Ongoing Role of FDA in Medication Error Prevention

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Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
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Learning Objectives

• Describe the Division of Medication Error Prevention and Analysis’ role in pre-marketing and post-marketing activities to prevent and address medication errors.

• Provide a brief overview of strategies aimed to increase the safe use of drug products by minimizing use error that is related to the design, naming, labeling, and/or packaging of drug products.

• Provide examples of regulatory action taken to address recent medication errors.

• Describe how you can help identify, prevent, and mitigate medication errors.
Presentation Outline

1. Introduction to DMEPA
2. Safety Considerations for Product Design
3. Safety Considerations for Labels and Labeling
4. Best Practices for Developing Proprietary Names for Drugs
5. Post Marketing Surveillance Activities
6. Your Responsibility in Medication Error Prevention
CDER Organizational Structure
Center for Drug Evaluation and Research (CDER)

Office of Surveillance and Epidemiology (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)
  - Division of Pharmacovigilance I, II (DPV I, DPV II)
  - Division of Epidemiology I, II (DEPI I, DEPI II)

Office of Medication Error Prevention and Risk Management (OMEPRM)
  - Division of Medication Error Prevention and Analysis (DMEPA)
  - Division of Risk Management (DRISK)
DMEPA Mission

To increase the *safe use* of drug products by minimizing use error that is related to the *naming, labeling, packaging, or design* of drug products
DMEPA Roles and Responsibilities

- Proprietary Names
- Medication Error Policy and Research
- Labels/Labeling/Packaging/Product Design
- Post-market Surveillance
- Human Factors

DMEPA
What is a “Medication Error”?

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.

Figure 1: Relationship between medication errors and ADEs

1Adapted from Figure 1 in Qual Saf Health Care 2004;13:306–314. doi: 10.1136/qshc.2004.010611

Culture of Safety

“People make errors, which lead to accidents. Accidents lead to deaths. The standard solution is to blame the people involved. If we find out who made the errors and punish them, we solve the problem, right?

Wrong. The problem is seldom the fault of an individual; it is the fault of the system. Change the people without changing the system and the problems will continue.”

Don Norman

The Design of Everyday Things
Proactive vs. Reactive Response to Medication Errors

• Reactive: Historically, some design issues with drug products were not identified and remedied until post-marketing
  – In some cases, the issues were only resolved after medication errors had reached and harmed patients

• Proactive: Today, design issues are identified proactively and addressed prior to marketing to prevent some medication errors from ever occurring
Confirmation Bias

Aoccdrnig to rscheearch at Cmabrigde Uinervtisy, it deosn't mttaer in waht oredr the ltteers in a wrod are, the olny iprmoetnt tihng is taht the frist and lsat ltteer be at the rght pclae. The rset can be a toatl mses and you can sitll raed it wouthit a porbelm.

Tihs is bcuseae the huamn mnid deos not raed ervey lteter by istlef, but the wrod as a wlohe.

Amzanig huh?
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DMEPA Involvement in Application Review

• DMEPA involved early on in the review process (as early as investigational new drug [IND] application phase)

• Provides input to Sponsors at this stage on product design and other aspects aimed at reducing medication errors
Early Stage Considerations: End Users and Environment of Use

- Considering end users during drug development can allow identification of risks that can lead to error
- Consider all users and all environments of use throughout the entire medication use process
Drug Product User Interface

• Most effective strategies focus on improvements to design of drug product user interface
  – Drug product user interface: all points of interaction between the product and the user (i.e., packaging, displays, controls, product labels, instructions for use, etc.)
• Evaluate how and why problems have occurred with similar products
  – Identify error prone features and eliminate them from design
  – Prevent same errors from occurring
• Consider lessons learned to minimize risks associated with the designs
Simulated Use Testing

• We recommend human factors studies be conducted to characterize risks as well as develop mitigation strategies.
  – Systematic collection of data from representative participants in realistic situations
  – Help determine whether users can safely and correctly perform critical tasks
  – Seeks to assess actual use
  – Results can be used to update the FMEA
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How Drugs are Stored
Look-alike Labels and Labeling
Principal Display Panel (PDP)

Established name or proper name

Product strength

Route of administration

Proprietary name

Warnings or cautionary statements

Mydrug (drugozide) Injection

50 mg/10 mL

(5 mg/mL)

For continuous infusion after dilution


10 mL single dose vial

Rx only

NDC 12345-6789-30
Information Crowding/Visual Clutter on Labels:

• When labels are crowded, important information may be difficult to read or easily overlooked
• Therefore, we ensure that
  – lines or blocks of text are separated by sufficient white space
  – Text is not superimposed by images or logos
  – Less important information is located on back panels, side panels, or in prescribing information
Route of Administration

• Avoid use of abbreviations
• Use positive statements instead of negative statements
  – E.g., May overlook the word “not” in
  – Affirmative statements help to ensure readers understand the intended route of administration, even if they do not read every word
Strength and Net Quantity Statements Placement & Prominence

Note the placement of strength and net quantity

Note the prominence of strength

Before

After
Product Strength – Differentiation

• **Strength Differentiation:**
  – We ensure that the product strength stands out on the container label and carton labeling

• **Techniques include:**
  – Boxing
  – Prominent typeface or type weight
  – Color differentiation
Product Strength – Unit of Measure

- Product strength designations should use a consistent unit of measure across all elements of labels and labeling.

- Metric Measurements
  - Dose or strength expression should appear in metric units of measure (mL, mg, and mcg).

Dosing for Perioperative Hypotension

Intravenous bolus administration: 50 mcg to 250 mcg

Strength expression on container label:

16.2 mg (1/4 gr)
Product Strength – Special Considerations

• **Small Volume Parenteral Products**
  – Strength per total volume followed by strength per milliliter (mL)
Dangerous Abbreviations, Acronyms, and Symbols

- Certain abbreviations, acronyms, and symbols are dangerous and should not be used*

- Non-standardized abbreviations, symbols, and dose designations can also lead to mistakes

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Intended Meaning</th>
<th>Misinterpretation</th>
<th>Correction</th>
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<tr>
<td>µg</td>
<td>Microgram</td>
<td>Mistaken as “mg”</td>
<td>Use “mcg”</td>
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Warnings for Critical Information

• Use affirmative statements
  – For intravenous infusion
  – Fatal if given by any other route
  – Must dilute before use

• Consider whether the statement is helpful to ensure safe use

**Doctor’s Prescription:**
Take 6 mg orally once daily.

**Patient:** Took 1 mg orally once daily.
*Patient stated she was following directions on the bottle*
Storage

• If the product has special storage requirements, we ensure that the storage information is prominent
  – Must be refrigerated
  – Protect from freezing

• If applicable, we provide instructions for pharmacists to dispense the drug product in special container
  – Store in the original package to protect from moisture.
  – Dispense in original, unopened container
Barcode

• Ensure there is enough blank space surrounding barcode to allow barcode scanning per 21 CFR 201.25(c)(1)(i)

• Ensure that the barcode is not placed in an area where it can be easily damaged because it appears at the point of label separation (e.g. perforation)

Figure 1. Barcode tears apart at perforation.
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Handwriting Legibility

Zyrtec
Lipitor
Avandia
Coumadin
Reminyl
Amaryl
Confirmation Bias

Advair
Advicor
Hydralazine
Hydroxyzine

Lamictal
Lamisil
Look Alike & Sound Alike Names

Presence of Modifier

Enablex or Effexor XR
Role of Electronic Prescribing

Proprietary Name (PN) Review

**OPDP**
Conducts **misbranding** assessment of the PN

**OND**
Provides **misbranding** and **safety** concerns with the proposed PN based on clinical, chemistry, and/or pharmacology data that may impact acceptability of the PN

**DMEPA**
Conducts **safety** assessment of the PN for risk of drug name confusion that may lead to medication errors
PN – Misbranding Assessment

Misbranding Assessment is conducted by the Office of Prescription Drug Promotion (OPDP)

DMEPA will object to a proposed name if it may misbrand the product for the following reasons:

• The proprietary name suggests that the drug is safer or more effective than has been demonstrated by scientific evidence.

• The proprietary name is “fanciful” and suggests that it has some unique effectiveness or composition when it does not. (21 CFR 201.10(c)(3)).
Proprietary Name – Safety Review

Focus: Prevent medication errors due to drug name confusion

21 CFR 201.10 (c.) The labeling of a drug may be misleading by reason (among other reasons) of: (5) Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.

Draft Guidance: Best Practices in Developing Proprietary Names for Drugs
## Preliminary Screening Assessment for Proposed Proprietary Names

<table>
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<tr>
<th>Step</th>
<th>Description</th>
<th>Compliance</th>
</tr>
</thead>
</table>
| 1    | There is **NO obvious similarities in spelling and pronunciation** to proprietary names, established names, or ingredients of other products.  
• Durezol vs. Durasal | ✔️ |
| 2    | There is **NO medical abbreviation incorporated** in the name.  
• Macrobid (BID = medical abbreviation for “twice daily”) | ✔️ |
| 3    | The name **does NOT contain any reference to an inert or inactive ingredient.** 21 CFR 201.10(c)(4) | ✔️ |
| 4    | The name **does NOT include or suggest the name of one or more, but not all, of its active ingredients.** 21 CFR 201.6(b) | ✔️ |
| 5    | The name **does NOT contain** United States Adopted Name (USAN) stem.  
• **USAN stem:** vir-, -vir-, -vir  
  **Prop. Names:** Combivir, Epivir, Norvir | ✔️ |
| 6    | The name is **NOT the same proprietary name as another product with completely different active ingredient(s).**  
• Allegra (fexofenadine hcl) vs. Allegra (diphenhydramine plus allantoin) | ✔️ |
| 7    | This name is **NOT being reused** after discontinuation of another product. | ✔️ |
When reviewing a proposed proprietary name, we consider:

– **spelling** of the name

– **pronunciation** of the name when spoken

– **appearance** of the name when scripted throughout the medication use system (e.g., prescribing, dispensing, administering)
Safety Assessment for Look-alike/Sound-alike Names

• Similarity in printing, writing, and speech
• Name Simulation Studies
  – Written and verbal prescriptions
• Similarity of names by using FDA’s Phonetic and Orthographic Computer Analysis (POCA) program and assessment of POCA scores

Phonetic and Orthographic Computer Analysis (POCA) Program.
http://www.fda.gov/Drugs/ResourcesForYou/Industry/ucm400127.htm
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DMEPA Post-Marketing Surveillance Activities

• Screen medication error reports submitted to FDA for potential safety signals
• Evaluate safety signals with others in FDA to determine if regulatory action is required
• Collaborate with other federal partners, researchers, and patient safety organizations such as ISMP
• Develop or review regulations, guidance, policies, and standards related to post-marketing surveillance
Post-Marketing Sources of Information

- Patients, consumers, and healthcare professionals
- FDA MedWatch (Direct Reports)
- Manufacturer
  - FDA

DMEPA Safety Evaluator
Possible Outcomes of Post-Marketing Surveillance

• Labels and labeling changes
• Product design changes
• Proprietary name changes
• Publication of Drug Safety Communications
• Publication of Consumer Updates
• Literature development
Post-Marketing Examples for Medication Error Prevention

- Insulin Pen Reuse
- Name Confusion with Brilinta and Brintellix
- Dose Confusion with Avycaz
- Dosing Errors with Noxafil
- Dosing Confusion with Insulin Human Injection U-500
Insulin Pen Reuse

• All marketed pens for diabetes management are intended for single patient use
  – Replacing the disposable needle does not prevent the transmission of blood borne pathogens

• Reports to the FDA and published data indicated that insulin pens were being used on multiple patients in the healthcare setting
  – Patients have been potentially exposed to blood born pathogens through sharing of insulin pens
Insulin Pen Reuse

• Factors Contributing to Errors
  – Misunderstanding of the differences in use between multidose vials and insulin pen cartridges
  – Misperception of infection risk with pens versus syringes
  – Lack of specific training on how to use pen devices
  – Insufficient education regarding the risk of pen sharing

• FDA required labeling changes for all injectable diabetes medications
  – “For Single Patient Use Only” added to all labels and labeling for these products
Insulin Pen Reuse

FDA Drug Safety Communication: FDA requires label warnings to prohibit sharing of multi-dose diabetes pen devices among patients

[2-25-2015]

Safety Announcement

In an effort to reduce the serious risk of infection spread through sharing of multi-dose diabetes pen devices intended for single patient use only, the U.S. Food and Drug Administration (FDA) is requiring additional label warnings prohibiting sharing of these injectable medicines. Insulin pens and pens for other injectable diabetes medicines should never be shared among patients, even if the needle is changed. Sharing pens can result in the spread of serious infections from one patient to another. To promote safe use, we are requiring that pens and packaging containing multiple doses of insulin and other injectable diabetes medicines display a warning label stating “For single patient use only.”
Insulin Pen Reuse

FDA now requires label warnings to prohibit sharing of multidose diabetes pen devices among patients.
Brilinta vs. Brintellix Name Confusion

• July 2015: FDA issued a Drug Safety Communication
  – As of June 2015, the FDA received 50 medication error reports describing brand name confusion with Brintellix (vortioxetine) and Brilinta (ticagrelor). In most cases, Brintellix was mistaken as Brilinta.
  – Some of the contributing factors to the name confusion included the following:
    • Both brand names begin with the same three letters.
    • Both brand names are presented when selecting medications in a computerized physician order entry (CPOE) system.
    • The pharmacist was not familiar with the new medication Brintellix and dispensed Brilinta.
Brilinta vs. Brintellix Name Confusion

FDA Drug Safety Communication: FDA approves brand name change for antidepressant drug Brintellix (vortioxetine) to avoid confusion with antiplatelet drug Brilinta (ticagrelor)

- Since the July 2015 DSC, the FDA received 5 additional cases describing brand name confusion involving Brilinta and Brintellix
- Recommended a proprietary name change for Brintellix
- FDA Action Taken: May 2016 name change to Trintellix

This is an update to the FDA Drug Safety Communication: FDA warns about prescribing and dispensing errors resulting from brand name confusion with antidepressant Brintellix (vortioxetine) and antiplatelet Brilinta (ticagrelor) issued on July 30, 2015.

Safety Announcement

[ 05-02-2016 ] The U.S. Food and Administration (FDA) has approved a brand name change for the antidepressant Brintellix (vortioxetine) to decrease the risk of prescribing and dispensing errors resulting from name confusion with the blood-thinning medicine Brilinta (ticagrelor). The new brand name of the drug will be Trintellix, and it is expected to be available starting in June 2016. No other changes will be made to the label or packaging, and the medicine is exactly the same.

Because of the lag time associated with manufacturing bottles with the new brand name, health care professionals and patients may continue to see bottles labeled with the brand name Brintellix during the transition period.
Dose Confusion with Avycaz

FDA Drug Safety Communication: FDA cautions about dose confusion and medication error with antibacterial drug Avycaz (ceftazidime and avibactam)

[09-22-2015]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is warning health care professionals about the risk for dosing errors with the intravenous antibacterial drug Avycaz (ceftazidime and avibactam) due to confusion about the drug strength displayed on the vial and carton labels. Avycaz was initially approved with the vial and carton labels displaying the individual strengths of the two active ingredients (i.e., 2 gram/0.5 gram); however, the product is dosed based on the sum of the active ingredients (i.e., 2.5 gram). To prevent medication errors, we have revised the labels to indicate that each vial contains Avycaz 2.5 gram, equivalent to ceftazidime 2 gram and avibactam 0.5 gram (see Photos).
Dose Confusion with Avycaz

- September 2015: FDA issued a Drug Safety Communication
  - Since Avycaz’s approval in February 2015, FDA received reports of three medication error cases related to how the drug strength was displayed on the Avycaz vial and carton labels (2 gram/0.5 gram per vial).
  - Our evaluation determined that previously approved beta-lactam/beta-lactamase antibacterial drug products express the strength as the sum of the two active ingredients in the labels (e.g., 1.5 gram or 3 gram of ampicillin/sulbactam).
  - Confusion arose when the vial and carton labels of Avycaz expressed the strength to reflect the individual active ingredients.
Dose Confusion with Avycaz

Before

After
Dosing Errors with Noxafil

FDA Drug Safety Communication: FDA cautions about dosing errors when switching between different oral formulations of antifungal Noxafil (posaconazole); label changes approved

[ 1-04-2016 ]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is cautioning that differences in dosing regimens between the two oral formulations of the antifungal Noxafil (posaconazole) have resulted in dosing errors. To help prevent additional medication errors, the drug labels were revised to indicate that the two oral formulations cannot be directly substituted for each other but require a change in dose. Direct mg for mg substitution of the two formulations can result in drug levels that are lower or higher than needed to effectively treat certain fungal infections.

Prescribers should specify the dosage form, strength, and frequency on all prescriptions they write for Noxafil. Pharmacists should request clarification from prescribers when the dosage form, strength, or frequency is not specified. Patients should talk to their health care professional before they switch from one oral formulation to the other.
Dosing Errors with Noxafil

• January 2016: FDA issued a Drug Safety Communication
  – Since the approval of the delayed-release tablet formulation of Noxafil in November 2013, FDA received eleven reports of wrong oral formulation being prescribed and/or dispensed to patients.
  – The delayed-release tablet has a higher bioavailability than the oral suspension.
    • Dose and frequency of administration for Noxafil depend on the particular formulation used and the indication for use.
  – The cases were a result of health care professionals not knowing that the two oral formulations cannot be substituted for each other without adjusting the dose due to differences in how the medicine is absorbed and handled by the body.
Dosing Errors with Noxafil

**Attention:** Noxafil Oral Suspension and Delayed Release Tablets are NOT interchangeable due to differences in the dosing of each formulation.
Insulin Human Injection U-500

• Approved in 1994 for patients requiring more than 200 units of insulin per day
• Multiple error reports noted during routine surveillance of post-marketing error reports
• Majority of the medication errors were due to dosing confusion
  – Dose prescribed in units corresponding to a U-100 syringe or in volume corresponding to tuberculin syringe markings
  – Dose administered without recognizing that the syringe markings do not directly correspond to U-500 dose
Insulin Human Injection U-500

• Factors contributing to errors
  – Inaccurate dosing associated with the lack of a dedicated dosing device and poor communication of the desired dose
  – Wrong product selection due to proprietary name confusion and poor communication of the dosing information
• Review concluded that administering U-500 insulin using a U-100 syringe is an unsafe practice
• The company was encouraged to consider methods to improve the safe use of this product, including the introduction of a prefilled pen device
Insulin Human Injection U-500

Two ways to administer U-500

With the KwikPen
U-500 KwikPen®

U-500 vial
With a vial and syringe

www.humulin.com
FDA approves a dedicated syringe to be used with Humulin R U-500 insulin

[7/8/16] Today, the U.S. Food and Drug Administration approved a dedicated syringe for the administration of Humulin R U-500 insulin, which is now the only device approved for use with U-500 insulin vial.

Humulin R U-500 insulin vial has been available with no dedicated device for delivery since 1994. To administer the insulin, healthcare practitioners and patients had to make dose conversions to deliver the appropriate dose using a U-100 insulin syringe or a tuberculin (volumetric) syringe. Since conversions are no longer needed with this new device, the Humulin R U-500 insulin vial label will be updated to remove the dose conversion information for U-100 and tuberculin syringes.
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FDA’s Responsibility

- Minimizing error potential PRIOR to approval
- Correcting problems quickly AFTER detection through post-marketing surveillance
- Risk Communication and Management
- Research
Pharmaceutical Industry Responsibility

• Clear & Concise Labeling
• Avoid Misleading or Confusing Proprietary Names
• Propose Packaging with Minimal Error Potential
• Swift action when problems occurs
Practitioner Responsibility for Medication Error Prevention

- Review product labeling information prior to using an unfamiliar medication
- Communicate clearly with others involved in patient care
- Involve patients in their care
- Report side effects and medication errors to the FDA MedWatch program
Patients’ Responsibilities

• Inquire and know the risks of treatment
• Expect and ask for medication counseling
• Report medication errors to FDA MedWatch program
Summary

• We encourage healthcare providers to report all medication errors to MedWatch.
• If we are aware of potential problems, we can work to provide effective interventions that may help minimize further errors.
• Post marketing experience also helps us anticipate potential errors.
• We aim to identify and address the risk prior to marketing to help prevent medication errors.
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<th>Resource</th>
<th>Website</th>
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<td><strong>Guidances for Industry</strong></td>
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<td><strong>Regulations</strong></td>
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