FDA Drug Topics: Nitrosamine Impurities in Drugs: What Health Care Professionals Need to Know

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Objectives

• Describe FDA’s role in helping to ensure the quality of drugs marketed in the U.S.

• Discuss the drug classes that have been affected by nitrosamine impurities

• Identify 3 ways to obtain information about medications recalled due to nitrosamine impurities
Outline

• Background information on nitrosamine impurities
• Nitrosamine impurities in drugs
• Understanding pharmaceutical quality
• FDA’s role in protecting the public
• Public outreach and engagement
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.
Patients expect safe and effective medicine with every dose they take.
Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects.
It is what gives patients confidence in their *next* dose of medicine.
Nitrosamines

- Organic compounds that we are exposed to in our everyday lives

- They exist in low levels in our water and foods
  - Meat
  - Vegetables
  - Dairy products
Nitrosamines

Come from chemical reactions and can form in drugs

N-Nitrosodimethylamine (NDMA)

N-Nitrosodiethylamine (NDEA)

N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
Risks

• Some nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time.

• People taking drugs that contain NDMA at or below the acceptable daily intake limits everyday for 70 years are not expected to have an increased risk of cancer.
Global Investigation

FDA’s Drug Safety website lists: ARBs, ranitidine and metformin

Acceptable daily intake limit of 96 nanograms of NDMA
Global collaboration

- Nitrosamine impurities task force meets weekly
- Global task force collaborates in real time
Sartans! (ARBs)

July 2018 – Voluntary recalls of Sartans announced

July 2018 - present – FDA continues meeting to address CGMP violations, update lab analysis of ARBs
Ranitidine

September 2019 – Alerting patients and health care professionals of NDMA found in samples of ranitidine

April 1, 2020 - FDA requested removal of all ranitidine products from the market
Nizatidine

• April 16, 2020 – FDA alerts patients and health care professionals to Amneal’s voluntary recall of Nizatidine
• FDA will continue to investigate the source of these impurities

• There are multiple reasons why NDMA can be present in drugs

Drugs and Impurities

• Understand Pharmaceutical Quality
Drug Master Files (DMFs)

- Submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products

- Allow parties to reference material without disclosing DMF contents

- Information contained in the DMF may be used to support
  - Investigational New Drug Application
  - New Drug Application
  - Abbreviated New Drug Application
  - another DMF
  - amendments and supplements to the above
Types of DMF

Type II

- Drug substance
- Drug substance intermediate and material used in their preparation
- Drug product

Type III

- Packaging material
Types of DMF

**Type IV**

- Excipient, colorant, flavor, essence, or material used in their preparation

**Type V**

- FDA accepted reference information (i.e. sterilization process validation in applications for human and veterinary drug products)
Timely Consults and Information Requests (TCIR) phase

Outgoing communications: FDA to ANDA, FDA to DMF

Where is the DMF: 
- With OGD
- With OPQ
- With OPQ/DMF under review
- With DMF holder

Type II API DMF Timeline

- DMF Submitted
- DMF Fee Paid
- ANDA receipt
- TCIR-Day 45
- ANDA Filing decision deadline
- 1st cycle DMF review
- IR to ANDA
- Mid-Cycle Discipline Review
- 2nd cycle DMF review
- DMF CR
- Mid-Cycle DRL
- IR to DMF

DMF due to OPQ
OPQ due to OGD
GDUFA Date

ANDA

DMF Fee
Paid

DMF
Submitted

TCIR-
Day 45

ANDA

Filing decision
deadline

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IR to
DMF

DMF

WHERE IS THE DMF:
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DMF Timeline – Original/New DMF

**Example**

**Type II API DMF Timeline**

- **DMF** Submitted
- **DMF Fee** Paid
- **ANDA** receipt
- **TCIR**
- **ANDA Filing decision deadline**
- **1st cycle DMF review**
- **Mid-Cycle Discipline Review**
- **2nd cycle DMF review**
- **Outgoing communications:** FDA to ANDA, FDA to DMF

**Suggested Communication points between DMF and ANDA**

- M-6
- M-3

**Months**

- M1
- M2
- M3
- M4
- M5
- M6
- M7
- M8
- M9
- M10

**Where is the DMF:**

- With OGD
- With OPQ
- With OPQ/DMF under review
- With DMF holder

**PRINT VERSION**
Major DMF Deficiencies in DS Explained

1. Inadequate selection or justification of starting materials.
2. Toxicological studies are needed to qualify an unqualified impurity.
3. Reference to a secondary DMF which has not been reviewed, is currently inadequate, or requires submission of a technical dossier from a third party supplier with significant additional manufacturing information.
4. Failure to provide adequate analytical methods or method validation which would require significant new method development.
5. Insufficient physical or chemical characterization data to demonstrate structure, form, or drug substance sameness (especially for complex active pharmaceutical ingredients (APIs)) in the DMF.
6. Major change in drug substance manufacturing process with inadequate supporting data.
7. Requirement to manufacture a new API batch.
8. Data reliability issue in the DMF or manufacturing/testing facilities.
Major DMF Deficiencies – DS Categories

- 307 DMFs reviewed by OPQ have major deficiencies
- 198 first cycle (64%), 109 subsequent cycles (36%)
- 68% due to impurity qualification

DMF with Major Deficiencies (n=251)

- One Category (80%)
- Two Categories (18%)
Nitrosamine Task Force

- **Office of the Center Director**
  - Counter-terrorism and Emergency Coordination Staff
  - Drug Shortage Staff

- **Office of Pharmaceutical Quality**
  - Office of New Drug Products
  - Office of Lifecycle Drug Products
  - Office of Testing and Research
  - Office of Policy for Pharmaceutical Quality
  - Office of Program and Regulatory Operations
  - Office of Quality Surveillance

- **Office of Compliance**
  - Office of Drug Security, Integrity and Response
  - Office of Manufacturing Quality

- **Office of Generic Drugs**
  - Division of Clinical Research
  - Clinical Safety Surveillance Staff

- **Office of New Drugs**

- **Office of Communications**
  - Division of Drug Information
  - Division of Health Communication

- **Office of Surveillance and Epidemiology**

- **Office of Executive Operations**
The Division of Drug Information is the Center for Drug Evaluation and Research’s focal point for public inquiries regarding human drug products.

The Division of Drug Information supports the Food and Drug Administration’s mission to promote and protect public health.
DDI Engagement

**Audience**

<table>
<thead>
<tr>
<th>1. Consumer</th>
<th>6. Other HCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Industry</td>
<td>7. Student</td>
</tr>
<tr>
<td>5. Pharmacist</td>
<td>10. Attorney</td>
</tr>
</tbody>
</table>

**Points of Contact in 2019**

- Phone: 42,477, 71%
- Email: 16,258, 27%
- Facebook: 830, 1%
- Letters: 487, 1%

**Contact Points by Year**

- 2017: Letters 920, Email 1149, Phones 696, Facebook 487, Letters 830
- 2018: Letters 16,258, Email 17,169, Phones 1,083, Facebook 487, Letters 830
- 2019: Letters 16,480, Email 44,834, Phones 42,477, Facebook 830
What is my risk of getting cancer?

Should I stop taking my medication?

Has my medication been recalled?

Why did it take FDA so long to find out about this?

Is telmisartan safe to take?

Can you check my NDC number?

I got a recall notice from my pharmacy. Am I in danger?

Why have they taken ranitidine off the shelf?

How can I get more information about NDMA?

Why did it take FDA so long to find out about this?
Main Message

- Patient safety is FDA’s top priority

- Patients should not stop taking their medications without first talking to their health care provider

- Health care providers and consumers can stay up to date with FDA resources
Resources

- FDA Website
- CDER Social Media
- Live Webinars
- DDI
FDA Website

- Updates and press announcements
  - Warning letters
  - Agency statements
  - Testing methods and results

- Recall information

- Q&A

- Drug shortages
Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan

Get current information about recalls of blood pressure medications

What do I need to know about this recall?

- What are valsartan, losartan, and irbesartan?
- Why are some valsartan, losartan, and irbesartan medicines being recalled?
- Which ARB medications are being recalled?
- Where do I find the manufacturer or repackager name and National Drug Code (NDC) of my medication?
- Where do I find the lot number of my medication?
- Should I continue taking my medication even if it has been recalled?
- What do I do with my unused medication?
- What should I know as a health care professional?

www.fda.gov/ARBrecalls
FDA Updates and Press Announcements on NDMA in Zantac (ranitidine)

4/16/2020: UPDATE - FDA alerts patients and health care professionals to Amneal’s voluntary recall of nizatidine

4/1/2020: PRESS RELEASE - FDA Requests Removal of All Ranitidine Products (Zantac) from the Market

2/27/2020: UPDATE - FDA alerts patients and health care professionals to American Health Packaging’s voluntary recall of ranitidine

1/8/2020: UPDATE - FDA alerts patients and health care professionals to two voluntary recalls of ranitidine

www.fda.gov/ranitidine
FDA Updates and Press Announcements on NDMA in Metformin

2/3/2020: STATEMENT- FDA posts laboratory testing results for NDMA levels in metformin

2/3/2020: Laboratory testing results for NDMA in metformin

12/5/2019: STATEMENT - Statement from Janet Woodcock, M.D., director of FDA’s Center for Drug Evaluation and Research, on impurities found in diabetes drugs outside the U.S.

FDA-published testing method to provide an option for regulators and industry to detect NDMA impurities

The link below is to an FDA-published testing method to provide an option for regulators and industry to detect nitrosamine impurities in metformin drug substances and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

- **LC-HRMS method**: an LC-MS method for the detection of NDMA in metformin drug substances and drug products.
Information about Nitrosamine Impurities in Medications

- Losartan Valsartan and other ARBs
- Ranitidine (Zantac)
- Metformin

www.fda.gov/nitrosamines
### Recalls, Market Withdrawals, & Safety Alerts

#### Search

Showing 1 to 10 of 257 entries (filtered from 1,260 total entries)

#### Filters

**Product Type**

- Drugs

- Clear Filters

#### Table of Recall Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Brand Name(s)</th>
<th>Product Description</th>
<th>Product Type</th>
<th>Recall Reason Description</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/27/2020</td>
<td>QuVa</td>
<td>R.E.C.K. (Ropivacaine, Epinephrine, Clonidine, Ketorolac) 50 ml in Sodium Chloride-60 ml BD syringe</td>
<td>Drugs</td>
<td>presence of particulate matter</td>
<td>QuVa Pharma, Inc.</td>
</tr>
<tr>
<td>04/20/2020</td>
<td>Fresenius Kabi</td>
<td>Ketorolac Tromethamine Injection, USP, 30 mg/mL, and Ketorolac Tromethamine Injection, USP, 60 mg/2 mL</td>
<td>Drugs</td>
<td>Presence of Particulate Matter</td>
<td>Fresenius Kabi USA, LLC</td>
</tr>
<tr>
<td>04/20/2020</td>
<td>B. Braun</td>
<td>Ceftazidime for Injection USP (2g) and Dextrose for injection USP (50 ml) in Duplex® Container</td>
<td>Drugs</td>
<td>Out-of-Specification Results for High Molecular Weight Polymers</td>
<td>Braun Medical Inc.</td>
</tr>
<tr>
<td>04/16/2020</td>
<td>Heritage</td>
<td>Tetracycline HCl Capsules, 250mg and 500mg</td>
<td>Drugs</td>
<td>Due to low out of specification dissolution results</td>
<td>Avet Pharmaceuticals Labs Inc.</td>
</tr>
<tr>
<td>04/15/2020</td>
<td>Gemini Laboratories</td>
<td>Nizatidine Oral Solution 15 mg/mL</td>
<td>Drugs</td>
<td>NDMA (N-Nitrosodimethylamine) impurity</td>
<td>Amneal Pharmaceuticals, LLC</td>
</tr>
</tbody>
</table>

[www.fda.gov/recalls](http://www.fda.gov/recalls)
A drug receives Resolved status when the Drug Shortages Staff (DSS) determines that the market is covered, based on information from all manufacturers. The market is considered covered when supply is available from at least one manufacturer to cover total market demand. However, some manufacturers may not have all presentations available. DSS monitors the supply of products with Resolved status. For the most current supply information, contact the manufacturers.

<table>
<thead>
<tr>
<th>Generic Name or Active Ingredient</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin Tablets</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>Resolved</td>
</tr>
<tr>
<td>Aminophylline Injection, USP</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Amoxapine Tablets</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate Tablets</td>
<td>Currently in Shortage</td>
</tr>
</tbody>
</table>
CDER
Social Media

• Facebook
• Twitter
• LinkedIn
Spans all FDA Centers

Target Audience:
- Consumers and patients

Posts:
- Drug Safety Communications
- Drug Approvals
- Press Announcements
- Patient Focused Drug Development Meeting Announcements
- News & Events for Human Drugs (CDER Conversations, From Our Perspective, Director’s Corner, Spotlight on CDER Science)
- Drug Information CE webinars for HCPs

www.facebook.com/FDA
FDA Drug Information
@FDA_Drug_Info

CDER-related content from DDI

Target Audience:
- HCPs, Industry, Patients, and Consumers

Posts:
- Drug Safety Communications
- Drug Approvals
- Press Announcements
- Drug Alerts and Statements
- Drug Safety Podcasts
- Drug Info Rounds
- Drug-related Immediate Public Notifications
- Drug Trials Snapshots
- News & Events for Human Drugs
- Guidance Documents
- CDER Impact Stories
- Drug Information CE webinars for HCPs

www.twitter.com/FDA_Drug_Info
GADIS: Global Alliance of Drug Information Specialists

Start a conversation in this group

FDA provides an update on its efforts to ensure the availability of alcohol-based sanitizer to help meet the demand for hand sanitizer during the COVID-19 pandemic: https://go.usa.gov/xvP6g.

CDER-related content from DDI

- **Target Audience:**
  - HCPs *(pharmacists)*

- **Posts:**
  - Drug Safety Communications
  - Drug Approvals
  - Press Announcements
  - Drug Alerts and Statements
  - Drug Safety Podcast
  - Drug Info Rounds
  - News & Events in Human Drugs
Media Intelligence

U.S. Food and Drug Administration

NDMA

time

high blood sugar

metformin
cancer
patients

Drug Evaluation and Research

meats, dairy products and vegetables

diabetes
drug
metformin

recalls
drug
diabetes
carcinogen
NDMA

agency

NDMA cancer

Possible Carcinogen
Upcoming Live CE Webinars

- FDA Drug Topics: Nitrosamine Impurities in Drugs: What Health Care Professionals Need to Know – May 5, 2020
- FDA Drug Topics: FDA’s Bad Ad Program – May 19, 2020

NEW! Home Study CE Webinars

- FDA Drug Information Resources and Applicability to Health Care Professionals
- Research Funding Opportunities to Reduce Preventable Harm
- Biosimilar and Interchangeable Biological Products: Basic Concepts and Practical Resources
- Drug Shortages: FDA Efforts, Current Challenges and Future Goals
- Introduction to the Office of Orphan Products Development (OOPD)
- FDA Regulation of Color Additives in Drug Products
- 3D Printing in Drug Development and Emerging Health Care

www.fda.gov/DDIwebinars
DDI Contact Information

Phone Contacts

• Drug Information 855-543-DRUG or 888-INFO-FDA
• MedWatch 800-FDA-1088
• Small Business and Industry Assistance 866-405-5367
• eIND requests during regular business hours

Email accounts

• DrugInfo@fda.hhs.gov
• CDERSBIA@fda.hhs.gov
• AskGDUFA@fda.hhs.gov

www.fda.gov/aboutDDI
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Questions?

Division of Drug Information
855-543-DRUG (3784)
301-796-3400
druginfo@fda.hhs.gov
www.fda.gov/aboutDDI