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

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Objectives

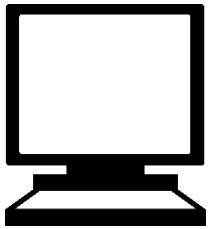
- Describe FDA's role in helping to ensure the quality of drugs marketed in the U.S.
- Discuss the drug classes that have been affected by nitrosamine impurities
- Identify 3 ways to obtain information about medications recalled due to nitrosamine impurities

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.




<u>Drugs are no different.</u>


FDA
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.

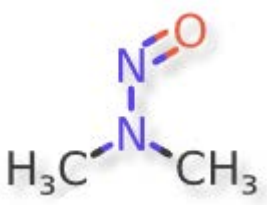
Nitrosamines

- 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

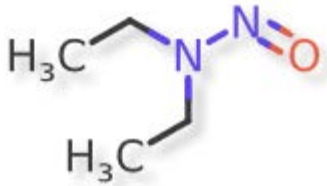
Nitrosamines

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

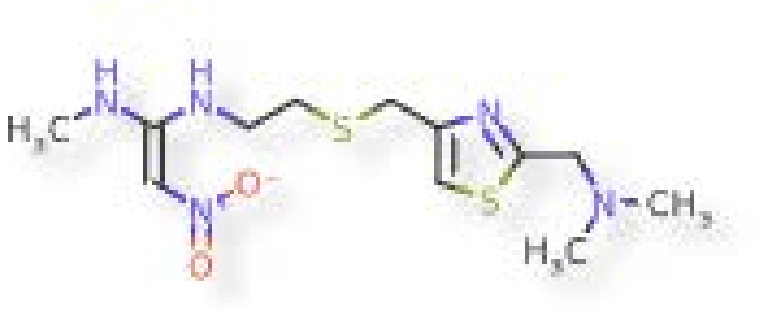
July 2018 - present – FDA continues meeting to address CGMP violations, update lab analysis of ARBs

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

- FDA will continue to investigate the source of these impurities
- There are multiple reasons why NDMA can be present in drugs

https://www.fda.gov/news-events/press-announcements/statement-janet-woodcock-md-director-fdas-center-drug-evaluation-and-research-impurities-found

Drugs and Impurities

- Understand Pharmaceutical Quality

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

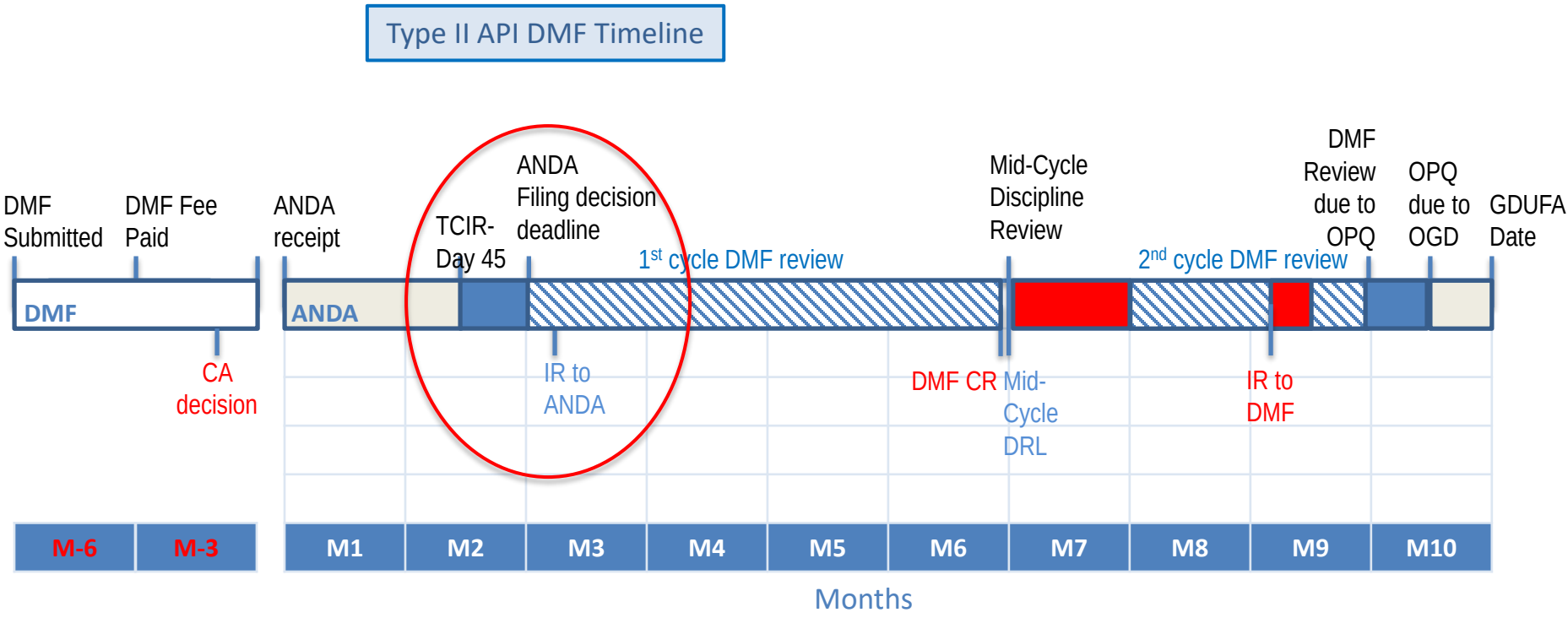
Type IV

- 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



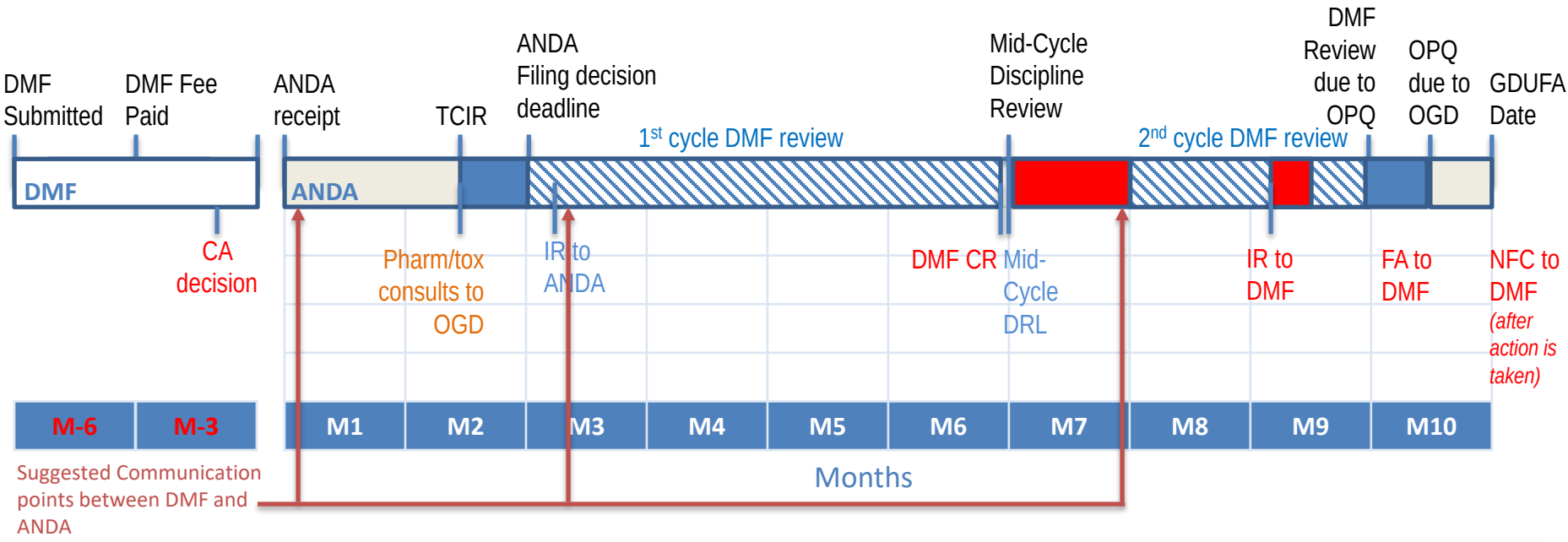
Outgoing communications: FDA to ANDA, FDA to DMF

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

DMF Timeline – Original/New DMF

Example

Type II API DMF Timeline



Outgoing communications: FDA to ANDA, FDA to DMF

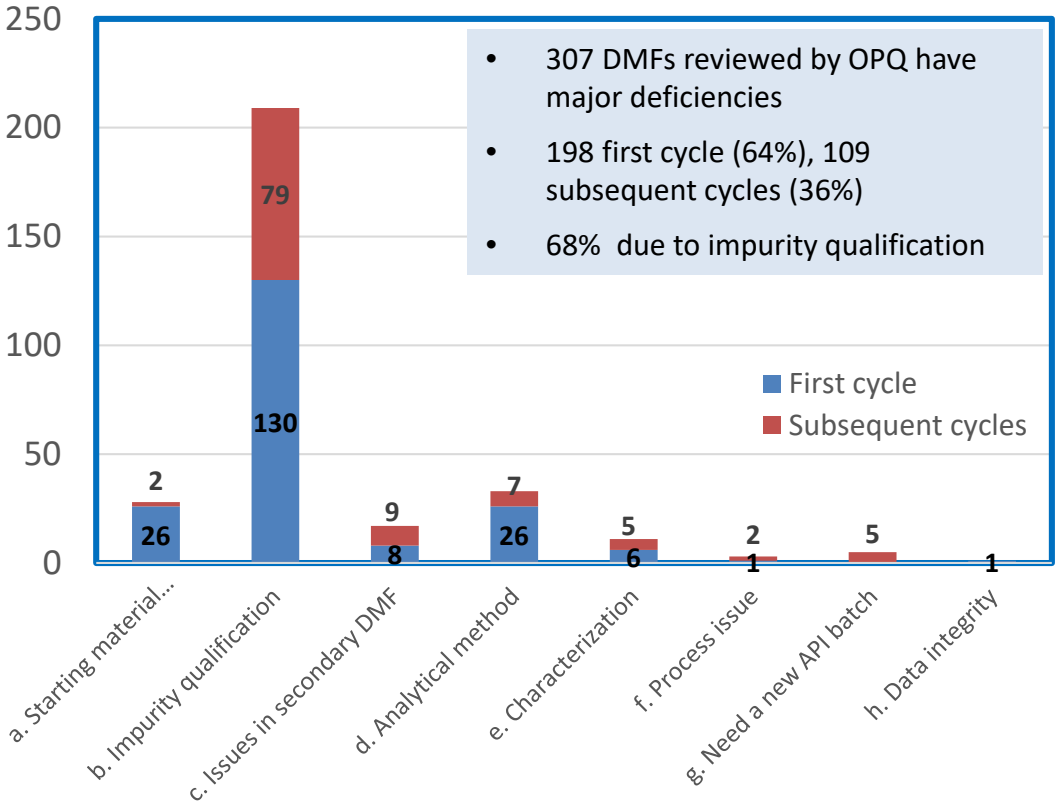
Where is the DMF: With OGD | With OPQ | With OPQ/DMF under review | With DMF holder

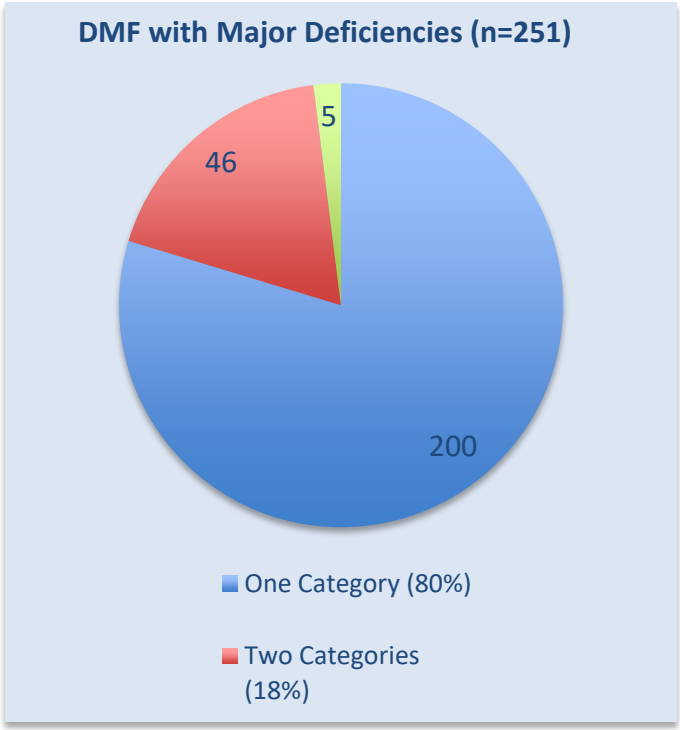
PRINT VERSION

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





Nitrosamine Task Force

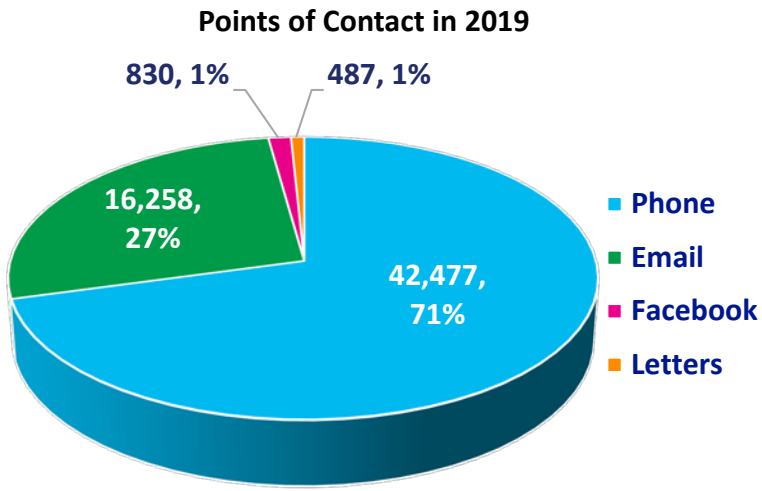
- **Office of the Center Director**
  - Counter-terrorism and Emergency Coordination Staff
  - Drug Shortage Staff
- **Office of Pharmaceutical Quality**
  - Office of New Drug Products
  - Office of Lifecycle Drug Products
  - Office of Testing and Research
  - Office of Policy for Pharmaceutical Quality
  - 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**

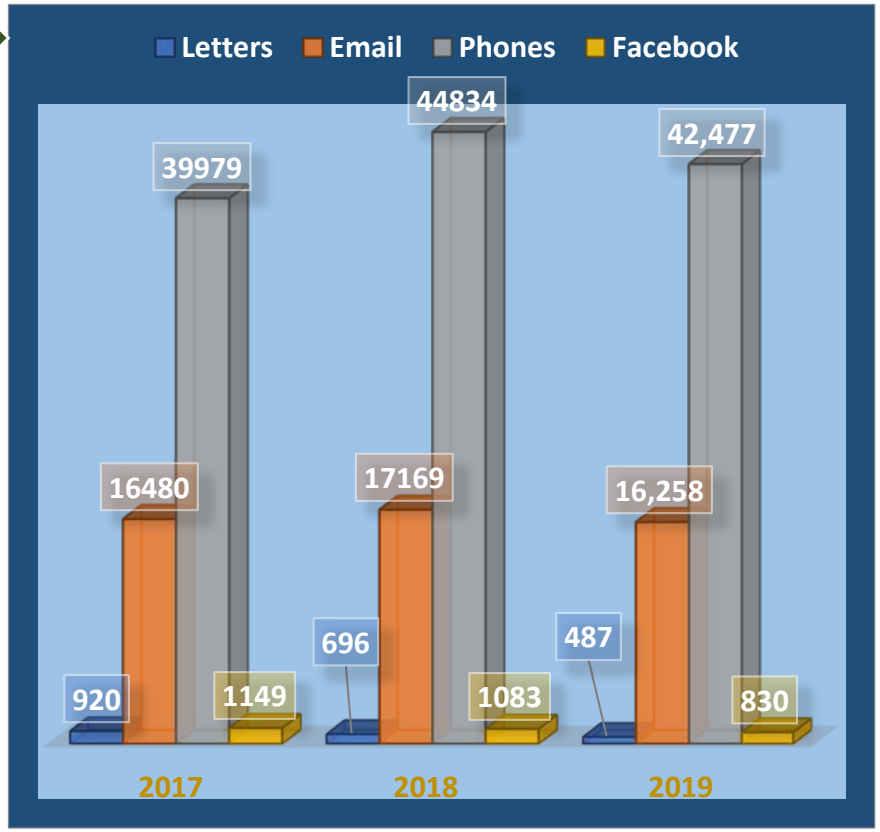
Division of Drug Information

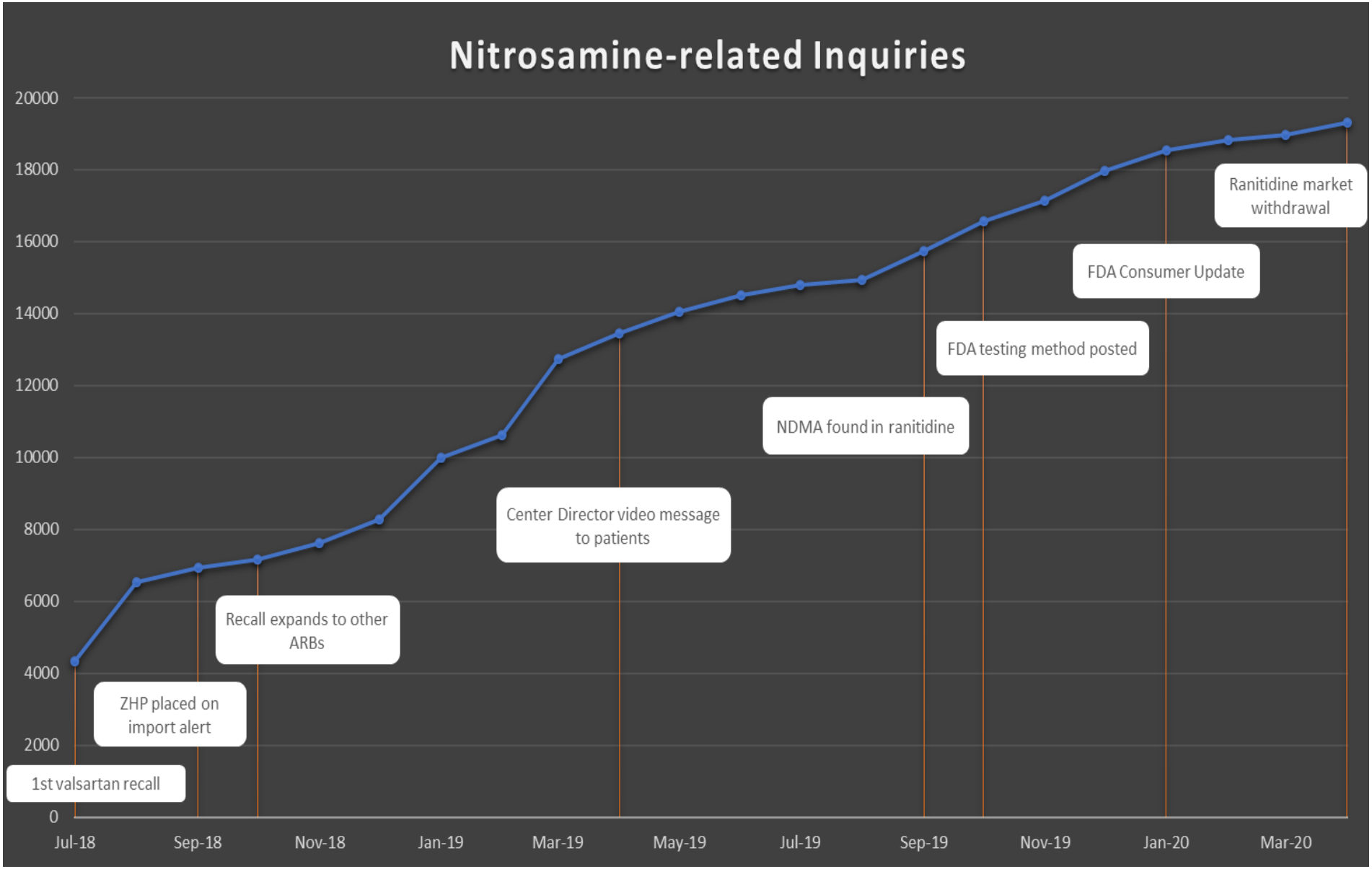
- The Division of Drug Information is the Center for Drug Evaluation and Research's focal point for public inquiries regarding human drug products
- The Division of Drug Information supports the Food and Drug Administration's mission to promote and protect public health

DDI Engagement

Audience	
1. Consumer	6. Other HCP
2. Industry	7. Student
3. Clinical Research	8. Nurse
4. Physician	9. Federal Agency
5. Pharmacist	10. Attorney






Nitrosamine-related Inquiries
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Jul-18
Sep-18
Nov-18
Jan-19
Mar-19
May-19
Jul-19
Sep-19
Nov-19
Jan-20
Mar-20
1st valsartan recall
ZHP placed on import alert
Recall expands to other ARBs
Center Director video message to patients
NDMA found in ranitidine
FDA testing method posted
FDA Consumer Update
Ranitidine market withdrawal


Should I stop taking my medication?
What is my risk of getting cancer?
Has my medication been recalled?
Why did it take FDA so long to find out about this?
How can I get more information about NDMA?
Can you check my NDC number?
Is telmisartan safe to take?
I got a recall notice from my pharmacy. Am I in danger?
Why have they taken ranitidine off the shelf?

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?

Search ARB Recalls List

FDA's Assessment of Currently Marketed ARBs

www.fda.gov/ARBrecalls

FDA Updates and Press Announcements on NDMA in Zantac (ranitidine)

QA on NDMA in ranitidine

Nitrosamine Impurities in Medications

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

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Nitrosamine Impurities in Medications

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

Information about Nitrosamine Impurities in Medications

Share | Tweet | Linkedin | Email | Print

Losartan Valsartan and other ARBs

Ranitidine (Zantac)

Metformin

What patients should know about nitrosamine impurities

What health care professionals should know about nitrosamine impurities

What industry should know about nitrosamine impurities

Q. What are nitrosamines?

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

Export Excel Show 10 entries

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

www.fda.gov/recalls

FDA Drug Shortages

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Current and Resolved Drug Shortages and Discontinuations Reported to FDA

Report a Drug Shortage | Contact Us | FAQ | Background Info | Get Email Alerts | Download Current Drug Shortages

Search by Generic Name or Active Ingredient: Enter at least three characters Submit

Current/Resolved Shortages | Discontinuations | Therapeutic Categories | **New and Updated**

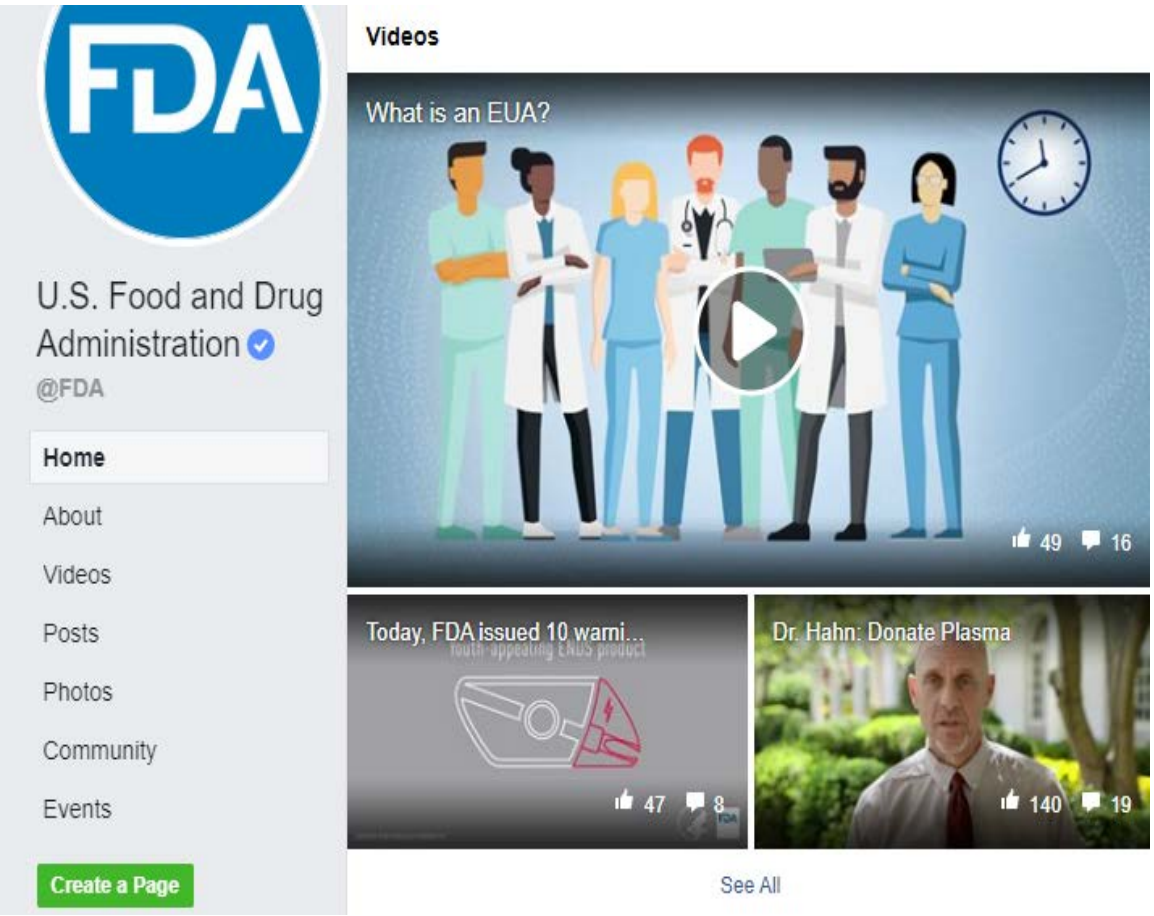
A drug receives Resolved status when the Drug Shortages Staff (DSS) determines that the market is covered, based on information from all manufacturers. The market is considered covered when supply is available from at least one manufacturer to cover total market demand. However, some manufacturers may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

Show 20 **entries** **Search:**

Generic Name or Active Ingredient	Status
Alogliptin Tablets	***Currently in Shortage***
Amino Acids	***Resolved***
Aminophylline Injection, USP	***Currently in Shortage***
Amoxapine Tablets	***Currently in Shortage***
Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate Tablets	***Currently in Shortage***

CDER Social Media

- Facebook
- Twitter
- LinkedIn

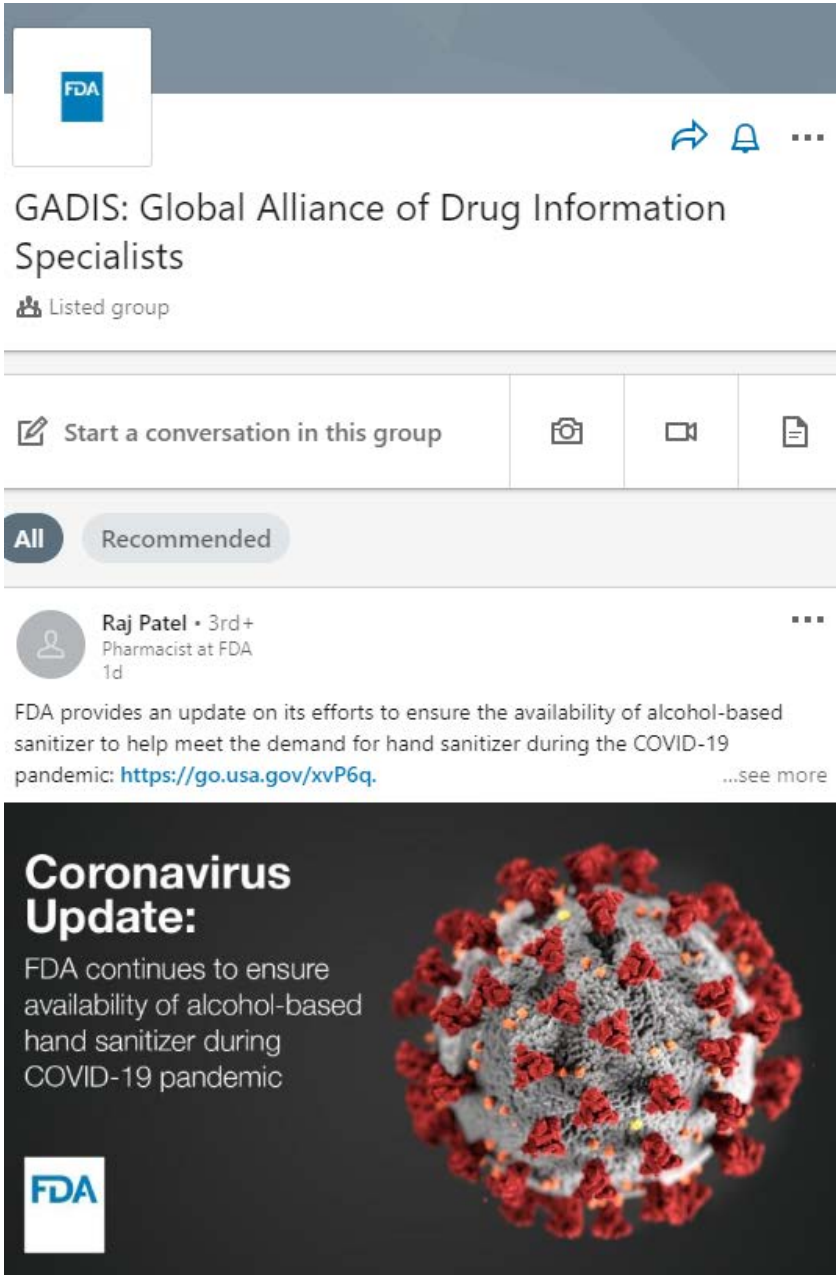


- **Spans all FDA Centers**
- **Target Audience:**
  - Consumers and patients
- **Posts:**
  - Drug Safety Communications
  - Drug Approvals
  - Press Announcements
  - Patient Focused Drug Development Meeting Announcements
  - News & Events for Human Drugs (CDER Conversations, From Our Perspective, Director's Corner, Spotlight on CDER Science)
  - Drug Information CE webinars for HCPs

www.facebook.com/FDA

- **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



- **CDER-related content from DDI**
- **Target Audience:**
  - HCPs **(pharmacists)**
- **Posts:**
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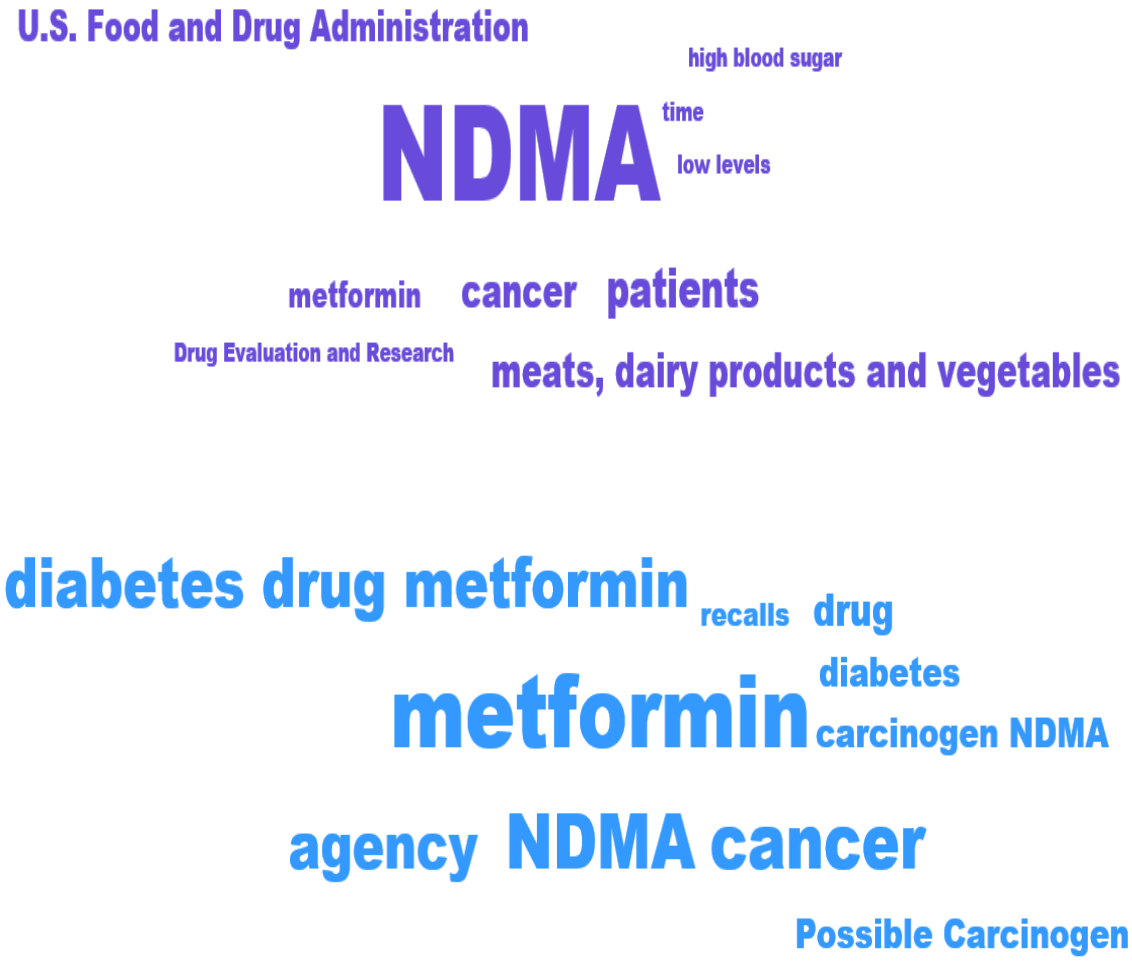
  - Press Announcements
  - Drug Alerts and Statements
  - Drug Safety Podcast
  - Drug Info Rounds
  - News & Events in Human Drugs

Media Intelligence



Division of Drug Information Webinars

Educational Webinars for Health Care Professionals and Students

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

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