U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Pediatric Compounded Medication Safety: Examining Error-Related and Spontaneous Adverse Events

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June 24, 2026

Objectives

- Describe the types of reports that may be considered an incident.
- Understand mandatory and voluntary adverse event reporting for compounded drugs
- Describe some of the reasons drugs may be compounded for pediatric patients.
- Discuss some of the factors that can contribute to medication errors
- Describe examples of medication errors and spontaneous adverse event reports received related to compounded drugs for pediatric use.

What is an incident?

Types of Reports:

- **Adverse Drug Experience**
  - 21 CFR 310.305
- **Complaints; Examples include:**
  - ✓ Product quality issues
  - ✓ Insanitary conditions
    - Section 501(a)(2)(A) of the FD&C Act
  - ✓ Failure of an outsourcing facility to comply with CGMP requirements

Adverse Event Reporting (503B)

- Mandatory reporting
  - Section 503B(b)(5) of the FD&C Act requires outsourcing facilities to report adverse events in accordance with content and format requirements established through guidance or regulation under 21 CFR 310.305 (or any successor regulations)
  - 21 CFR § 310.305 “Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.”
  - Outsourcing facilities are required to report:
    - Serious **AND** unexpected adverse events
      - Within **15 calendar days** of receipt
    - Follow-up reports
      - Within **15 calendar days** of receipt of new information or as requested by FDA

Adverse Event Reporting (503A)

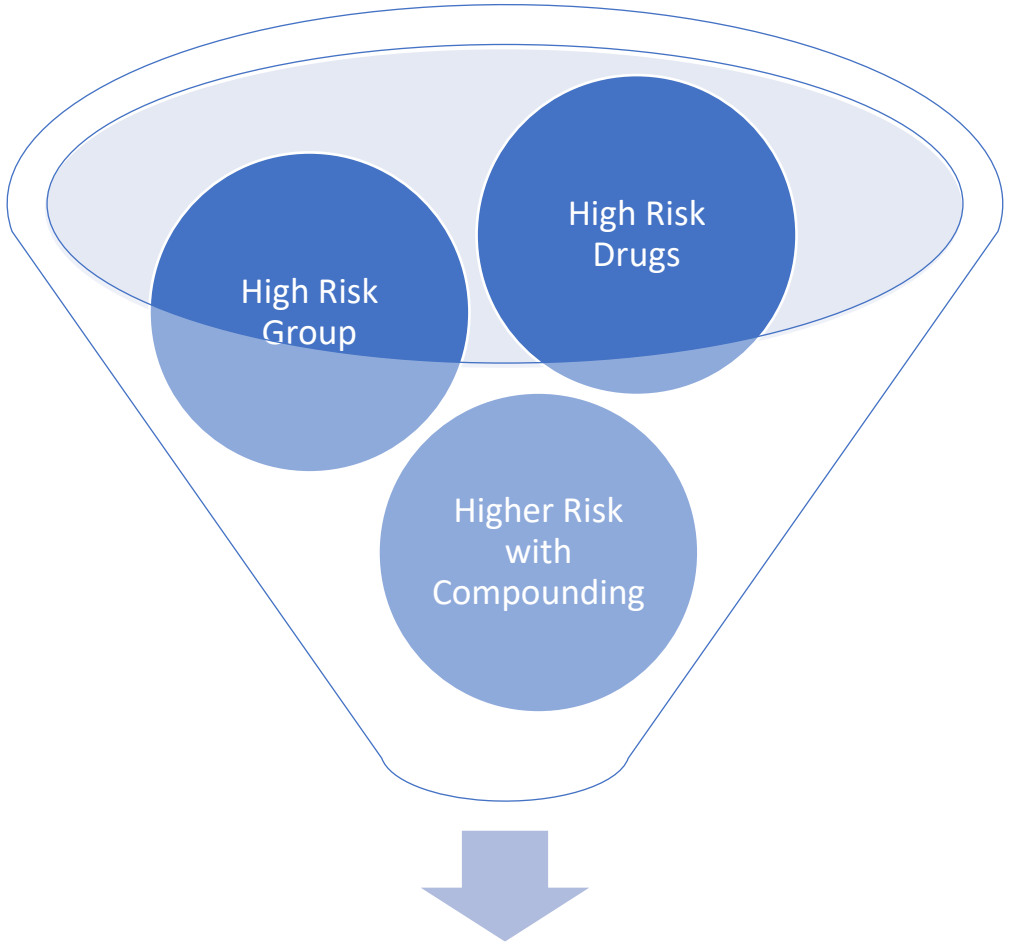
- Voluntary reporting
  - 503A facilities generally do not submit reports of adverse events to FDA
  - State-licensed pharmacies, healthcare professionals and consumers
  - MedWatch reports

Reports Received by FDA

- Small subset
- Information received by FDA is limited
- Causality and root cause often cannot be determined

Why are medications for pediatric use being compounded?

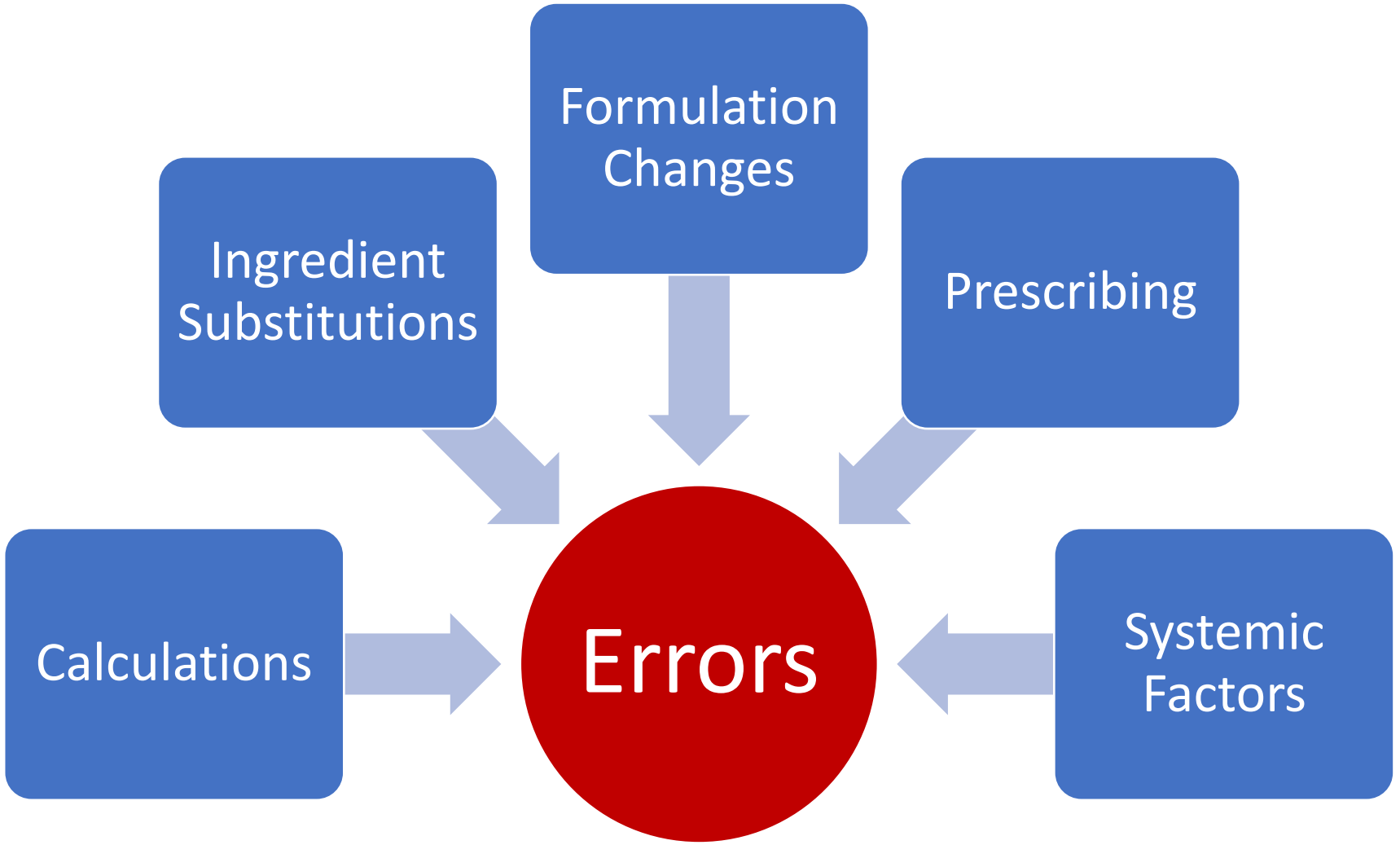
- Lack of commercially available formulations specific to pediatric patients
  - Ease of administration
  - Taste
  - Dosing
  - Allergies or intolerances



Increased Safety Risk

“The pediatric medication-use process is complex and error-prone because of the multiple steps required in calculating, verifying, preparing, and administering doses.”

“Medication Error and Its Contributing Factors Among Pediatric Patients Diagnosed with Infectious Diseases Admitted to Jimma University Medical Center, Southwest Ethiopia: Prospective Observational Study” https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7501953/


Formulation Changes
Ingredient Substitutions
Prescribing
Calculations
Errors
Systemic Factors

Case Examples

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Case Examples: Calculation Error

- Case Example 1:
  - Pediatric patient of unknown age received compounded clonidine oral suspension
  - Heart rate in the 30’s
  - Chest compressions 100-fold error in dosage.

- Case Example 2:
  - 3-year-old patient received compounded clonidine oral suspension
  - Unresponsive and bradycardic Rapid onset of depressed mental status, loss of muscle tone, and pallor within 15 minutes.
  - Last bottle of clonidine was thicker and milkier; this one was thinner, clearer, and much easier to shake.
  - Received approximately 800 times the intended dose.

Case Example: Formulation/Starting Ingredients

- Case Example 3:
  - 3 pediatric patients received compounded clonidine suspension from the same pharmacy
  - Symptoms including unconsciousness/unresponsiveness, unexplained crying fits, bradycardia, slow breathing rate, pinpoint pupils
    - 2 patients intubated
  - New clonidine prescription bottle
  - Pure clonidine powder used
    - Estimated drug concentration ~1000x the prescribed concentration

Case Example: Formulation/Starting Ingredients

- Case Example 4:
  - Pediatric patient of unknown age received compounded clonidine suspension
  - Lethargic
  - Compounder reviewed their logs and informed patient's mother that everything looked correct but sent for testing
  - Test results: clonidine content was 2842 mcg/mL instead of 25 mcg/mL
  - Pure clonidine powder was used

Case Example: Compounding Formulas

- Case Example 5:
  - 7-year-old patient received compounded guanfacine suspension
  - Became extremely lethargic within 45 minutes of taking the dose
  - Slept most of the day and refused to eat or drink.
  - Compounded product had different storage requirements and a different smell and consistency than previous fills
  - Guanfacine was prepared in a concentration of 1 mg/1mL instead of 1 mg/5mL, resulting in a significant increase in dose.

Case Example: Potential Prescribing Error

- Case Example 6:
  - Pediatric patient of unknown age received compounded clonidine 0.1 mg/mL suspension
  - Dosing was perceived as too high by pharmacist
  - Pharmacist confirmed dose with the physician
  - Patient's mother called the next day stating she was on the way to the emergency room with the child.

Case Example: Potential Medication Error

- Case Example 7:
  - 3-year-old patient received compounded clonidine suspension
  - Unconscious, hallucinated, disoriented, and inconsolable within 30 minutes of dose from a newly refilled bottle
  - Medication appearance significant different: liquid was lighter, thinner than usual
  - Local hospital discharged patient who tested positive for RSV
  - Patient worsened at home.
  - Second hospital started IVs, X-ray, ultrasound, and administered two rounds of Narcan
  - Admitted to PICU and intubated, brain MRI, lumbar puncture, blood work
  - Bradycardia with suspected clonidine overdose
  - Hospital did not test the compounded product and patient's mother could not test due to cost restraints

Case Example: Manufacturer/Compounder Switching

- Case Example 8:
  - 5-year-old patient had stable graft function for 4 years, and a second patient stable for 10 years.
    - Patients converted to compounded tacrolimus suspension for insurance reasons.
    - Both experienced kidney transplant rejection requiring hospitalization and serious immunosuppression treatment.
    - Reporter attributed this to formulation differences between brand and compounded product.

What themes do we see in these examples?

- First dose from a new bottle
- Product looked different
- Compounding Errors
  - Misplaced decimal points
  - Incorrect formulation and/or ingredients
  - Storage of ingredients
  - Lack of verification process
- Incorrect dose prescribed
- Drugs with a narrow therapeutic index

What needs can be addressed?

- Reporting
- Proactive Monitoring
- Increased safety in compounding
- Education
- Commercially available pediatric formulations

Thank You!

References and Resources

1. Food and Drug Administration. Guidance for Industry. *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (*May 2022) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors
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3. Health Canada, Tacrolimus and the Risk of Graft Rejection due to Medication Errors: Inadvertent Switching between Different Oral Formulations, July 22, 2019.
4. Institute for Safe Medication Practices (ISMP), Safeguard pediatric patients – act upon the 2025 KIDs list, ISMP Medication Safety Alert! Acute Care, 2025;30(18):1-3.
5. Otero MJ, B Rodríguez Marrodan, N Prieto Santos, E Villalobos Pinto, S Manrique Rodríguez, R Padilla Peinado, CM Fernández-Llamazares, and A Madrid Rodríguez, 2025, Recommendations for the safe use of high-risk medications in pediatrics, Anales de Pediatría (English Edition), 103(1), https://doi.org/10.1016/j.anpede.2025.503815