COVID-19 Response and Guidance Updates

Donald D. Ashley, J.D.
Director, Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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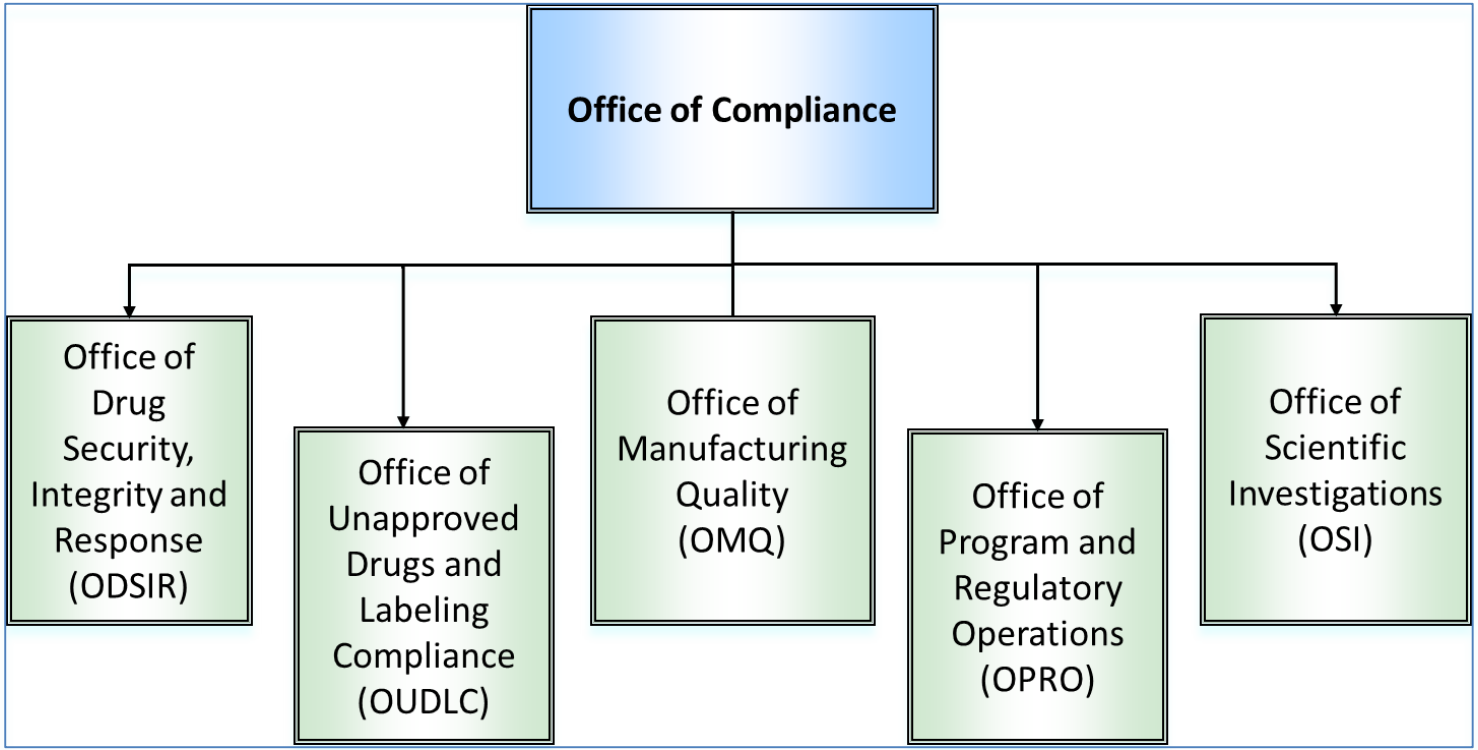
CDER - Office of Compliance

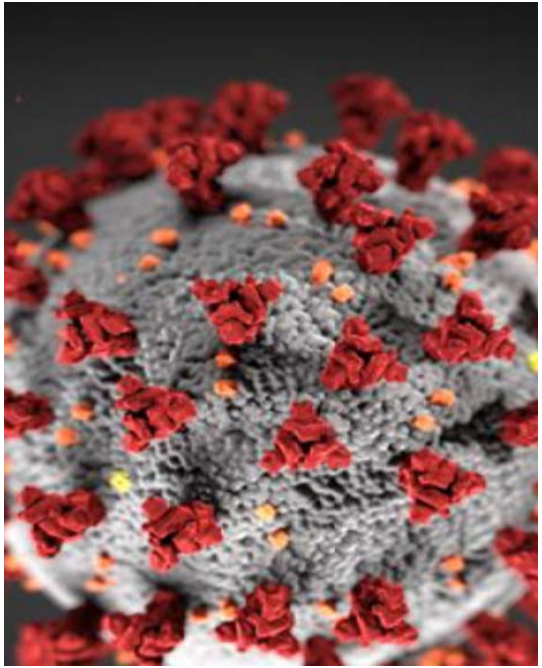
MISSION

To shield patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and risk-based enforcement action.

CDER - Office of Compliance



Response to the Pandemic



- Working to increase patient access to critically needed medications in shortage
- Protecting patients from fraudulent COVID-19 products
- Protecting the public from poor quality and unsafe hand sanitizers

Addressing Shortages of Critical Medications Needed to Treat Hospitalized COVID-19 Patients

Regulatory Discretion

To mitigate shortages of medications used to treat COVID-19 patients, CDER Compliance has issued **more than 35 regulatory discretion decisions**.

- Cisatracurium
- Etomidate
- Midazolam
- Propofol
- Heparin
- Albuterol
- Azithromycin

Temporary Compounding Policies

1.Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency Guidance for Industry

2.Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency Guidance for Industry

Comparison of Discretion Policies

Outsourcing Facility	Pharmacy Compounders
Temporary Enforcement Discretion Related To: • "Essentially a copy" provision • 503B bulks list • CGMP for stability studies/expiration dates	**Temporary Enforcement Discretion Related To:** • "Essentially a copy" provision • Prescription requirement
Required Circumstances Include • Limited to list of drugs • Hospital first attempts to obtain FDA-approved drugs • Beyond use date and limited stability testing considerations • Weekly reporting	**Required Circumstances Include** • Limited to list of drugs • Hospital first attempts to obtain FDA-approved drugs or drugs from Outsourcing Facilities • No objection by board of pharmacy • Must identify hospital & COVID-19 treatment • Hospital to identify patients within one month • Beyond use date limited • Reporting of adverse events

Drugs Covered by Discretion Policies

Updated October 13, 2020 - List of Drugs Used for Hospitalized Patients with COVID-19 [formerly "Appendix A"] Now Found on the Web

Products are all aqueous solutions for injection:

Cisatracurium besylate	Ketamine hydrochloride
Dexamethasone sodium phosphate	Lorazepam
Dexmedetomidine hydrochloride	Midazolam hydrochloride
Epinephrine	Morphine Sulfate
Etomidate	Norepinephrine bitartrate
Fentanyl citrate	Rocuronium bromide
Furosemide	Vancomycin hydrochloride
Hydromorphone hydrochloride	Vecuronium bromide

Temporary Compounding Policies

Four Additional Guidances

1. Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-10 Public Health Emergency
2. Temporary Policy Regarding Non-Standard PPE Practices for Sterile Compounding by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency
3. Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic
4. Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency

Protecting Patients and Consumers from Fraudulent COVID-19 Products

Fraudulent COVID-19 Claims

- Market flooded with products making unproven claims
- Products are unlawful and put patients at risk

Corona-Cure Coronavirus Infection Prevention Nasal Spray

$19.99

ADD TO CART

Buy with PayPal

More payment options

CURRENTLY OUT OF STOCK. EXPECT SHIPMENTS TO BE READY 3/23/2020

Our instant protection nasal spray is designed to protect your vulnerable nasal passages from infection by the 2019 Novel Coronavirus specifically and other viruses in general. The

Fraudulent COVID-19 Claims

CDER/Compliance Response	Product Examples
• Conducting ongoing surveillance • Issued **85+** warning letters for products claiming to treat COVID-19 • Issued **10+** warning letters to internet pharmacies • Vast majority stopped selling products or took down claims	• Chlorine Dioxide • Colloidal Silver • CBD • Copper • Honey • Botanical Oils

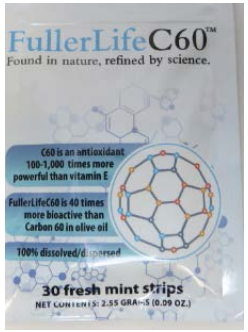
InfoWars/Alex Jones Silver Gargle

Seanjari Preeti Womb Healing COVID19 Cough Syrup

Examples of Violative Products

Herbal Amy's Coronavirus Core Tincture

Miracle Mineral Solution (MMS)



Carbon60 Mint Strips

CopperTouch Sani-Disc

Federal Civil Enforcement Actions

- Genesis II Church
- Xephyr LLC dba N-Ergetics
- White Eagle Native Herbs

FDA will continue to take action against firms endangering the public health.

Poor Quality and Unsafe Hand Sanitizers

COVID19 Pandemic

- Prompts Surge in Hand Sanitizer Use
- Thousands of new products and manufacturers
- Dozens of new manufacturers producing methanol contaminated hand sanitizers

Drug Registration and Listing

Since March 1, 2020

- More than 4,600 different registrants
- Listed more than 15,000 OTC products with alcohol as active ingredient
- New firms, including many cosmetic companies, distilleries and other first time OTC drug manufacturers

Surge in Hand Sanitizer Imports

55 Gallon Drums

Jugs in the back of a truck

No Inspections Required

Dr. Janet Woodcock:

"[W]e still face some challenges in ensuring the safety of imported drugs entering our drug supply. Under our current authorities, ***foreign-based manufacturers of certain drugs can legally ship drugs to the United States without ever having been inspected by FDA.*** *Drugs in this category typically include* ***OTC monograph drugs*** *. . . . This* ***increases the risk of exposing American patients to unsafe or ineffective drugs and requires resource-intensive efforts on FDA's part to identify and respond to any problems that arise subsequently."***

Testimony before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations on December 10, 2019.

Screening at the Border

- Customs and FDA screening hand sanitizer products at the border
- Referring suspect shipments to FDA Labs for further testing

FDA Lab Findings

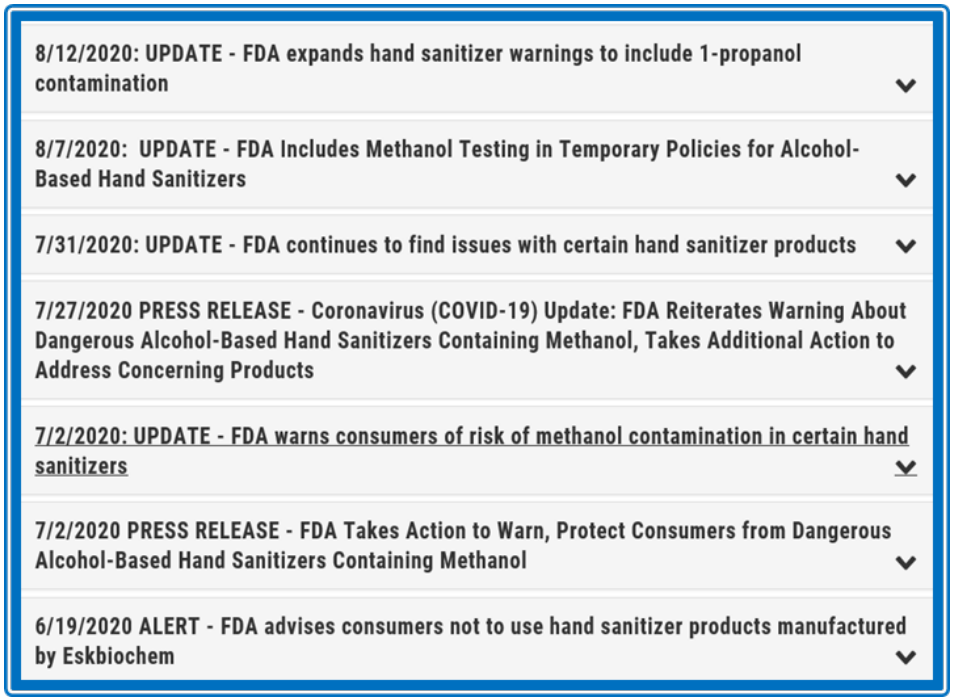
- Observed methanol ranging from 1% to 80% in many hand sanitizer products from Mexico
- Sub-potent levels of ethanol
- High degree of variability between and within lots of the same product
- Confirmed 1-propanol contamination in a few cases

Serious Adverse Events and Deaths from Methanol Contamination

Yip L, Bixler D, Brooks DE, et al. Serious Adverse Health Events, Including Death, Associated with Ingesting Alcohol-Based Hand Sanitizers Containing Methanol — Arizona and New Mexico, May–June 2020. MMWR Morb Mortal Wkly Rep 2020;69:1070–1073. DOI: http://dx.doi.org/10.15585/mmwr.mm6932e1external icon

FDA Response

- Recommending recalls
- Notifying the public
- Produced list of potentially dangerous hand sanitizers consumers should not use.
  - *https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use*

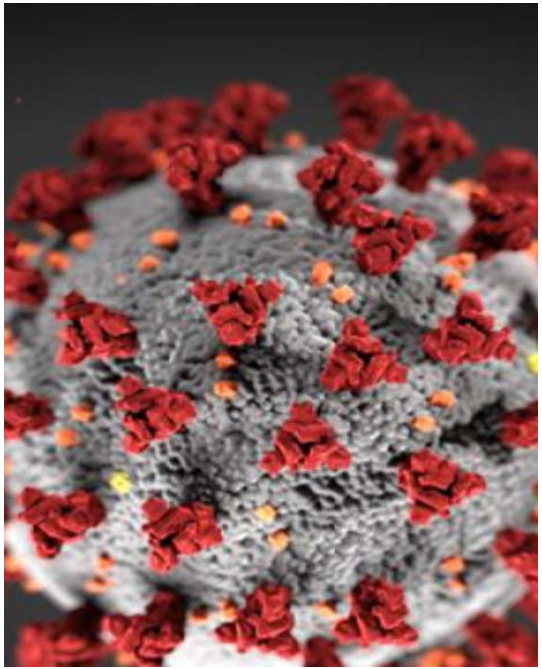


FDA Response

- Firms added to import alert 66-78 to prevent future shipments: https://www.accessdata.fda.gov/cms_ia/importalert_1166.html
- Warning Letters
  - Adulteration
  - Unapproved new drug
  - Misbranding

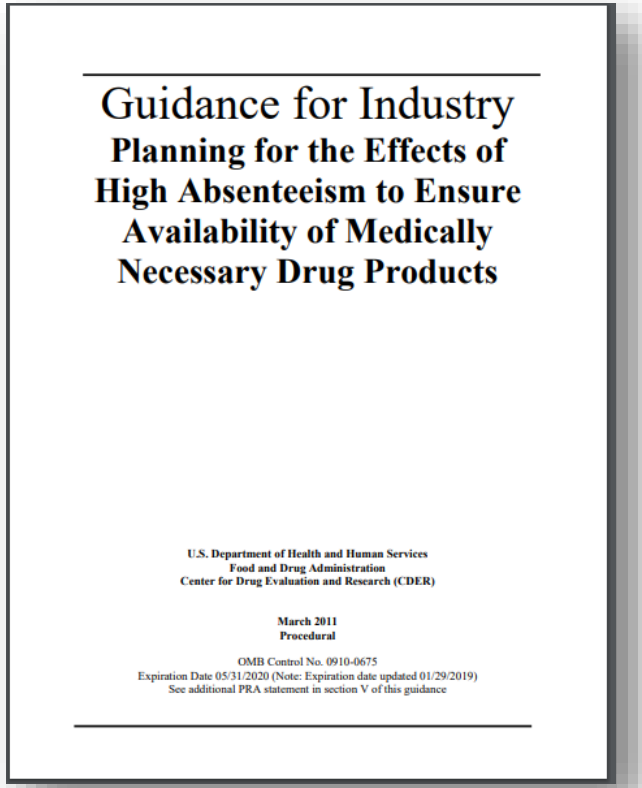
U.S Pharmacopeia

- Formally requested that USP modify the alcohol/dehydrated alcohol monographs to include identity testing for methanol.
- On September 1, 2020, USP updated its alcohol and dehydrated alcohol monographs to specifically require an identity test for methanol.



Additional COVID-19 Guidances

Manufacturing During the Pandemic



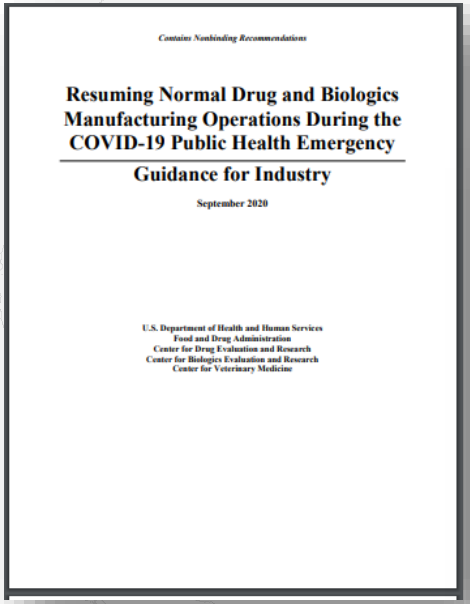
Guidance for Industry

Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2011
Procedural

OMB Control No. 0910-0675
Expiration Date 05/31/2020 (Note: Expiration date updated 01/29/2019)
See additional PRA statement in section V of this guidance



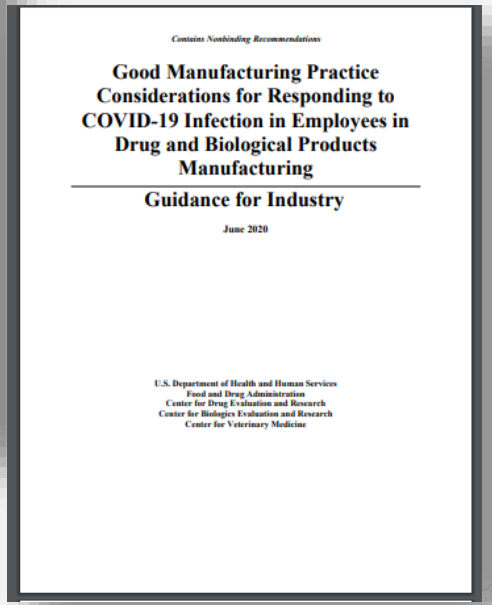
Contains Nonbinding Recommendations

Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency

Guidance for Industry

September 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Veterinary Medicine



Contains Nonbinding Recommendations

Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing

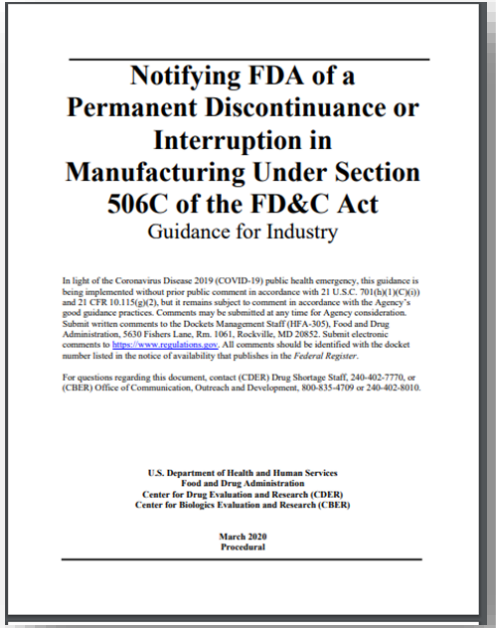
Guidance for Industry

June 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Veterinary Medicine

Shortage Reporting

- Must report permanent discontinuance or interruption in manufacturing at least 6 months in advance [or no later than five days after when not forseeable]
- FDA requests that sudden unexpected spikes in demand also be reported
- Reporting helps prevent or mitigate shortages of such products
- Covered drug and biologic products only
- Who reports?
  - NDAs, ANDAs and BLAs → applicant reports
  - Without NDA or ANDA → drug manufacturer reports



Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act

Guidance for Industry

In light of the Coronavirus Disease 2019 (COVID-19) public health emergency, this guidance is being implemented without prior public comment in accordance with 21 U.S.C. 701(h)(1)(C)(i)) and 21 CFR 10.115(g)(2), but it remains subject to comment in accordance with the Agency's good guidance practices. Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact (CDER) Drug Shortage Staff, 240-402-7770, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

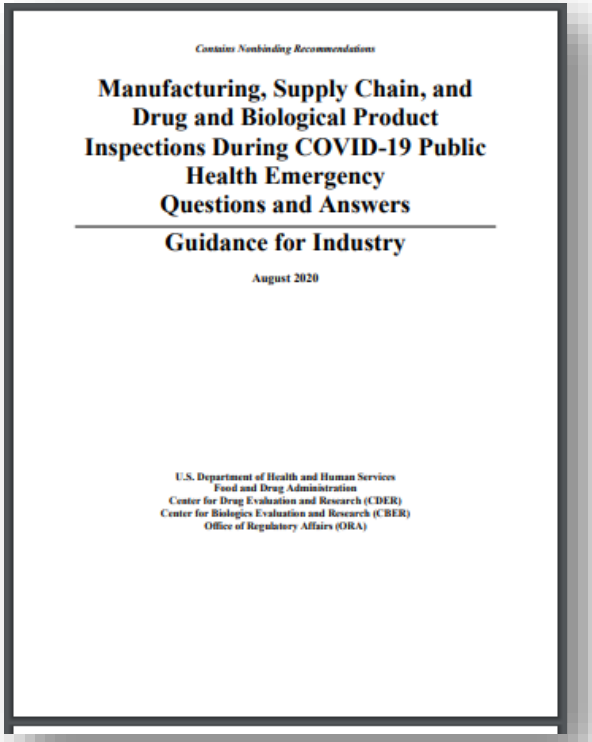
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2020
Procedural

Facility Inspections

- Common queries related to inspections for facilities manufacturing pharmaceutical products and sites involved in the conduct of clinical, analytical, and nonclinical studies

- **<u>Examples of questions:</u>**
  - *How are inspections impacted by COVID-19?*
  - *What types of inspections would be deemed "mission critical"?*
  - *How will FDA ensure the quality of imported products while inspections are limited?*



Contains Nonbinding Recommendations

Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers

Guidance for Industry

August 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

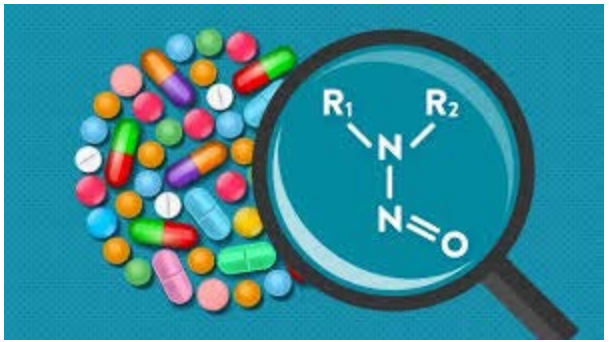
For questions regarding this document, contact (CDER) Dongmei Lu 240-402-7966.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2020
Pharmaceutical Quality/ Manufacturing Standards/
Current Good Manufacturing Practice (CGMP)

FDA

Nitrosamine Guidance



Nitrosamine Impurities

- NDMA and other nitrosamines are commonly found in low amounts in foods, beverages, cosmetics and water
- Probable human carcinogens
- Recently found in drugs such as angiotensin II receptor blockers (ARBs), ranitidine, nizatidine and metformin

Recommended Acceptable Intake

- Acceptable intake (AI) limits for six nitrosamines
- If ≥2 nitrosamines detected and total impurities exceed 26.5 ng/day, contact FDA
- If a different nitrosamine is detected, refer to ICH M7(R1) and contact FDA

Nitrosamine	AI Limit (ng/day)
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Causes of Nitrosamine Impurities

- **General Conditions** = secondary, tertiary or quaternary amines + nitrite salts under acidic reaction conditions
- Contamination in vendor-sourced raw materials
- Recovered solvents, catalysts and re-agents
- Quenching process
- Lack of process optimization and control
- Non-API sources of contamination

Recommendations for Industry

- Conduct risk assessment for nitrosamines for **all** products
- If any risk is identified, conduct confirmatory testing
- If nitrosamines are detected:
  - conduct root cause analysis, and
  - implement changes to manufacturing process to prevent/reduce nitrosamines.
- Report changes implemented to FDA

Recommended Timeline

- Complete risk assessment for **all** approved or marketed drug products by March 2021
- Confirmatory testing and submission of changes to drug applications should be completed by September 2023

Thank You