Setting the Table for Successful and Safe Medication Handling

To Crush or Not to Crush: Challenges & Risks of Crushing/Compounding Medications

Today’s Webinar and Speakers

Supported by unrestricted educational sponsorship from CMP Pharma

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Learning Objectives and Goals

• Discuss the genesis over concerns about the safe handling of medications
• Explore some reasons that medication handling matters, especially from the clinical and the practical perspectives
• Review the challenges and risks associated with crushing and compounding medications
• Identify new regulations and standards used as benchmarks
• Introduce a novel product which provides an alternative pathway and addresses the concerns for health care workers and patients

NEW REGULATIONS AND STANDARDS
We have a host of new regulations promulgated by federal and state agencies which have placed an increased emphasis on compounding and handling medications, from "cradle to grave". Patient, and workplace safety, a priority.

EFFECTIVE DATES
Regulations and standards have been on the books and now to be enforceable, some since August 21, 2019 and others on December 1, 2019.*

ORGANIZATIONS: Federal and State
- Handling, Storage, and Disposal: EPA and state agencies; DEA; NIOSH, CMS, individual state Boards of Pharmacy
- Standard Setting Organizations: USP ( is not a regulatory agency )
- Compounding: oversight by FDA, CDC, OSHA

*enforceability varies from state to state, check with individual state as to which regs have been adopted or delayed
Safe Medication Handling: Crushing Tablets, Opening Capsules

What are some reasons that medications are crushed or opened?

• Pathophysiology: Dysphagia diagnosis
• With altered food consistencies (puree, chopped) or use of thickened liquids -> clues to promote proper swallowing of medications
• Route of Administration: NPO-> via enteral feeding tube
• Person centered care planning-> resident/patient preference
• Compliance to med regimen; with MD order for “crush and mix with food”
• Nurse decides to do so ; to encourage speed & compliance

Medication Administration: Concerns Begin With the Prescriber’s Orders or Rx

What are concerns for a Prescriber, Pharmacist, Nurse, Administrator ?

Prescriber:
• How do I know that a patient needs their medications to be crushed?
• How do I know that it is appropriate to crush or open a medication?
• Will the patient take the medication or refuse due to poor palatability?
• Can’t I just order a liquid dosage form of the med ?

Pharmacist:
• Can the medication be crushed, opened, or administered through a tube?
• Are there any special manufacturer specifications or administration instructions to follow?
• Does the nurse know to crush and prepare each med separately , a CMS standard of practice ?
• What about HANDLING of Hazardous Drugs (new emphasis ) at the facility?
Concerns Over Medication Administration and Handling, Continued

What are concerns for a Prescriber, Pharmacist, Nurse, Administrator?

Nurse:
• What if I crush a med which should not be?
• What if I mix a crushed med (or meds) with applesauce and the patient refuses?
• Will the taste of the crushed med mix be so terrible that the patient will choke?
• OMG! I won’t have enough time to crush all the meds; how will I finish the med pass on time?!?

Administrator:
• Will we be looking at an F-Tag for medication administration error rate above 5% (F 759)?
• Storage and Handling of meds (F 755)?
• Will we be increasing our out to hospital rate due to aspirations? Non compliance with meds?
• Is the staff squandering time, crushing a med that’s available as a liquid formulation?
• Can we reduce expenses (PPE) by using a product not on the NIOSH Hazardous Drug list?

Clinical Concern: Swallowing and Why Dysphagia Matters, Common Types

Oral Dysphagia (high dysphagia)
• Tongue weakness, difficulty chewing food, or problems transporting food from the mouth

Pharyngeal Dysphagia
• Issues in the throat, often caused by a neurological problem that affects the nerves

Esophageal Dysphagia (low dysphagia)
• Issues with the esophagus

Patients who do not have dysphagia may experience the symptoms of dysphagia, due to:
• Cognitive impairment
• Incorrectly compounded medication by caregiver

Dysphagia is a Consequence of Common Pathologies We See Frequently

**Major Causes**
- Stroke
- Parkinson’s Disease
- ALS
- Multiple Sclerosis
- Cerebral Palsy

**Other Causes**
- Achalasia
- Diffuse spasm
- Esophageal ring
- Myasthenia gravis (Goldflam disease)
- Radiotherapy (neck and head area)
- Cleft lip and palate
- Scleroderma
- Esophageal cancer
- Esophageal stricture
- Xerostomia

**The Challenges & Risks of Crushing/Compounding**
Crushing/Compounding: Concerns Start in the Provider Pharmacy

- Patient Safety
- Toxicity
- Consistent Dosing
- Potency
- Efficacy
- Workplace Safety at Crushing/Compounding Facilities (USP <795>, <797>, and USP <800>)
- Limited stability (shelf life)
- Highly inconvenient for patients and caregivers
- Frequently require additional preparation by the patient or caregiver
- Exhibit a wide variation in potency, resulting in dosage inconsistencies

SOURCE: Kindy K, Sun L, Crites A. Compounding pharmacies have been linked to deaths, illnesses for years. Washington Post. February 7, 2013.

Crushed/Compounded Formulations Create Dosing Inconsistencies and FDA Concerns

- Crushed/compounded formulations can exhibit a wide variation in potency due to non-uniformity of compounded materials.
- The dosing inconsistencies of compounded suspensions have long been a persistent challenge for pharmacists and patients.
- Crushed/compounded formulations are not tested for Safety or Efficacy
  - **Centers for Disease Control and Prevention investigators, 2007:** Compounded drugs have a higher risk of contamination than commercially manufactured drugs, and compounding pharmacies have “generally lower quality-control standards than pharmaceutical manufacturers”

SOURCE: Kindy K, Sun L, Crites A. Compounding pharmacies have been linked to deaths, illnesses for years. Washington Post. February 7, 2013.
Compounded Formulation Testing by FDA

- **2001 FDA Survey:** 10 of the 29 compounded products surveyed failed quality testing, with potency ranging from 59% to 89% of the target dose.
- **2006 FDA Survey:** 12 of the 36 compounded products surveyed failed quality testing, with potency ranging from 68% up to 268% of the labeled dosage.

Crushed/Compounded Formulations: Not FDA Approved or GMP Compliant

- Extemporaneous or batch compounds are not FDA approved.
- Not manufactured in GMP facilities (a standard of practice).
- Not tested to assure potency, uniformity, and sterility/bioburden.

Crushing/Compounding & The FDA

Increasing Scrutiny Over Compounding and Crushing: FDA Concerns

- Crushed/compounded formulations have come under increasing scrutiny from the FDA
- The FDA recently released stricter guidance regarding crushing/compounding
- New guidance recommends against using crushed/compounded products considered “essentially copies of a commercially available drug product” without permission
- Guidance recommended drugs not be crushed/compounded if FDA-approved alternative exists

“Compounded drugs should only be distributed to meet the needs of patients whose medical needs cannot be met by an FDA-approved drug”

Scott Gottlieb, MD: Former FDA Commissioner
USP <797> and USP <800>

USP <797>: Safety in Compounding

- Provides the standards for Compounding Sterile Preparations
- Helps to ensure patients receive quality preparations that are free from contaminants
- Helps to ensure that preparations are consistent in intended identity, strength and potency.
- Describes a number of requirements, including:
  - Responsibilities of compounding personnel
  - Training
  - Environmental monitoring
  - Storage and testing of finished preparations
USP <800>: Safety in Handling

- Provides standards for safe handling of Hazardous Drugs to minimize the risk of exposure to healthcare personnel, patients and the environment
- Describes healthcare facility requirements for the handling of hazardous drugs, including:
  - Responsibilities of personnel handling hazardous drugs
  - Facility and engineering controls
  - Procedures for deactivating, decontaminating and cleaning
  - Spill control
  - Documentation
- Applies to all healthcare personnel who receive, prepare, administer, transport or otherwise come in contact with hazardous drugs and all the environments in which they are handled

NIOSH List Of Hazardous Drugs
NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings

NIOSH considers a drug to be hazardous if it exhibits one or more of the following characteristics in humans or animals:

- Carcinogenicity
- Teratogenicity or developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- Structure and toxicity profiles of new drugs that mimic existing hazardous drugs

Last complete update in 2016, drugs being added regularly

NIOSH Tables: How Are Drugs Classified?

- Drugs are categorized into 3 TABLES:
  - Table 1: Antineoplastics
  - Table 2: Non-Antineoplastics
  - Table 3: Non-Antineoplastics with Adverse Reproductive Effects

- Each table carries definition of risks and recommendations for handling

- **Manipulation or crushing of tablets or capsules** triggers the need to follow the guidelines for handling
  - Whenever possible, the use of liquids or suspensions rather than manipulating or crushing should be the product of choice
Effects Of Improper Handling Of Hazardous Drugs In The Workplace

Exposure to hazardous drugs in the workplace has been associated with:

- Skin-related effects
- Ocular effects
- Flu-like symptoms
- Headache
- An increase in fetal abnormalities, fetal loss, and fertility impairment
- Increased spontaneous abortions
- Increase in learning disabilities among offspring

NIOSH Guidance on Crushing/Compounding

- "Some drugs defined as hazardous may not pose a significant risk of direct occupational exposure because of their dosage formulation (for example, coated tablets or capsules)"
- "However, they may pose a risk if the formulations are altered, such as by crushing tablets or making solutions from them outside a ventilated cabinet"

"Crushing tablets or opening capsules should be avoided and liquid formulations should be used whenever possible"
Enforcement

• Items on the NIOSH list are subject to legally enforceable regulatory guidelines *
• Not following these protocols is a reportable offense

* regulatory agencies include: individual states boards of pharmacy (USP 795,797,800) ; CMS surveyors and OSHA (800 )
• USP makes recommendations; considered to be standards until adopted by regulatory agencies; revised 795, 797 standards are on hold as of this webinar date .

Medications With Crushing/Compounding Safety Protocols (A Partial List from NIOSH Tables)

• Spironolactone
• Valcyte
• Retrovir
• Zytiga
• Gilotrif
• Hexalen
• Inlyta
• Targettin
• Bosulif
• Xeloda
• Leukeran
• Xalkori
• Cytoxan
• Tafinlar
• Sprycel
• Xtandi
• Tarceva
• Vepesid; VP 16
• Afinitor
• Hydrea
• Imbruvica
• Gleevec
• Tykerb
• Revlimid
• CeeNU
• Alkeran
• Purinethol
• Mexate-AQ
• Lysodren
• Tasigna
• Votrient
• Pomalyst
• Iclusig
• Matulane
• Stivarga
• Jakafi
• Nexavar
• Sutent
• Temodar
• Thalomid
• Thioguanine
• Hycamtin
• Mekinist
• Vesanoid
• Zelboraf
• Erivedge
• Zolinza
• Imuran
• Sandimmune; Neoral; Gengraf
• Cellcept
• Prograf
• Casodex
• Propecia; Proscar
• Accutane, Claravis
NIOSH List Example: Spironolactone Tablets

• Spironolactone
  • An aldosterone antagonist used as a potassium-sparing diuretic
  • For patients who suffer from: chronic heart failure, edema caused by heart or liver failure, and/or hypertension

• Spironolactone tablets
  • Have an FDA black box warning – tumorigen in chronic toxicity studies in rats
  • Spironolactone appears on the NIOSH list

SOURCES: NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016

NIOSH and Handling Recommendations: PPE/Engineering

Table 5. Personal protective equipment and engineering controls for working with hazardous drugs in healthcare settings*

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Activity</th>
<th>Double chemo-therapy gloves</th>
<th>Protective gown</th>
<th>Eye/face protection</th>
<th>Respiratory protection</th>
<th>Ventilated engineering control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types of</td>
<td>Receiving, unpacking, and</td>
<td>no (single glove can be</td>
<td>yes, when spills</td>
<td>yes, when spills</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>hazardous drugs</td>
<td>placing in storage</td>
<td>used, unless spills</td>
<td>and leaks occur</td>
<td>and leaks occur</td>
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<tr>
<td>Intact tablet or</td>
<td>Administration</td>
<td>no (single glove can be</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>N/A</td>
</tr>
<tr>
<td>capsule</td>
<td>from unit-dose package</td>
<td>used, unless spills</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Tablets or capsules</td>
<td>Cutting, crushing, or</td>
<td>yes</td>
<td>no</td>
<td>yes, if not done</td>
<td>yes</td>
<td></td>
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<td></td>
<td>manipulating tablets or capsules,</td>
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<td></td>
<td>handling uncoated tablets</td>
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<td>device</td>
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<tr>
<td>Administration</td>
<td>no (single glove can be used)</td>
<td>no</td>
<td>yes, if vomit</td>
<td>no</td>
<td>N/A</td>
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<td>spit up</td>
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</tbody>
</table>

*https://www.cdc.gov/niosh/topics/hazdrug/pubs.html
NIOSH and Handling Recommendations: PPE/Engineering

NIOSH List Example: Spironolactone

- Crushing or compounding spironolactone tablets require special safety protocols:
  - Double chemotherapy gloves
  - Protective gowns
  - Ventilated engineering control when compounding
  - Eye/face and respiratory protection (if not crushed/compounded in a control device)

- A facility’s Assessment of Risk (AoR) for each drug on the NIOSH list determines the actions for compliance

- Failure to follow these protocols could result in a failed inspection or worse

SOURCES: NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016
FDA-Approved Liquid Product Case Study: CaroSpir

- CaroSpir is a liquid oral suspension of spironolactone developed and manufactured by CMP Pharma
- The first and only FDA-approved oral suspension of spironolactone
- Provides a stable, ready to use, and consistent liquid treatment option of spironolactone for adult patients with dysphagia
CaroSpir: FDA Approved Indications

Indications And Usage
CAROSPIR is an antagonist of aldosterone indicated for:

• The treatment of NYHA Class III-IV heart failure and reduced ejection fraction to increase survival, manage edema, and to reduce the need for hospitalization for heart failure
• Use as an add-on therapy for the treatment of hypertension, to lower blood pressure in adult patients. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions
• The management of edema in adult cirrhotic patients when edema is not responsive to fluid and sodium restrictions

CaroSpir: Contraindications

Contraindications
CAROSPIR is contraindicated for patients with the following conditions:
• Hyperkalemia
• Addison’s disease
• Concomitant use of eplerenone

Warnings And Precautions/Adverse Reactions
CAROSPIR may cause the following conditions.
• Hyperkalemia
• Hypotension and Worsening Renal Function
• Electrolyte and Metabolic Abnormalities
• Gynecomastia
• Impaired neurological function/ coma in patients with hepatic impairment, cirrhosis and ascites

The most common adverse reaction (incidence > 5%) with CAROSPIR treatment is the increased occurrence of gynecomastia in men.
The Advantage: An Oral Suspension of Spironolactone

- Prior to the approval of CaroSpir, spironolactone had only been available in a tablet dosage form
- Dysphagic patients who suffer from CHF, edema caused from CHF & Cirrhosis, and hypertension are often prescribed spironolactone
- Previously, these patients had to be prescribed a crushed/compounded oral liquid form of spironolactone

FDA Approved Product Is Preferable To Crushed/Compounded Spironolactone Tablets

For Workplace Safety

- FDA-approved liquid
- CaroSpir does not have a black box warning
- The USP <800> guidelines for handling a NIOSH listed drug such as spironolactone tablets being crushed or compounded do not apply to CaroSpir
- The USP <800> guidelines for administering any liquid form of a NIOSH drug would apply, based on the facility’s Assessment of Risk (AoR) of the drug
FDA Approved Product Is Preferable To Crushed/Compounded Spironolactone Tablets

• For HCPs and Pharmacists
  • Eliminates the risk to the institution and patient by removing the uncertainties around uniformity, potency, efficacy and safety because it provides a stable and consistent dose every time
  • Allows institution and HCPs to be compliant with FDA regulations and USP<800> guidelines for manipulating tablets
  • Eliminates the need for additional preparation by the pharmacist or patient
  • Has a shelf life of 24 months
  • Manufactured in a high-quality GMP facility and is tested for potency and accuracy
  • Stays compliant

Important Pharmacokinetic Differences with CaroSpir
Important Pharmacokinetic Differences with CaroSpir

- CaroSpir is not therapeutically equivalent to Aldactone Tablets
- CaroSpir results in 15 to 37% higher serum concentration compared to Aldactone tablets

*When you crush/compound spironolactone does it behave like the tablet or like our liquid?*

Thank You
American Society of Consultant Pharmacists (ASCP)
USP/EPA Toolkit

• Toolkit available by December 2019
  • USP <800> Pharmacy Policy & Procedures
    • Facilities
    • Pharmacies
  • Hazardous Drug Risk
    • Hazardous Drug Risk Acknowledgement
    • Hazardous Drug Risk Assessment
    • Instructions for Use
  • EPA Policy & Procedure
    • Facilities
    • Pharmacies