NIPTE Workshop 2024:

Injectables with Complex Formulations and Assessment

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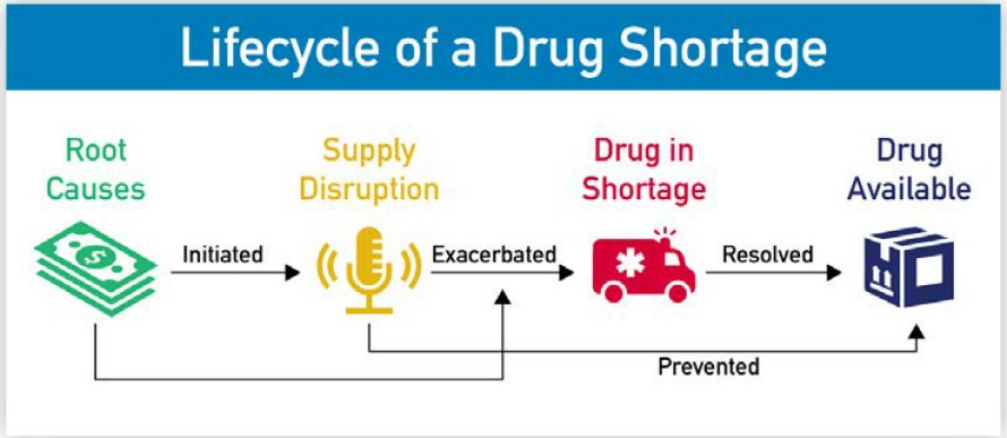
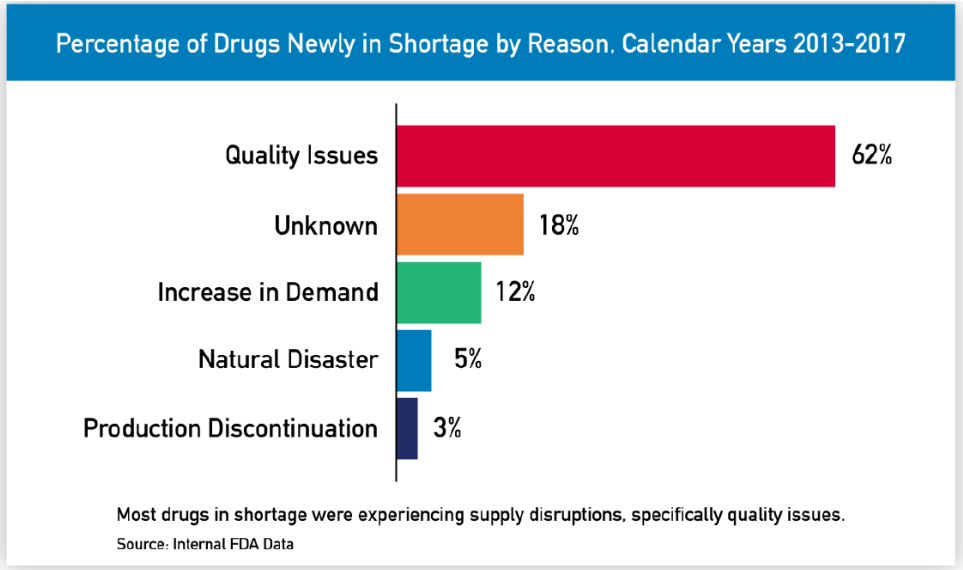
DRUG SHORTAGES





- Root causes of drug shortages
  - Low profitability
  - Quality
  - Complex supply chains
  - Natural disasters
  - Regulatory hurdles

- Between 2013 to 2017, FDA analyzed 163 CDER-regulated drugs that went into shortage. Of the 163 drugs in the sample, 63% (103) were drugs administered by injection.

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Drug Shortages: Root Causes and Potential Solutions, 2019 published; 2/21/20 updated

HOW TO ADDRESS DRUG SHORTAGES

During CY 2022, FDA's Center for Biologics Evaluation and Research (CBER) and FDA's Center for Drug Evaluation and Research (CDER) worked with manufacturers to successfully prevent 222 drug shortages by using a range of available tools, including regulatory flexibility and discretion when appropriate.

➢ Public Communications*

- In November 2022, FDA issued the immediately-in-effect guidance for industry ***Compounding Certain Beta-Lactam Products in Shortage Under Section 503A of the Federal Food, Drug, and Cosmetic Act*** to help alleviate the shortage of amoxicillin for oral suspension (available at https://www.fda.gov/media/163367/download).
- In July 2022, FDA issued the ***Changes to Disposable Manufacturing Materials: Questions and Answers*** guidance for industry about making changes to applications regarding disposable manufacturing materials (e.g., sterilizing filters, single use systems) (available at https://www.fda.gov/media/160300/download) .
- In May 2022, FDA issued a draft guidance for industry, ***Risk Management Plans to Mitigate the Potential for Drug Shortages***, to help manufacturers develop, maintain, and implement, risk management plans to proactively assist in the prevention of human drug product and biological product shortages (available at https://www.fda.gov/media/158487/download) .
- FDA posts a public, up-to-date list of drugs and biological products that the Agency has determined to be in shortage.

➢ Leveraging FDA's Tools

- Expedited its reviews of approximately 80 original ANDAs and over 70 ANDA supplements.
- Expedited its assessments of manufacturing supplements to facilitate the manufacturing capacity for COVID-19 therapeutic biologics.
- Exercised regulatory flexibility and discretion in 85 instances to increase supplies of critically needed medications.

FDA U.S. FOOD & DRUG ADMINISTRATION

*Tenth Annual Report on Drug Shortages for Calendar Year 2022

HOW TO ADDRESS DRUG SHORTAGES
ROLE OF GENERIC DRUGS

- Generic drugs increase the affordability of medications and access to care.

- Generic injectables are susceptible to supply disruptions and shortages. Manufacturers often rely on outside entities to provide active pharmaceutical ingredients and finished dosage forms to help lower the cost of production[1].

- Specialties in need of generics and subject to drug shortages[2]
  - Infectious diseases
  - Oncology
  - Emergency and critical care
  - Pain management

[1]Tenth Annual Report on Drug Shortages for Calendar Year 2022
[2]Factors involved in U.S. Generic Drug Shortages, Affordable Medicines, Published June 18th, 2020

Break-out:

How to expedite development and regulatory assessment of complex injectable products

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COMPLEX INJECTABLES – OPPORTUNITIES AND CHALLENGES

Examples of complex injectables

- Long-acting drug products
  - Microparticles
  - In situ forming depots
  - Drug substance suspensions
  - Multivesicular liposomes
- Products containing nanotechnologies
  - Iron colloids
  - Liposomes
  - nanoparticles
- Others
  - Emulsions
  - Peptide and oligo products

Opportunities

Specialties in need

- Infectious diseases
- Oncology
- Emergency and critical care
- Pain management

Challenges

- Formulation development
  - Reverse engineering (Excipients)
  - Formulation characterization and in vitro drug release testing
  - Manufacturing
  - Quality specifications
- Bioequivalence studies
  - Complex study design
  - Lengthy study
  - Study subjects

GDUFA RESEARCH PROGRAM

Goals of research

- Better understand formulation design and clinical pharmacology of complex products to describe and predict what they do.
  - Assessing new analytical methods for characterizing complex excipients
  - Investigating effect of formulation and manufacturing process parameters on product performance
  - Developing in vitro release testing methods and exploring in vitro in vivo correlations
  - Developing modeling and simulation methods to facilitate in vivo bioequivalence evaluation

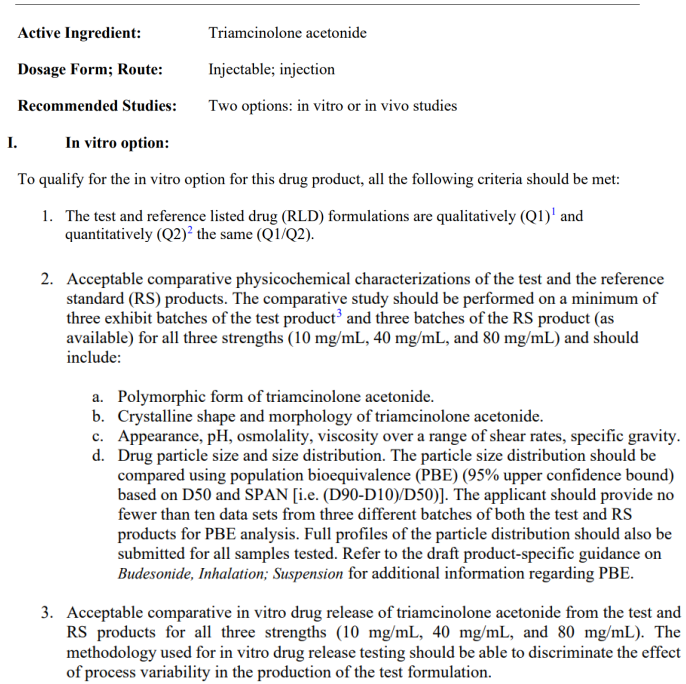
- Explore novel bioequivalence studies for complex products.
  - Bioequivalence based on In vitro studies only: a totality of evidence approach
  - Bioequivalence based on a combination of in vitro and in vivo/ex vivo studies
  - Develop alternate statistical approaches for evaluating in vitro characterization data

TOOLS TO FACILITATE PRODUCT DEVELOPMENT AND ASSESSMENT

- Product-specific guidances (PSGs) https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

An example PSG containing a non-clinical based approach:

- In vitro only approaches have been recommended for some injectable suspension products
  - Recommends qualitative and quantitative sameness (Q1/Q2), comparative physicochemical characterization and in vitro drug release testing



Active Ingredient: Triamcinolone acetonide

Dosage Form; Route: Injectable; injection

Recommended Studies: Two options: in vitro or in vivo studies

I. In vitro option:

To qualify for the in vitro option for this drug product, all the following criteria should be met:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).

2. Acceptable comparative physicochemical characterizations of the test and the reference standard (RS) products. The comparative study should be performed on a minimum of three exhibit batches of the test product[3] and three batches of the RS product (as available) for all three strengths (10 mg/mL, 40 mg/mL, and 80 mg/mL) and should include:

   a. Polymorphic form of triamcinolone acetonide.
   b. Crystalline shape and morphology of triamcinolone acetonide.
   c. Appearance, pH, osmolality, viscosity over a range of shear rates, specific gravity.
   d. Drug particle size and size distribution. The particle size distribution should be compared using population bioequivalence (PBE) (95% upper confidence bound) based on D50 and SPAN [i.e. (D90-D10)/D50)]. The applicant should provide no fewer than ten data sets from three different batches of both the test and RS products for PBE analysis. Full profiles of the particle distribution should also be submitted for all samples tested. Refer to the draft product-specific guidance on *Budesonide, Inhalation; Suspension* for additional information regarding PBE.

3. Acceptable comparative in vitro drug release of triamcinolone acetonide from the test and RS products for all three strengths (10 mg/mL, 40 mg/mL, and 80 mg/mL). The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

- GDUFA Science and Research Report: The FY 2022 report is available at https://www.fda.gov/drugs/generic-drugs/fy-2022-gdufa-science-and-research-report
- Various trainings, webinars, and workshops

  CDER Small Business and Industry Assistance (SBIA) https://www.fda.gov/drugs/development-approval-process-drugs/cder-small-business-industry-assistance-sbia

  The Center for Research on Complex Generics (CRCG) https://www.fda.gov/drugs/guidance-compliance-regulatory-information/center-research-complex-generics

Discussion:

How to expedite development and regulatory assessment of complex injectable products