Safety Considerations for Product Design to Minimize Medication Errors

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2016
Drug Safety

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Contains Nonbinding Recommendations

Safety Considerations for Product Design to Minimize Medication Errors

Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The recommendations in this guidance apply broadly to the development of drug and biologic products. Accordingly, this guidance is intended for sponsors of investigational new drug applications (INDs); applicants of new drug applications (NDAs), biologics licensing applications (BLAs), abbreviated new drug applications (ANDAs);[2] and manufacturers of prescription drugs marketed without an approved application or over-the-counter (OTC) monograph drugs. This guidance provides a set of principles for using a systems approach to minimize medication errors relating to product design and container closure design and thus enhance patient safety.

The recommendations in this guidance document are intended to provide best practices on how to improve the drug product and container closure design for all prescription and nonprescription drugs and biologic products regulated by the Center for Drug Evaluation and Research (CDER), which are referred to collectively in this guidance as *products*.[3] The guidance also provides examples of product designs that have resulted in postmarketing medication errors. Many

[1] This guidance has been prepared by the Division of Medication Error Prevention and Analysis in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] This guidance applies to ANDAs to the extent that the applicable product, including its underlying design and other development determinations, is not required to be the same as its reference listed drug (RLD). *See* Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) and its implementing regulations.

[3] For drug-device combinations, there are additional considerations that should be evaluated before approval as defined in 21 CFR 4.2. For additional information on product design, risk management and human factors, and related processes relating to medical devices and drug-device combination products, see AAMI/ANSI/ISO 14971:2007/(R)2010, *Medical devices – Application of risk management to medical devices*; FDA guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* available on FDA Medical Devices guidance Web page at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

medication errors can be avoided at the design stage by drawing on lessons learned from past medication errors and by conducting proactive risk assessments before marketing.

This guidance does not describe how to conduct, document, and submit risk assessments, or how such assessments, if conducted, will be evaluated by the Agency.

This guidance, which focuses on minimizing risks associated with the design of the drug product and its container closure system, is the first in a series of three planned guidances to minimize or eliminate hazards contributing to medication errors at the product design stage. The second guidance focuses on minimizing risks associated with the design of drug product container labels and carton labeling,[4] and the third focuses on minimizing risks when developing and selecting proposed proprietary names.[5]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On September 27, 2007, the reauthorization and expansion of the Prescription Drug User Fee Act (PDUFA IV) was signed into law as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). This reauthorization of PDUFA significantly broadened and strengthened FDA's drug safety program, facilitating more efficient development of safe and effective new medications for the American public. As part of the reauthorization, FDA committed to certain performance goals.[6] One of the goals was to implement measures to reduce medication errors related to look-alike and sound-alike proprietary names, unclear label abbreviations, acronyms, dose designations, and error-prone labeling and packaging designs. These measures include publishing guidance describing practices for naming, labeling, and

[4] FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling to Minimize Medication Errors*. When final, this guidance will represent the FDA's current thinking on this topic. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] FDA draft guidance for industry *Best Practices in Developing Proprietary Names for Drugs*. When final, this guidance will represent the FDA's current thinking on this topic.

[6] See letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record (goals letter). At http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

packaging to reduce medication errors, after public consultation. In June 2010, FDA held a public workshop and opened a public docket to receive comments on this topic.[7]

A. Recommendations to Minimize Medication Errors

In 2000, the Institute of Medicine (IOM) published a report entitled *To Err Is Human: Building a Safer Health System*.[8] The report stated that from 44,000 to 98,000 deaths occur yearly due to medical errors, making medical errors the eighth leading cause of death in the United States.[9] The report identified medication errors as the most common type of error in health care. Seven thousand (7,000) deaths annually were attributed to medication errors.[10] In the report, IOM recommended that FDA:

- Develop and enforce standards for the design of drug packaging and labeling that will maximize safety in use; and
- Require pharmaceutical companies to test proposed drug names to identify and remedy potential sound-alike and look-alike confusion with existing drug names.[11]

In addition to the IOM recommendations, the Secretary of Health and Human Services published a report entitled *Bringing Common Sense to Health Care Regulation: Report of the Secretary's Advisory Committee on Regulatory Reform* (November 2002). This report recommended that FDA adopt safe labeling practices for all FDA-regulated products to improve patient safety and decrease preventable adverse events.

In July 2006, the IOM published a report entitled *Preventing Medication Errors*. In this report, the IOM cited labeling and packaging issues as the cause of 33 percent of medication errors,

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[7] See April 12, 2010, Workshop Notice and Request for Comments (75 FR 18514), Docket No. FDA-2010-N-0168.

[8] Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err Is Human: Building a Safer Health System*. Institute of Medicine, National Academies Press: Washington DC, 2000.

[9] American Hospital Association. Hospital Statistics. Chicago. 1999. See also: Brennan TA, Leape LL, Laird NM., et al. Incidence of Adverse Events and Negligence in Hospitalized Patients: Results of the Harvard Medical Practice Study I. N Engl J Med. 324:370-376, 1991; Leape LL, Brennan TA, Laird NM, et al. The Nature of Adverse Events in Hospitalized Patients: Results of the Harvard Medical Practice Study II. N Engl J Med. 324(6):377-384, 1991; Centers for Disease Control and Prevention (National Center for Health Statistics). Births and Deaths: Preliminary Data for 1998. National Vital Statistics Reports. 47(25):6, 1999, cited in *To Err Is Human*, p. 1.

[10] Phillips, DP, Christenfeld, N, and Glynn, LM. Increase in US Medication-Error Deaths between 1983 and 1993. The Lancet. 351:643-644, 1998, cited in *To Err Is Human*, p. 2.

[11] This effort is also consistent with FDA's May 10, 1999, report to the FDA Commissioner titled *Managing the Risks From Medical Product Use*, which underscored the importance of providing an adequate risk assessment associated with the use of drug products, including a mandate to reduce medication errors from proprietary name confusion.

including 30 percent of fatalities from medication errors.[12] The report stated that "[p]roduct naming, labeling, and packaging should be designed for the end user — the provider in the clinical environment and/or the consumer."[13] The report also urged the Agency to incorporate principles of cognitive and human factors engineering in its review process to address issues concerning information presentation in labeling and naming.[14]

B. Safety by Design: A Systems Approach to Medication Error Prevention

Drug product design features that predispose end users to medication errors may not always be overcome by product labeling or health care provider or patient[15] education. It is therefore preferable to eliminate, or minimize to the extent possible, these hazards from the product design. It is not possible to predict all medication errors; however, medication errors can be minimized by conducting premarketing risk assessments to evaluate how users will interact with the drug product within various environments of use within the medication use system. using well-established human factors engineering analytical methods.

Error prevention in manufacturing is not a new concept. Corrective and Preventive Action, Change Control, and Quality Risk Management are well-recognized elements of current good manufacturing practice (CGMP) for drug products that focus on investigating, understanding, and correcting identified risks and managing the changes necessary for correction to prevent their recurrence while preventing unintended consequences.[16] The same principles can be applied to the overall design of a drug product to identify and eliminate design features that may contribute to medication errors.

FDA expects manufacturers to consider the use of these analytical methods when developing drug products to build safety into drug product throughout its lifecycle and to identify those safety characteristics of the product that they consider to be critical.

III. WHAT TO CONSIDER AT EARLY STAGE OF DRUG PRODUCT DESIGN TO MINIMIZE MEDICATION ERRORS

For a drug, the product design and user interface typically include the following elements:

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[12] Aspden P, Wolcott JA, Bootman JL, Cronenwett LR, eds. *Preventing Medication Errors*. Institute of Medicine, The National Academies Press: Washington, DC. 2006. Chapter 6, p. 275.

[13] IOM, *Preventing Medication Errors*. Chapter 6, Recommendation 4, p. 280.

[14] IOM, *Preventing Medication Errors.* Chapter 6, Actions to Improve Drug Naming, Labeling, and Packaging, pp. 281-282.

[15] In this document the term *patient* refers to the "patient and consumer" to address end users of both prescription and over-the-counter (OTC) drugs.

[16] FDA guidance for industry on *Quality Systems Approach to Pharmaceutical CGMP Regulations*.

- active ingredient
- strength
- dosage form
- product appearance
- size[17]
- shape
- palatability
- storage and handling
- indication
- type of container/closure used to package the product
- the label affixed to the container/closure
- secondary packaging such as outer carton or overwraps into which the container/closure is placed
- the labeling information describing the dose, preparation, and administration that accompanies the drug product

The term *user interface* is used to refer to all components of a product with which a user interacts (e.g., sees and touches), such as labels and packaging, and the container/closure system interacts, such as controls and displays. How a user locates and interprets the information necessary to use the product is critical to the product's safe and effective use. Because labeling, packaging, and nomenclature have been identified as key system elements that have great influence on medication use, any weaknesses or failure in the design of these elements can cause medication errors that lead to patient harm.[18,19] Therefore, the goal is to design a drug product that enables safe and correct use and eliminates or reduces design elements which could cause use related hazards.

In order to identify and assess potential medication errors, the product designer must understand how the drug product will be used, including who will handle or use the product, , the chronicity of use, the environments of use, and how the end users will interact with the drug product (e.g., the product, container closure, container label, and accompanying labeling). Additionally, it is necessary to consider any regulatory or professional standards that may apply to the preparation and administration of the type of drug product. To ensure that the proposed product is safely used, these factors should be considered at the start of and throughout product development before the design is finalized. Iterative modifications to the product design can be made throughout development in the interest of avoiding medication errors.

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[17] FDA guidance for industry *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules.*

[18] Cohen, Michael R., ed. *Medication Errors*, 2d ed. Washington, DC: American Pharmacists Association. Chapter 4 — Causes of Medication Errors; System elements implicated in Errors, p. 56.

[19] Institute of Medicine, *To Err is Human – Building a Safer Health System (*1999) and *Preventing Medication Errors (2006).*

A. End Users and Environments of Use

In U.S. health care, there are many process steps involved in the procurement, preparation, dispensing, and administration of a drug product. A drug product can have multiple end users with different levels of education and training across multiple environments of care.

End users need to perform critical tasks correctly in order to use the drug product safely and correctly. End users could include anyone involved in routine procurement, stocking, storage, and administration of the drug product, such as the patient or patient's caregiver, the prescribing physician, nurse, pharmacist, or pharmacy technician, among others. Products should be designed so that foreseeable end users can perform critical tasks using the drug product-user interface without making unintentional medication errors and without being exposed to unnecessary safety hazards. Considering the end users and environments of use during drug development can allow identification of hazards that could lead to medication error during actual use. Because the environments of use are unlikely to adapt to accommodate a particular product, the drug product design and user interface should fit the end users' needs within the typical environments of use. You should not expect that the end users or the environments of use will change to fit the use of the drug product.

There may be multiple environments of use depending on the medication and indication. Common environments of use for drug products include the following:

- hospitals
- long-term care facilities
- physician offices
- dialysis centers
- other free-standing outpatient care centers
- retail pharmacies
- retail outlets for OTC drugs
- specialty pharmacies
- emergency transport
- patient homes

These environments of use may also contain a variety of sub-environments. For example, a hospital environment of use can include the pharmacy, operating room, emergency department, patient unit, critical care facilities, and outpatient clinic. To the extent possible, consider how the use of the product may differ in varying typical environments of use for the product under development.

There also may be many environmental factors that could influence medication use within each of these settings, such as equipment, tools, computer software, lighting, distractions, workplace interruptions, background noises, institutional policies, common professional standards, and procedures. To the extent possible, these factors, if relevant to the use of the product, should also be considered with respect to how they might affect the product's safe use.

When designing a product, you should consider the following factors with respect to your analysis of the intended user population and environments of use. This analysis informs drug product design and enables you to make choices that can avoid elements that may predispose the product to medication error.

1. End Users

The following questions should be considered with respect to identifying the composition of the end user groups and understanding the use tasks for each end user group:

- Is there a single end user group or are there multiple end user groups that might use the product differently (e.g., physicians, pharmacists, nurses and/or patients)?
- Are end users diverse in a variety of factors such as age (e.g., pediatric, adult, and geriatric patients), education, experience, or training?
- How complex is the proposed product? Does it take multiple steps to deliver the product? Is extensive manipulation by the end users required? Is user training expected or required?
- What critical tasks must end users perform? Do critical tasks differ between end user groups?
- What characteristics might the end users have that could affect their ability to use the drug correctly (e.g., physical strength, stamina, dexterity, flexibility, coordination, vision, hearing, memory, disease state, mental clarity, ability to swallow, tolerance of medications that are unpalatable or difficult to swallow or ingest)?
- Does the end user require a specific skill set to use the product and administer the product safely? Is this skill set similar or dissimilar for closely related products?
- What is the end user's understanding of the product or similar products? Is knowledge gained from previous use of the same or closely related products, or non-similar products packaged in similar container closures, likely to influence users' understanding or expectations of the product under development?

2. Environments of Use

The following questions should be considered with respect to the environments of use so that the product has an optimal design for typical environments of use:

- In what environments might the product be used? What are the typical lighting levels, noise levels, distractions, physical environments, and available technology? What else might the end users be attending to while using the product? How likely are the end users to be distracted when using the product?

- How are drugs stored and obtained within this environment? Are there other areas where the product might be used or stored that are not typical?

- Are other, similar products also used within this environment (e.g., same or similar drug class, same or similar packaging design)? If so, is their use similar to use of the product being proposed? Have medication errors been associated with the use of similar products in this environment?

- Is the product a variant of something already used in this environment (e.g., extended release dosage form of an existing immediate release product)? Do the products have characteristics that might make the variation between these products difficult to distinguish, allowing possible medication errors to go undetected (e.g., color, shape, size, taste, smell, etc.)?

- Is this product atypical for use within this environment? What impact will the introduction of this new product have within this environment?

- Are there established standard practice guidelines for dispensing and administration of the product or similar products?

B. Drug Product-User Interface

The most effective strategies to address use-related medication errors focus on improvements to the design of the drug product-user interface. A well-designed user interface facilitates correct actions and prevents or discourages actions that could result in medication error. Safety by design should be considered at all steps in the development process, especially when making decisions on what the finished dosage form of the drug will be, what physical characteristics it will have, and what type of container closure will be used for marketing.

It is critical to evaluate what effect each design choice and modification will have on the end user. At the early stages of a drug product's development, the primary focus is generally on the product's clinical safety and efficacy. It is at this time that the indication, patient population, dosing, finished dosage form, and strength are usually established. Many decisions regarding the design of a drug product are driven by clinical studies and manufacturing constraints to ensure that the drug product is safe and effective and meets CGMP quality standards. However, certain product modifications based on manufacturing constraints or clinical issues may inadvertently create the opportunity for medication error when the finished dosage form of the drug product is finalized. Additionally, influences independent of clinical and manufacturing constraints, such as marketing considerations, may also affect product design. Relying solely on controlled clinical trials to evaluate product performance and user interactions is often an inadequate means of assessing a product's performance from a user's perspective because the controlled environments in place during clinical trials do not reflect actual use conditions in which the product will be made available to patients. Therefore, user interaction data obtained during clinical trials may be inadequate to assess whether a drug product can be used safely and correctly. Simulated use studies with representative users from the intended end-user population may be more suitable for this purpose.

A proactive risk assessment should start with an evaluation of why and how problems have occurred with similar products and should be conducted before finalizing the physical design features of a drug product. You can obtain medication error report information from FDA's Web site, other regulators, your own safety databases, and published literature. When identified early, error-prone features can be eliminated from the design so that the same type of medication error does not occur with the product under development. Once a drug product reaches the final stages of development, it may be difficult to change product features such as shape, size, strength, and dosing because such changes may require the collection of additional clinical or chemistry, manufacturing, and controls data to support even minor modifications. Should sponsors have questions or desire feedback on specific product designs, they should contact FDA to request clarification or input as soon as possible.

The following sections provide examples of known problems and medication errors due to design of the drug product and container closure systems. These medication errors could have been avoided if product modifications had been evaluated using proactive risk assessments before finalizing the design. Sponsors should consider the lessons learned from these experiences to help minimize risks associated with drug product designs and container closure systems.

1. Points to Consider During Development of the Product Dosage Form Design

- Solid Oral Dosage Forms

  If multiple strengths are being developed to cover the therapeutic dosing range, ideally they should look different from each other (e.g., color, shape, size, imprint). Adequate differentiation may reduce the risk for harm if an overdose or underdose occurs due to administration of an incorrect strength. Solid oral dosage forms that look similar to one another have led to the dispensing and administration of the wrong strength of a drug product ("look-alike" errors).

  - The imprint code may be critical to identifying the product when the dosage form is separated from the commercial product packaging. It is important to avoid the use of similar imprint codes and to consider how the codes are imprinted on multiple products within product lines. It is also important to ensure they are legible. Also, if possible, consider using the product name along with a numeric code or product strength to help distinguish different products with similar imprint codes. Absence of the imprint code or an imprint code that is difficult to see or identical or similar to imprint codes of other products have contributed to the dispensing and administration of the wrong drug product and wrong strength.

  - While the use of symbols, lines, and other graphics as part of an imprint code may help to uniquely identify a product, in some cases such graphics have led to difficulties in identifying a solid oral dosage form. Electronic databases that are used to identify drug products generally use alphanumeric searches to cross-reference imprint codes to drug products. Also, descriptors on patient information

(labels and Instructions for Use) may be less ambiguous if alphanumeric codes are used. Moreover, the use of lines as part of an imprint code has been misinterpreted as a score mark for splitting of tablet or the Arabic numeral "1." Including a letter or number as a part of the imprint code, while not required under 21 CFR 206.10, is encouraged to reduce medication errors by increasing the reliable identification of drug products compared to a symbol or logo by itself.

- Avoid product designs that resemble candy (e.g., a lollipop).

- Consider the size, coating, and palatability of oral products. A drug product can become a choking hazard due to the size of the tablet or capsule. If the tablet or capsule coating is too sticky, it can become lodged in the patient's throat or gastrointestinal tract. Tablets that have a larger cross-sectional area (e.g., tablets that are thicker, wider, or more spherical) would generally be more difficult to swallow than tablets of the same volume but with smaller cross-sectional areas. Tablet coating, weight, surface area, disintegration time, palatability, and propensity for swelling should also be considered when designing oral products to avoid medication errors related to swallowability and patient compliance.[20]

- Hardness or friability of tablets should be evaluated before marketing. Excessive hardness of tablets has led to medication administration errors. FDA has received reports of chewable tablets being too hard to chew and breaking teeth and dentures and of tablets being too friable to remove intact from a blister pack.

- During development of an extended or delayed release product, it is helpful to make the strengths of the extended or delayed release product different from those of immediate-release products. Having distinct strengths may help minimize the risk of medication errors in prescribing, such as omission of modifiers or incorrect use of modifiers, leading to dispensing and administration of the immediate-release product instead of the intended extended- or delayed-release product. The risk for medication error can be increased when strengths overlap or the strength of the extended release product is achievable from the marketed immediate-release product strength.

- Tablet Scoring

  - Ensure that tablet scoring is consistent with the recommended dosing. Scores that produce doses that are incongruent with the dosage and administration of a drug have led to medication dosing errors and should be avoided. For example, the dosing of a drug may be in 10 milligram (mg) increments, yet the score produces halves that yield 5 mg when 5 mg is not a recommended dose.

[20] See FDA guidance for industry *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules*.

- The user's ability to break the tablet should be tested with the intended patient population. Tablets that are physically difficult for the end user to split along the score line, and splits that do not produce an even distribution of drug, have led to medication dosing errors (for example, a 15 mg tablet that is scored, but yields 9 mg in one portion and 6 mg in the other).[21]

- Tablets that should not be split for reasons relating to product performance should not be scored. Tablets that should not be split but contain a score or score-like markings (e.g., lines and other symbols) have resulted in adverse events related to inappropriate absorption of the drug because they were split. Examples of products whose performance may be altered by splitting include extended or delayed release dosage forms, abuse-deterrent formulations, and friable tablets.

- Transdermal Systems

  - Sponsors should consider how a transdermal product will be handled by the patient, health care professional, and/or caregiver. Transdermal systems should incorporate a drug-free area or peel-away backing that would provide protection against accidental exposure to the drug when handled or applied. Problems can also arise if the size of the system is too large or too small for proper manipulation or handling of the system during application.

  - Transdermal systems that are difficult to see present safety issues. Transdermal systems that are clear, translucent, or colored to match human skin tones can make it difficult to find the patch on the patient and have led to medication administration errors when patients or caregivers fail to remove old systems and apply more than one system at a time. Clear or translucent patches may also be difficult to find if they detach prematurely from a patient, thereby increasing the potential for secondary or accidental exposure of the drug to a health care provider, caregiver, or child.

  - Transdermal systems should include an identifying label on the backing membrane that includes the drug name and strength printed with ink that has adequate contrast and remains visible for the duration of system wear. See draft guidance for industry, *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* for additional guidance on labeling of transdermal systems.[22]

[21] FDA guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.

[22] FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. When final, this guidance will represent the FDA's current thinking on this topic.

- Product Strength

  - Check for consistency between the drug product strength and dosing. Developing a product strength that is incongruent with the dosage and administration of the product complicates the calculation, preparation, and administration of a dose and has led to medication dosing errors. For example, developing a product with a usual dose of 300 mg could be a problem when the product is only available as a 100 mg vial. If three vials are needed to make up the full dose rather than a single vial, the product may be prone to medication dosing and administration errors. Multiple units (e.g., tablets, capsules, vials, or syringes) required to achieve a usual single dose have led to medication dosing errors because of users making miscalculations or forgetting how many units have already been administered.[23] Additionally, titration of dosing should be considered when developing product strengths to ensure that intermediate doses are achievable.

  - Dosing devices for liquid oral dosage forms should be appropriate to the doses to be measured.[24] The principles outlined in the guidance entitled *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products* are also generally applicable to orally ingested prescription liquid drug products. Additionally, avoid developing an oral solution that cannot be measured with a standard dosing device. The dosing device should deliver an oral solution in a volumetric unit of measure consistent with recommended dosing and should utilize metric units. Medication dosing errors have been reported when an oral dosing device is labeled in milligrams but the dose is prescribed in milliliters, leading to patients being unable to measure a specific volume of oral solution.

- Intravenous Products

  - To the extent possible, avoid developing intravenous products already in solution that require a two-step dilution prior to administration. Users might fail to dilute such products because they are already in solution, or they might dilute them incorrectly, leading to medication dosing and administration errors.

  - Dry powder products packaged with a special diluent are often separated from the diluent during product storage. This has resulted in preparation of the product with the wrong diluent or an incorrect amount of diluent. Even when not separated, the diluent has been administered instead of the drug. When feasible, dry powder products requiring the use of special diluents should be packaged in a

[23] Another example of incongruence between a product strength and dosage and administration would be to express the product strength on the label in percentage, but the dosage and administration of the drug in milligrams (see FDA draft guidance *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*).

[24] FDA guidance for industry, *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products*, addresses issues concerning dosing devices for OTC liquid drug products.

container closure system that allows for the drug and diluent to be physically linked or packaged in a ready-for-infusion solution.

2. Points to Consider During Development of the Container Closure Design

The container is defined as the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product (see 21 CFR 600.3(bb)). The closure is the cap, stopper, or seal. For drug-device combination products, the container closure can be the physical device.

Selection of the container closure should be based not only on stability and manufacturing considerations, but also on the ability of the design to protect against improper use.

The best container closure designs are those that do not require extensive end-user training and that make sense for the dose, route, and method of administration. Improper container closure system designs have contributed to medication errors including wrong routes of administration, wrong doses, and incorrect use. Especially problematic container closure systems include those that are (1) incongruent with the intended dosage and administration of the product or are (2) atypical for similar products marketed with a different type of container closure. These types of container closure systems should be redesigned because they cannot be remedied with additional label/labeling statements or health care provider and patient education.

- Drug products should not be packaged in a container/closure system that implies or affords a route of administration other than the route intended, unless there are no other options available, because this practice has led to wrong routes of administration. Examples include:

  - Oral/topical drug products packaged in vial containers used for injectable drugs have led to inadvertent, intravenous administration of the oral or topical product.

  - Oral inhalation products packaged in capsules have led to the capsule being swallowed whole rather than the contents of the capsule being delivered by the inhalation route.

  - Topical products packaged in containers with closures that look similar to eye, ear, nasal, or oral products have led to administration of the topical product in the eye, ear, nose, and mouth.

- To the extent possible, container closures should not look confusingly similar to those of other products within the same product line or a different product line. Distinguish container closures by size, shape, color, tactile features, or some other means when possible. Doing so will minimize potential product selection errors. Drug products packaged in container closures that have a similar appearance have led to product selection errors in which the wrong drug or wrong strength have been dispensed and administered. Examples that have contributed to product selection errors resulting in dispensing the wrong drug or wrong strength include, but are not limited to:

- Vials that have the same shape, size and same cap color that are stored side-by-side or in close proximity to one another.

- Blister packaging using similar graphic designs for all strengths or for all products within a company's entire product line.

- Syringes that are the same size and contain the same fill volume but contain different drugs or different strengths.

- Bulk or unit-of-use bottles that are all the same size or similar in size but contain different net quantities (e.g., 30, 60, 90 tablets).

- Products that require further dilution prior to administration should not be packaged in containers that could afford direct administration. Packaging products in such containers can lead to incorrect routes or methods of administration (e.g., a prefilled syringe may lead to intravenous push rather than intravenous infusion because a prefilled syringe is typically used for direct administration). Additionally, dual-chambered bags or compartmentalized syringes have led to the administration of the contents of one compartment without proper mixing of the two ingredients. Ensure that the bag or syringe does not support separation and consequent administration of the contents of only one compartment.

- Small-volume and large-volume injectable products whose labeling advises against admixing with other drugs should be packaged in a container with a single port. In situations where a single port is not possible, the secondary port should be made non-accessible by placing an aluminum cap over the port. Additional instructions or warning statements on the labels and labeling, in addition to the aluminum cap, can help to further mitigate the risk of medication error.

- Commercial containers should not provide an amount of drug that is incongruent with recommended doses. This has led to overdose with products designed with excessive fill volume, such as single-dose injection vials.[25]

- The amount of residual drug in a system after use should be minimized to the lowest possible level. Transdermal systems that contain a large reservoir of drug that is not depleted prior to removal of the system have led to adverse events, overdose, and accidental ingestion by children and pets, particularly when not disposed of properly.[26]

- Drug-device combination products (such as inhalers and prefilled pens) that have an unusual or unexpected device operation; have inadequate protection against incorrect use; have confusing or complex controls, labeling, operation; or have defeatable or ignorable

[25] See FDA guidance for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*.

[26] See FDA guidance for industry *Residual Drug in Transdermal and Related Drug Delivery Systems*.

safety features have led to dose omission errors, wrong-dose errors, and errors in administration and should be avoided.

- If container closures serve as the container labels, they should not have illegible lettering or make information such as product name and strength difficult to read. Avoid container closures that provide poor visual contrast between the container closure material and label information, such as foil, clear labels on glass/plastic syringes, or information etched on the syringe itself, or materials that have no affixed label but deboss or emboss the information directly on the container closure, such as a low-density polyethylene vial. These practices have led to incorrect doses and wrong-drug errors.

- Thoughtful use of unit-of-use container closures (e.g., blister packaging, calendar-packaging, sachets, and pouches) that can be dispensed intact to patients may help to reduce medication errors. Such packaging may minimize certain medication dispensing errors that can occur when repackaging from a bulk container into patient-specific containers. Some unit-of-use containers may also reduce medication administration errors if they are designed in a manner that improves patient adherence to the prescribed dosing regimen (e.g., by providing guidance on the method of administration, time of administration, or day of administration). When developing unit-of-use packaging, we recommend that it be congruent with the dosage and administration of the product and carefully designed so that it does not lead to incorrect dosing.

- Sponsors should ensure they comply with the Consumer Products Safety Commission's (CPSC's) requirements for special packaging to confer child resistance, particularly if you intend for the package to be dispensed directly to patients.[27] The use of child-resistant packaging helps to minimize accidental ingestions.

IV. PROACTIVE RISK ASSESSMENTS

Proactive risk assessments that reflect human and environmental factors in drug product use should be employed from the earliest stages of product design to help manufacturers anticipate potential use-related medication errors, identify the need for iterative design modifications, and ensure that such modifications do not introduce unintended consequences. Ideally, proactive risk assessments that employ analytical approaches (e.g., exploratory or formative evaluations and simulated use testing) should occur as early in the drug product design development process as feasible and before the product design is finalized. Considering the end users' needs, environments of use, and contexts of use in the development and design of a drug product alongside commercialization aspects can reduce post approval safety issues.

[27] CPSC regulations specify standards and test procedures for special packaging under 16 CFR part 1700. Full text of 16 CFR part 1700 is available at http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=f7656d60087382747f4b158e150c9b4a&n=pt16.2.1700&r=PART&ty=HTML#se16.2.1700_12

Many tools exist to support proactive risk assessments that can help identify use-related medication errors and potential harm. For products that are drug/device combinations, we refer you to the guidance for industry and FDA staff, *Applying Human Factors and Usability Engineering to Medical Devices*, *January* 2016.

To identify medication error concerns relating to product design and the container closure, CDER staff routinely employ failure mode and effects analysis (FMEA) and simulated use testing (i.e., human factors or user testing). We recommend that you use these tools in the development of your drug product so that medication errors and use-related hazards can be identified and remedied prior to marketing.[28]

A. Failure Mode and Effects Analysis

FMEA is a systematic evaluation of the proposed product within the medication use system and provides an understanding of the relative impact of different types of system failures that may affect use-related medication error and prioritization of risk. FMEA also provides for a multidisciplinary review that considers everyone in the medication use process. This systematic evaluation includes:

- Analyzing all steps involved in user interactions with the drug product within the anticipated environments of use.
- Identifying potential use-related medication errors and system failures that could occur at each step of the medication use process.
- Estimating the probability of occurrence of identified potential medication errors and system failures.
- Assessing potential effects and the severity of consequences of identified potential medication errors and system failures.

FMEA can be expanded to include:

- Identifying mitigation strategies that can address identified risks.
- Evaluating the success of the mitigation strategies at reducing risks to acceptable levels, either by reducing the probability that a problem will occur or by reducing the severity of the problem's potential consequences.

[28] If you have questions regarding the use of FMEA and simulated use testing, please consult the Division of Medication Error Prevention and Analysis.

We refer you to the *Handbook of Human Factors and Ergonomics in Health Care and Patient Safety* for the recommended steps for conducting a use-related medication error FMEA.[29]

B. Simulated Use Testing

Simulated use testing involves systematic collection of data from representative end users' realistic use of early, interim, or final product designs, including product labels and labeling. Data are obtained in a variety of ways including direct observation, subjective user feedback (including feedback on observed or potential medication errors), and manual and automated measures of user performance.

Simulated use testing is helpful in determining whether the product design enables or hinders end users to safely and correctly perform the critical tasks involved in using the product. Simulated use testing seeks to assess actual use and expands results obtained through analytic approaches such as FMEA. The results of simulated use testing should also be used to update the FMEA to include additional use-related risks that were not previously anticipated.

In addition to conducting risk assessments before a product is submitted for approval, these assessments should also be conducted before any subsequent product modifications such as additions to a product line (e.g., adding an extended release formulation), changes to a currently marketed product (e.g., new strength, new dosage form, new packaging configuration, new indication, new delivery system). If a product is being revised to address a known problem or medication error, the risk assessment should also consider whether the proposed change will introduce new types of medication errors or proliferate already known problems. In this situation, it also is essential to conduct a root cause analysis (RCA) to understand the causes (i.e., the how and why) of the problem or medication error. RCA, although retrospective, is another tool that the CDER medication error staff use when evaluating postmarking problems or medication errors and when evaluating proposed remedies for those problems or errors. Knowledge gained from evaluating RCA of a known postmarketing medication error can also be applied to the premarket safety assessments of other products. FDA recommends that you also conduct a RCA in the design process when problems are identified. Understanding how and why medication errors occur is essential to any risk assessment.

V. CONCLUSION

To avoid safety issues and costly redesigns after a product enters the market, it is important to consider the end user(s) in their environments of use early in the development and design of a drug product. FDA recommends the use of risk assessments early and throughout the development and design of a drug product. Identification of clinically relevant characteristics of the drug product during development will highlight potential areas for risk assessment. Risk

[29] Carayon, Pascale, ed. 2012. *Handbook of Human Factors and Ergonomics in Health Care and Patient Safety*, 2d ed. Boca Raton: CRC Press. Chap. 29 — Human Factors Risk Management for Medical Products, Failure Mode and Effects Analysis, pp. 479-486.

assessments also are valuable for identifying potential medication errors that may result from postmarketing changes or additions to an already marketed drug product throughout its lifecycle.

GLOSSARY

Container closure system: A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A *packaging system* is equivalent to a container closure system.

End user: *End users* include, but are not limited to, the patient, patient's caregiver, prescribing physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in routine procurement, stocking, storage, preparation and administration of medications.

Failure Mode and Effects Analysis (FMEA): A systematic, proactive tool used to define, identify, and eliminate known and/or potential failures, problems, and errors.[30]

Label: As defined in section 201(k) of the FD&C Act (21 U.S.C. 321(k)), the term *label* means a display of written, printed, or graphic matter upon the immediate container of any article.

Labeling: As defined in section 201(m) of the FD&C Act, the term *labeling* means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."

Package: A *package* or *market package* refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap). A market package is the article provided to a pharmacist or retail customer upon purchase and does not include packaging used solely for the purpose of shipping such articles.

[30] *Handbook of Human Factors and Ergonomics in Health Care and Patient Safety*. Chapter 29, p.480.