FDA Drug Topics:
Drug Shortages: Root Causes and Potential Solutions

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Learning Objectives:

1. Identify what FDA can and cannot do to prevent and mitigate drug shortages
2. Describe how to report a drug shortage to the FDA
3. Summarize pharmaceutical Industry's role in drug shortage prevention and mitigation

Drug Shortage Mission

- Our mission is to prevent, mitigate and alleviate drug shortages
- Patient and practitioner access to life-saving medication is our #1 priority
- Drug Shortage Staff works with professional organizations, patient groups, clinicians and other stakeholders (DEA, CMS, EMA, etc.)

Brief History

- Part of FDA's Center for Drug Evaluation & Research (CDER)
- Drug Shortage Program began in 1999
- 2011- President Obama signed *Executive Order 13588-Reducing Prescription Drug Shortages*
- 2012-Requirements to Industry For Early Notifications Under Section 506C of the FD&C Act
- CDER Drug Shortage Program (DSP) changed to Drug Shortage Staff (DSS) in 2012
- Moved under the CDER Office of the Center Director in 2014
- Additional drug shortage staff in other Centers (e.g. CBER, CDRH)
- Coronavirus Aid, Relief, and Economic Security Act (CARES Act) 2020

FDA Drug Shortage Staff (DSS)

Drug Shortage Staff: The program office that is designated by FDA to oversee and facilitate the resolution of all drug shortage situations

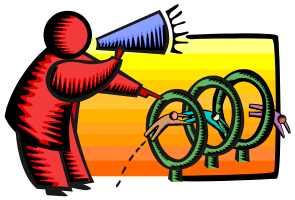
DSS serves to support FDA's mission of ensuring that safe and effective drugs are available to patients

- Facilitate temporary and long-term strategies to address shortages
- Coordinate for timely and comprehensive risk/benefit decisions
- Distribute information (web posting, professional organizations, e.g. ASHP)

Often working across suppliers, facilities, and issues - multiple moving parts, urgency

→ Maintain availability while minimizing risk to patients

FDA Drug Shortage Staff - Key Communications



Data Comparison: CDER Drug Shortage vs ASHP Website

- FDA receives information provided by manufacturers
- ASHP receives information from practitioners unable to get product
- FDA does not consider a product to be in shortage if one or more manufacturers are able to supply the full market demand for the product
- ASHP's Drug Shortage website provides information about which manufacturers have the drug available and which ones do not, since supply chain disruptions may occur when all previous manufacturers are not yet back on the market

Contrasting the FDA (CDER) and ASHP Drug Shortage Websites: What are the differences?		
	FDA	**ASHP**
Purpose	Provides information obtained from manufacturers about current shortages, estimated duration, and discontinuations and provides information about FDA's and other stakeholders' roles in addressing and preventing shortages	Notification of new shortages and status of ongoing shortages; drug shortage management resources
Audience	Public	Healthcare practitioners
Scope of shortage list	All drugs are listed that are confirmed to be a national shortage by FDA. A shortage is considered to be the period of time when the demand for the drug within the United States exceeds the supply of the drug. **Note:** A separate shortage webpage[i] for vaccines and some biologics is maintained by the Center for Biologics Evaluation and Research.	All drug and biologic shortages reported and confirmed with manufacturer that are national in impact. **Note:** ASHP frequently lists more shortages than FDA.
Source of shortage report	Manufacturers notify FDA of production disruption and voluntarily provided updates. Reports are also received from ASHP and from public via drugshortages@cder.fda.gov **Note:** Manufacturer-provided information represents shortage status at drug firm level	Voluntary reports from practitioners, patients, pharmaceutical industry representatives and others **Note 1:** Information is updated based on release dates from manufacturers. **Note 2:** Reports reflect status at healthcare provider level.
Criteria for inclusion on list	Manufacturers cannot meet current market demand for the drug based on information provided by manufacturers and market sales research	(1) Shortage is verified with manufacturers and (2) affects how pharmacy prepares or dispenses a product, or (3) requires use of alternative drugs, which may affect patient care
Criteria for resolving shortage	One or more manufacturers are in production and able to meet full market demand	All manufacturers of the drug restore all formulations and dosage sizes to full availability. **Note:** Product are listed despite partial or restricted availability as supply chain disruptions can result in intermittent shortages at the provider or patient level
Reason for shortage	Provided by manufacturers using reasons required by legislation.[ii] FDA encourages firms to provide additional information about reasons and other information which, if proprietary, is nondisclosable without the firms' permission.	Provided by manufacturer, if willing to disclose. **Note:** May differ from FDA's due to different sources of information and legislation requiring FDA to use specified reasons
Other information	Estimated duration, links to regulatory information such as recalls and Dear Healthcare Provider Letters	Estimated duration, list of available products, implications for patient care and safety, shortage management strategies, therapeutic alternatives

Developed by: Food and Drug Administration Drug Shortage Staff, American Society of Health-System Pharmacists, and the University of Utah Drug Information Service. August 2014

[i] URL : http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/ucm351921.htm

[ii] From the Food and Drug Administration Safety and Innovation Act. 2012. A reason selected from the following categories must be provided for each drug on the shortage list: (a) Requirements related to complying with good manufacturing practices (b) Regulatory delay (c) Shortage of an active ingredient (d) Shortage of an inactive ingredient component (e) Discontinuation of the manufacture of the drug (f) Delay in shipping of the drug (g) Demand increase for the drug.

Important Definitions

Drug Shortage or Shortage: A period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug (21 CFR 314.81). DSS determines if a shortage concern exists, and what FDA action if any is needed. DSS is designated to oversee and facilitate the resolution of all drug shortage situations.

In general, the Agency focuses on shortages of products that have a significant effect on public health:

- **Life Supporting or Life Sustaining**

  A drug product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life (21 CFR 314.81).

- **Debilitating Disease or Condition**

  A drug product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning (21 CFR 314.81). Equivalent to serious disease or condition (80 FR 38915).

- Including any such drug used in **emergency medical care** or during **surgery** or any such drug that is critical to the public health during a **public health emergency** declared by the Secretary under section 319 of the Public Health Service Act.

Notification Requirements Under Section 506C of the FD&C Act and FDA Regulations

Notify DSS no later than 5 days after a manufacturing interruption (21 CFR 314.81), ahead of any supply disruption at **drugshortages@fda.hhs.gov** (80 FR 38915)

Manufacturers are required to notify the FDA of a permanent discontinuance in the manufacture of a covered drug or an interruption of the manufacture of a covered drug that is likely to lead to a meaningful disruption in the supply of the drug in the United States

- "At least 6 months in advance of the date of the permanent discontinuance or interruption in manufacturing; or, if 6 months' advance notice is not possible no later than 5 business days after the…permanent discontinuance or interruption in manufacturing occurs"
- Not limited to medically necessary products
- Regardless of market share, or number of companies marketing, or wholesaler volumes
- The CARES Act amended section 506C of the FD&C Act to add notification requirements for APIs for covered drugs, to add information that must be provided in a notification, and to clarify the category of covered drugs.

Manufacturers Report on Potential Impact to Supply

At the time of any change in manufacturing that may lead to a reduction in supply of a product*, e.g.:

- Plans for upgrade or remediation
- Manufacturing issues
- Raw material batch failures
- Particulate issues
- Sterility issues

*Note, product refers to a specific strength, dosage form, and route of administration

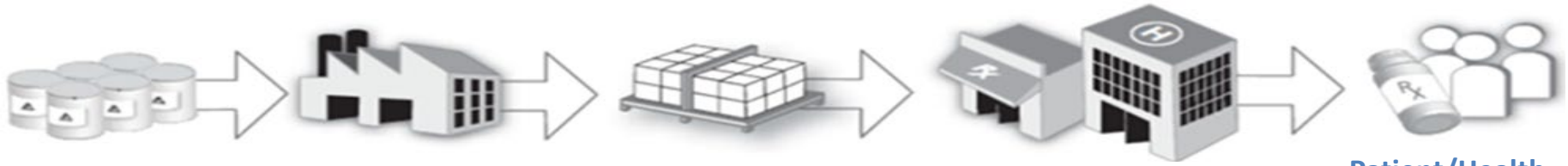
Manufacturers Report on Potential Impact to Supply

FDA is asking manufacturers to notify FDA <u>ahead</u>, not as, or after, they are unable to fill orders or unable to meet expected demand

Best Practices

"We have placed the following product(s) on hold pending an investigation. Due to the investigation being in progress and the completion date being not estimated at this time, we wanted to inform Drug Shortage of this potential for a supply interruption."

Drug Supply Chain – 1st Tier



Supplier

Manufacturer

Wholesaler

Pharmacy/Hospital

Patient/Health Care Provider

Inventory/Production Data:
Voluntarily Supplied
Supply Interruptions:
Required per FDASIA

Sales/Market Share Data:
Reported to FDA via annual report and other channels

Inventory/Supply Interruptions:
Voluntarily Supplied

Public Notifications:
FDA Drug Shortages email account

Opportunities and Challenges to Assist with Shortages

FDA will work closely with manufacturers to address problems

- We can advise, assist, and expedite inspections and reviews, but the manufacturer must fix the problem

What we CAN require:

- Notification by manufacturers (FDASIA)
  - Supply disruptions
  - Delays
  - Discontinuations
  - Notification of certain manufacturing changes

What we CANNOT require:

- A company to make a drug
- A company to make more of a drug
- How much of a drug is distributed and which purchasers will be given priority

The Agency's Approach to Prevention and Mitigation

Early notification is key!!

- Prioritize products that are medically necessary
- Risk/Benefit of the drug in question
- Maintain availability while minimizing risk to patients
- Work with firms to address problems
  - We can advise, assist, and expedite inspections and reviews, but the manufacturer must fix the problem

The Agency's Approach to Prevention and Mitigation

- Drug shortages cannot always be prevented
  - Unanticipated events occur

    Manufacturing breakdown or natural disaster(Hurricanes & Floods)
  - Sometimes alternate manufacturer may not make up production shortfall
  - If systemic issues are present, the plant may have to close to repair
  - The FDA and the manufacturer can work together to encourage smart distribution (*allocation*)

FDA Toolbox

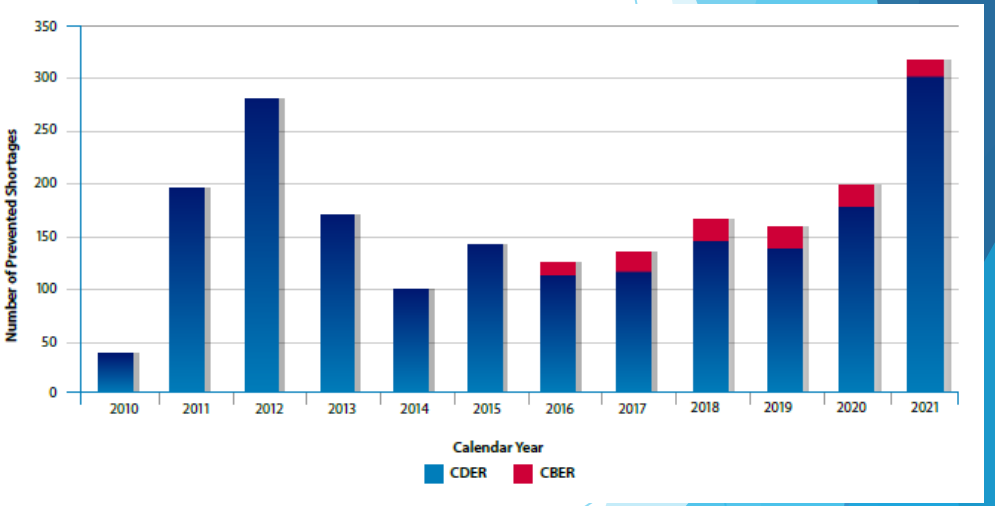
- **Proactive outreach through CDER NextGen Drug Shortage Emergency Event Portal**
- **Communicate possible shortage concerns on a market shortfall to other suppliers**
- **Prompts firms to look at demand and supply**
- **Regulatory Discretion:**
  - Manufacture of medically necessary products during remediation
  - Use of additional safety controls
    - Filters with injectable products to remove particulate concerns
    - Extra testing at plant
    - 3rd party oversight of production
    - Special instructions for safe use

FDA Toolbox

- **Expedited review of company proposals**
  - New manufacturing sites, increased expiry date, new raw material source, changes in specifications, etc.
- **In rare cases, temporary exercise of regulatory flexibility and discretion regarding importation from other countries**
  - Dextrose 5% in Water, SWFI, Technetium injection, IV Saline Solution, Hydromorphone Injection, Potassium Chloride injection, Sodium Bicarbonate Injection, Bupivacaine Injection, Cefotaxime Injection
  - Past importation of Foscarnet and Thiotepa lead to new US approvals

Impact of Early Notifications to the FDA

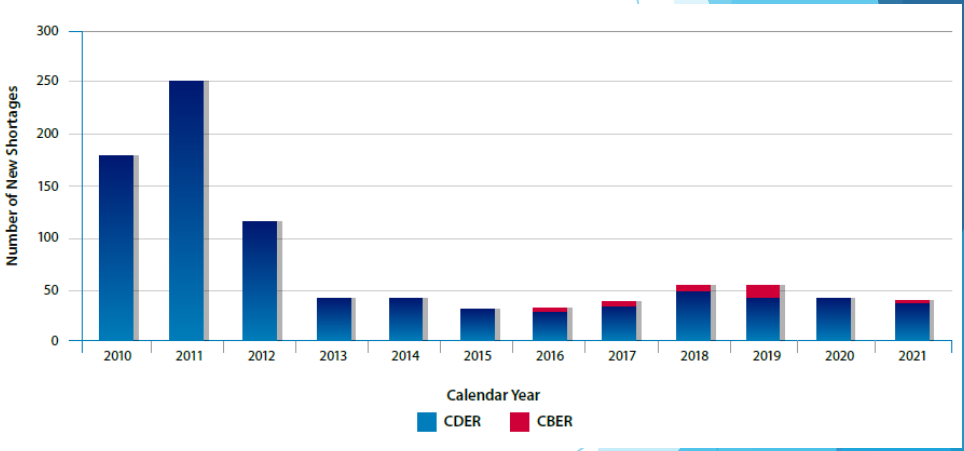
- Ongoing dialogue/work with industry – high numbers of prevented shortages continue
- Depending on the precipitating events, some drug shortages can endure for months to years. (Ex: Plant remediations and agency approvals)



Total Prevented US Drug Shortages Per Year

Current Challenges: New shortages and persistent shortages

- Shortages peaked in 2011 at 251 and continued to decline through 2016. Shortages rose again in 2017 and 2018 due in part to the 2017 hurricane impact as well as ongoing problems with manufacturers. Numbers of new shortages holding steady in 2021 with 38 new shortages.
- Depending on the precipitating events, some drug shortages can endure for months to years. (Ex: Plant remediations)



Total New US Drug Shortages Per Year

COVID-19 Pandemic: Ensuring Ongoing Supply

Current Challenges:

- Increased demand – IV narcotics, IV fluids, etc.
- Competition on manufacturing lines and in facilities due to limited capacity and vaccines/related products being made on the same lines
- Industry-wide short supply of manufacturing components (e.g. filters) and other commodities (glass, vials, stoppers, bags)

COVID-19 Pandemic: Ensuring Ongoing Supply

FDA efforts include:

- Drug Shortage Staff early outreach to manufacturers (Jan. 2020)
- Intra- and interagency coordination (HHS, CDC, NIH, FEMA)
- Guidance posted to Coronavirus Disease 2019 (COVID-19)
- Emergency Use Authorizations

Regulatory agility to assist manufacturers during a shortage:

- Expedited approvals which will help increase production
- Temporary extended use of distributed lots near expiration
  - https://www.fda.gov/drugs/drug-shortages/search-list-extended-use-dates-assist-drug-shortages
- Expiry extension for hand sanitizers.
- Solicitation for additional supply streams for critical products (Propofol & CRRT)
- Vecuronium and Rocuronium market stabilization through mitigation efforts (temporary packaging and communication-ISMP)

Current Drug Shortages

- Emergency syringes – long term shortage, worsened by COVID-19 impact (epinephrine, dextrose)
- IV fluids – increased demand
- Electrolytes, injectable anesthetics
- Injectable narcotics

Other shortage issues involve IV flush products, empty syringes, bags, needles, and tubing and we are coordinating with our Center for Devices colleagues on these issues

Role of Industry to Help Prevent and Mitigate Drug Shortages

- Understand the frailties of their supply chain
- Communicate early about potential shortages
- Provide shortage information for posting on FDA website when a shortage is unavoidable
- Provide short term and long term plans for preventing and addressing shortages while maintaining and improving quality
- Work with FDA to minimize shutdowns or slowdowns that will lead to shortages

Additional Steps

FDA announced July 12, 2018, that a new FDA Task Force was implemented to identify more enduring solutions for shortages. A public meeting was held November 27th, and additional stakeholder engagement has been conducted. The report was published October 29, 2019.

The report identifies three root causes for drug shortages:

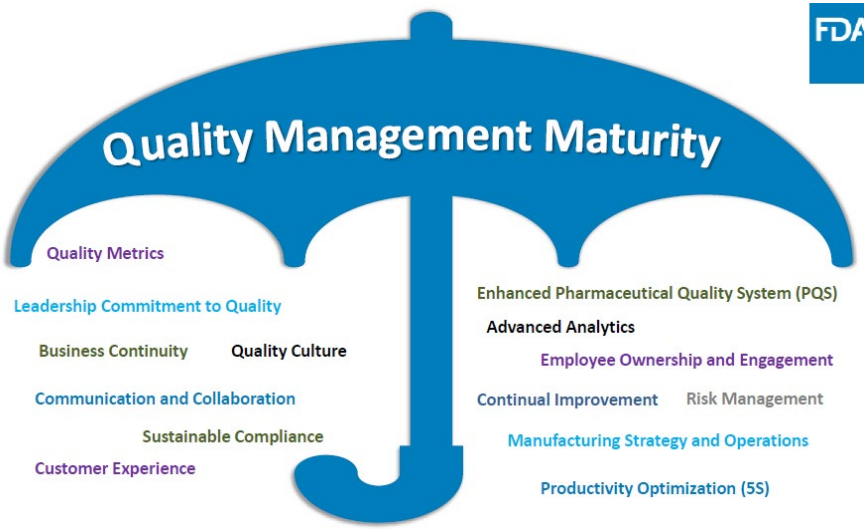
1. Lack of incentives for manufacturers to produce less profitable drugs
2. The market does not recognize and reward manufacturers for "mature quality systems" that focus on continuous improvement and early detection of supply chain issues; and
3. Logistical and regulatory challenges make it difficult for the market to recover from a disruption.

The report also recommends enduring solutions to address drug shortages. These solutions include:

1. Creating a shared understanding of the impact of drug shortages on patients and the contracting practices that may contribute to shortages;
2. Developing a rating system to incentivize drug manufacturers to invest in quality management maturity for their facilities; and
3. Promoting sustainable private sector contracts (e.g., with payers, purchasers, and group purchasing organizations) to make sure there is a reliable supply of medically important drugs.

Quality Management Maturity

- Quality Management Maturity (QMM) is the state attained when drug manufacturers have consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement
- QMM draws on Quality Metrics and ICH Q12



Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals (4/2022): https://www.fda.gov/media/157432/download

Risk Management Plans

- CARES Act added Section 506C(j) to the FD&C Act
  - Each Manufacturer of:
    - A drug that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery or any such drug that is critical to the public health during a public health emergency declared by the Secretary … that is not a radio pharmaceutical drug product or any other product as designated by the Secretary; or
    - Any active pharmaceutical ingredient or any associated medical device used for preparation or administration including in the drug
  - Shall develop, maintain, and implement, as appropriate, a redundancy risk management plan that identifies and evaluates risks to the supply of the drug, as applicable, for each establishment in which such drug or active pharmaceutical ingredient of such drug is manufactured
- FDA draft guidance *Risk Management Plans to Mitigate the Potential for Drug Shortages* has recently published

Enduring Solutions: What's Still Needed?

- Companies need to have Risk Management Plans in place – build better inventories of finished product and raw materials and components, have a backup plan for when things fail or demand increases
- Redundancy in manufacturing and suppliers –encouraging industry to have "warm" lines and components and supplies at the ready for critical drugs
- More capacity, additional manufacturers making critical drugs
- Communication is Key
    - Guidance to Industry issued April 2020 requesting notifications on increased demand in addition to supply disruptions
    - Ongoing Collaboration – Industry, Outside Stakeholders

Challenge Questions

Q1: What can FDA require a company to do to prevent and mitigate drug shortages?

A. Make a product
B. Make more of a product
C. Determine how a product is distributed and which purchasers will be given priority
D. Submit notifications

Challenge Questions

Q1: What can FDA require a company to do to prevent and mitigate drug shortages?

A. Make a product
B. Make more of a product
C. Determine how a product is distributed and which purchasers will be given priority
D. Submit notifications

Challenge Questions

Q2. How do you report a drug shortage to the FDA?

A. Submit a notification through the NextGen Portal
B. Email the drug shortage staff at drugshortages@fda.hhs.gov
C. Call the drug shortage staff at 240-402-7770
D. All of the above

Challenge Questions

Q2. How do you report a drug shortage to the FDA?

A. Submit a notification through the NextGen Portal
B. Email the drug shortage staff at drugshortages@fda.hhs.gov
C. Call the drug shortage staff at 240-402-7770
D. All of the above

Challenge Questions

Q3. What is the pharmaceutical industry's role in drug shortage prevention and mitigation?

A. Understand the frailties of their supply chain
B. Provide notifications for potential shortages
C. Provide shortage information for posting on FDA website when a shortage is unavoidable
D. All of the above

Challenge Questions

Q3. What is the pharmaceutical industry's role in drug shortage prevention and mitigation?

A. Understand the frailties of their supply chain
B. Provide notifications for potential shortages
C. Provide shortage information for posting on FDA website when a shortage is unavoidable
D. All of the above

Contacts:

Current shortage information updated daily at:
https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

To contact DSS:

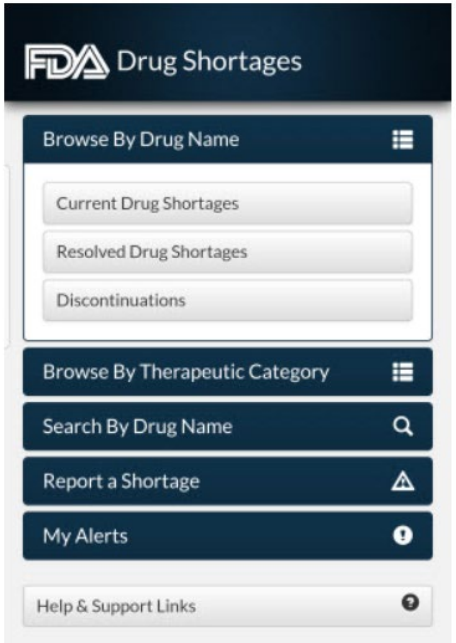
Email: drugshortages@fda.hhs.gov

FDA Drug Shortages Homepage:

https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm

Drug Shortage Mobile APP

FDA Drug Shortages Mobile App



Download on the App Store

ANDROID APP ON Google play

Receive notifications when there is
about a drug product shortage or a
therapeutic categories.

FDA Drug Shortages RSS Feed

References

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- FDA Strategic Plan for Preventing and Mitigating Drug Shortages: https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf
- Letters of Non-Compliance with Notification Requirement: https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm403902.htm