX4311A	ER	750	12	0.0
Sun	JKX3507A	ER	750	0	0.0
Sun	HAC0070A	ER	500	0	0.3
TAGI	5852011075	ER	750	0	0.0
TAGI	5852012018	ER	750	0	3.8
TAGI	5842010052	ER	500	0	0.9
TAGI	5842011197	ER	500	5	10.2
TAGI	5852010018	ER	750	0	0.0
TAGI	5842010241	ER	500	0	0.7
TAGI	5852007022	ER	750	0	0.0
TIME	XP0132	ER	500	24	0.0
TIME	XP0099	ER	500	36	0.0
TIME	9R0016	ER	750	30	0.0
Viona	M011304	ER	750	19	100.7

Products were sourced by Stanford School of Medicine and Valisure, LLC in 2021, after the FDA-announced recalls of metformin products beginning on June 11, 2020. Bottles were tested in quadruplicate and values of NDMA and DMF are reported as the mean value.

**eAppendix Table 5. Pre-recall levels of contaminants for immediate-release and extended-release metformin by lot number**

Labeler	Lot Number	Formulation	Dose	NDMA (ng)	DMF (µg)
ACI	C105019A	IR	500	0	0.4
ACI	D105019	IR	500	0	0.6
ACI	D105061	IR	500	0	3.0
American	184759	IR	1000	27	0.9
Amneal	AM180405A	IR	850	27	113.6
Ascend	4200024C	IR	1000	15	16.7
Ascend	4200061B	IR	1000	30	204.0
Ascend	4980028B	IR	500	14	16.0
Aurobindo	MTSA19016-B	IR	500	6	16.7
Aurobindo	MTSA19070-C	IR	500	0	9.8
Heritage	4521630A	IR	1000	6	20.9
Heritage	4500753A	IR	500	31	215.5
Heritage	4510157A	IR	850	78	413.3
Megalith	442180318	IR	1000	0	0.0
Westminster	B107261B	IR	1000	0	0.0
Westminster	B105067	IR	500	0	0.0
Actavis	1354471A	ER	750	277	232.9
Actavis	1376339M	ER	500	213	242.1
AiPing	190300211	ER	500	0	1.3
AiPing	190200411	ER	1000	14	0.4
Amneal	HD03319A	ER	500	1,460	175.1
Amneal	AM190107AA	ER	500	1,348	207.4
Amneal	AM180770A	ER	750	329	230.0
Amneal	HM02918A	ER	500	1,429	184.6
Apotex	NE5801	ER	500	152	1.7
Apotex	NG2595	ER	750	0	0.0
EPIC	190101111	ER	500	27	4.0
Granules	4910134A	ER	500	8	34.5
Ingenus	19388005	ER	1000	17	16.6
Lupin	G901203	ER	500	69	16.2
Mylan	3090719	ER	1000	39	27.5
Nostrum	MEF290206	ER	1000	1	10.2
Oceanside	19D125P	ER	500	24	0.0
Sun	JKU2539A	ER	500	0	0.0
Sun	JKU0880A	ER	750	0	0.0
TAGI	5841910035	ER	500	0	0.0
TAGI	5841905129	ER	500	0	7.0
TIME	XP9004	ER	500	397	0.0

Products were sourced by Valisure, LLC in 2019, prior to the FDA-announced recalls of metformin products beginning on June 11, 2020. Bottles were tested once and single values are reported.