Guidance for Industry

Safety Considerations for Product Design to Minimize Medication Errors

DRAFT GUIDANCE

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

December 2012
Drug Safety

Guidance for Industry

Safety Considerations for Product Design to Minimize Medication Errors

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Center for Drug Evaluation and Research

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Draft – Not for Implementation

Guidance for Industry[1]

Safety Consideration for Product Design to Minimize Medication Errors

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I. INTRODUCTION

This guidance provides sponsors of investigational new drug applications (INDs), new drug applications (NDAs), biologics licensing applications (BLAs), abbreviated new drug applications (ANDAs), and nonprescription drugs marketed without an approved application (e.g., under a monograph) with a set of principles for developing drug products using a systems approach to minimize medication errors relating to product design. Improvements in a drug product's design can enhance patient safety by reducing medication errors, adverse events, and patient harm resulting from such errors. The recommendations in this guidance document are intended to improve the drug product and container closure design at the earliest stages of product development for all prescription and nonprescription drug[2] products. Many medication errors can be avoided by drawing upon lessons learned from other drug product errors and by evaluating the drug product using proactive risk assessments before marketing to reduce risks associated with a drug product's overall design.

This guidance, which addresses safety aspects of drug product design, is the first in a series of three planned guidances to minimize risks contributing to medication errors. The second guidance will focus on minimizing risks with the design of drug product container labels, carton labeling, and packaging configurations, and the third guidance will focus on minimizing risks with drug product nomenclature.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements

[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 (CDER).

[2] In this document the term *drug* refers to both drugs and therapeutic biologic products regulated by CDER.

are cited. The use of the word *should* in FDA's 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). The reauthorization of PDUFA significantly broadens and strengthens the Food and Drug Administration's (FDA) drug safety program, facilitating more efficient development of safe and effective new medications for the American public. As part of the reauthorization of PDUFA, FDA committed to certain performance goals.[3] One of the goals was to implement various 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, including publishing guidance describing practices for naming, labeling, and 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.[4]

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*.[5] 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.[6] 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.[7] 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

[3] 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.

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

[5] 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.

[6] 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.

[7] 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.

- Require pharmaceutical companies to test proposed drug names to identify and remedy potential sound-alike and look-alike confusion with existing drug names.[8]

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 drug 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, including 30 percent of fatalities from medication errors.[9]

The July 2006 IOM report stated that "Product naming, labeling, and packaging should be designed for the end user — the provider in the clinical environment and/or the consumer.[10] The report also urged the Agency to incorporate better principles of cognitive and human factors engineering to address issues concerning information presentation in labeling and nomenclature.[11]

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

Drug product design features that predispose end users to errors may not always be overcome by product labeling and health care provider or patient[12] education; it is therefore preferable to eliminate these risk factors from the drug product design to reduce the risk of medication errors. It is not possible to predict all medication errors; however, errors can be minimized by assessing, prior to marketing, how users interact with the drug product within the medication use system or environment of use. This can be accomplished by employing proactive risk assessments using well-established human factors engineering analytical methods.

Error prevention in manufacturing is not a new concept. Corrective and Preventive Action (CAPA), Change Control, and Quality Risk Management are well-recognized current good manufacturing practice (CGMP) regulatory concepts that focus on investigating, understanding, and correcting identified risks, and managing the changes necessary for correction to prevent their recurrence while preventing unintended consequences.[13] The Center for Devices and

[8] 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.

[9] 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.

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

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

[12] For this document, *patient* refers to the patient and consumer to address end users of prescription and over-the-counter (OTC) drugs.

[13] Guidance for industry on *Quality Systems Approach to Pharmaceutical CGMP Regulations*, September 2006. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs

Radiological Health (CDRH) and medical device manufacturers routinely apply the principles of human factors when evaluating device design to minimize use related errors.[14] The Center for Food Safety and Applied Nutrition (CFSAN) uses Hazard Analysis and Critical Control Points (HACCP) to address food safety through analysis and control of biological, chemical, and physical raw material production, procurement, handling, manufacturing, distribution, and consumption of the finished product.[15] The same principles can be applied proactively to the overall design of a drug product to identify and remedy risks that contribute to medication errors.

FDA expects manufactures to develop drug products by applying these analytical methods to build safety into the drug product design during early development and throughout a drug product's life cycle.

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

For a drug, the product design or user interface includes the active ingredient, strength, dosage form, product appearance, size, 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, and the labeling information describing the dose, preparation, and administration that accompanies the drug product. How a user finds and interprets the information necessary to use the product is critical to the safe use of the drug product. 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.[16,17] Therefore, the goal is to design a drug product that enables safe and correct use and minimizes the chance for health care practitioners, patients, and caregivers to make mistakes.

To identify and understand how a medication error might occur, it is necessary to have a complete and accurate understanding of how the drug product will be used, the environments of use, and how the end users will interact with the drug product design (e.g., the container closure, container label, and accompanying labeling) to identify and make decisions about the use of the

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guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

[14] See FDA guidances: *Do it by Design, An Introduction to Human Factors in Medical Devices*, December 1996; guidance for industry and FDA *Premarket and Design Control Reviewers*: *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, July 18, 2000; and draft guidance for industry and Food and Drug Administration staff - *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, June 22, 2011; available on FDA Medical Devices guidance Web page at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm (when final, this guidance will represent FDA's current thinking on this topic).

[15] http://www.fda.gov/Food/FoodSafety/HazardAnalysisCriticalControlPointsHACCP/default.htm

[16] *Medication Errors*, 2nd Edition; (Michael R. Cohen, Ed.), American Pharmacists Association; Chapter 4- Causes of Medication Errors; System elements implicated in Errors, page 56.

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

product. 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, the intended users and use environments should be considered at the start of product development, before the design is finalized, so that modifications to the product can be made in the interest of avoiding errors.

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.

For a drug product, the end users include, but are not limited to, the patient, patient's caregiver, the prescribing physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in routine procurement, stocking, storage, and administration of medications (e.g., medication technicians). Sponsors should evaluate and understand essential characteristics of all intended user groups for the purpose of evaluation and design activities using proactive risk assessments. All individuals in the intended user population should be able to use the drug product without making unintentional errors or without being exposed to unnecessary safety risks. Considering the end users and environments of use during drug development can allow identification of risks that could lead to error within the environment of use. Because the environment of use is unlikely to adapt to accommodate a particular product, the drug product-user interface or design should fit the end users' needs within that fixed environment of use, rather than considering that the end users or the environment of use will change to fit the use of the drug product.

Furthermore, there may be multiple environments of use depending on the medication and indication. Common environments of use for drug products include 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, and the patient's home. There are also a variety of subenvironments of use within each one of these larger environments of care. For example, a hospital environment of use can include the pharmacy, operating room, emergency department, patient unit, critical care facilities, and outpatient clinic.

In addition to the numerous types of environments of use for a drug product, there are many environmental factors that influence the medication use within each of these settings, such as equipment, tools, computer software, lighting, distractions, workplace interruptions, background noises, and institutional policies, common professional standards and procedures. These factors should also be considered with respect to how they may influence the end user's behavior and use of the drug product.

When designing a product, sponsors should consider the following factors with respect to the intended user population and environments of use. This analysis informs drug product design

and enables sponsors to make choices that can avoid elements that may predispose the product to use error.

1. End Users

The following questions should be considered with respect to the end users:

- Who are the end users? Are there multiple user groups that might use the product differently?
- How diverse are the end users in terms of age (e.g., children, adults, elders), education, experience, and training?
- What is the complexity of 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 the user perform?
- 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)?
- How knowledgeable is the typical end user (e.g., physician, nurse, technician, caregiver, and patient)? What is the end user's understanding of the product or similar products?
- 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?
- 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:

- In what environments might the product be used? What are the lighting levels, noise levels, distractions, physical environment, 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 there similar products used within this environment? If so, is their use similar to use of the product being proposed? Have there been medication errors associated with the use of similar products in this environment?

- Is the product a variant of something already used in this environment (i.e., extended-release dosage form of immediate release product)? Do the products have characteristics that might make the variation between these products difficult to distinguish, allowing possible errors to go undetected?

- 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 the dispensing and administration of the product or similar products?

B. Drug Product-User Interface

The most effective strategies to address use-related 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 error.[18]

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 clinical safety and efficacy of the drug. 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 the drug product is safe, effective, and meets CGMP quality standards. However, certain product modifications based on manufacturing constraints or clinical issues may inadvertently create the opportunity for use error when the finished dosage form of the drug product is finalized. Additionally, influences independent of clinical and manufacturing constraints such as marketing also drive the 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 environment in place during clinical trials does not reflect use in the "real world."

Therefore, it is crucial to evaluate the product design using proactive risk assessments before finalizing the design. Testing the design using proactive risk assessments before finalizing the

[18] FDA draft guidance, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, June 22, 2011. When final, this guidance will represent FDA's current thinking on this topic.

design helps identify risks that can contribute to medication error and provides qualitative information that is informative for improved design iterations.

Evaluation of why and how problems have occurred with similar products can be helpful and should be conducted before finalizing the physical design features of a drug product. When identified early, error prone features can be eliminated from the design so that the same type of 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, strength, and dosing because such changes may require the collection of additional clinical or CMC data to support even minor modifications.

The following sections provide examples of known problems and errors due to poor design of the drug product and container closure systems. These 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 their designs.

1. Commonly Reported Problems and Errors Relating to Product Design

- Solid Oral Dosage Forms:

  - If multiple strengths are being developed, they should look different from each other, especially to reduce the chances of use errors that can result in harm if an overdose 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. This error has been attributed to inadequate differentiation among dosage strengths with respect to tablet/capsule color, size, and shape.

  - The imprint code may be critical to verifying the solid oral dosage form. It is important to consider how similar the codes are imprinted across products and within product lines and to ensure they are legible. Also consider using the product name rather than a numeric code. Imprint codes that are absent, difficult to see, and similar to imprint codes of another product have led to the dispensing and administration of the wrong drug product and wrong strength.

  - Avoid development of products that resemble candy (e.g., 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.

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

- Tablet Scoring

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

  - The 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 dosing errors (for example, a 15 mg tablet that is scored, but yields 9 mg in one half and 6 mg in the other half (see FDA guidance entitled *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*)).[19]

  - Tablets that should not be split should not have a score. 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.

- During development of an extended- or delayed-release product it is helpful to make the strengths of the extended- or delayed-release product distinct from the immediate-release products. Failures in prescribing, such as omission of modifiers or incorrect use of suffixes, can lead to dispensing and administration of the immediate-release product instead of the intended extended- or delayed-release product. This can occur because all product characteristics overlap, or the strength is achievable from the marketed immediate-release product strength.

- Transdermal Systems

[19] FDA draft guidance for industry, *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*, August 2011. When final, this guidance will represent FDA's current thinking on this topic.

- Sponsors should consider how a transdermal product will be handled by the patient, healthcare professional, and/or caregiver. Transdermal systems should be developed with a drug-free area or peel-away backing that would provide protection against accidental exposure of the drug to the healthcare provider or caregiver. Problems can also arise if the size of the system is too large or too small and the user cannot manipulate the system properly during application.

- Transdermal systems that are difficult to locate and identify present safety issues. Transdermal systems that are clear, translucent or are colored to match human skin colors can make it difficult to find the patch on the patient, and have also led to 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 healthcare provider, caregiver or child.

- Product Strength

  Check for consistency between the drug product strength and dosing. Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculation of dosage and has led to dosing errors. For example, the strength may be expressed on the label in percentage, but the dosage and administration of the drug is described in milligrams. Another example of this type of problem would include a product with a usual dosage of 300 mg when the product is only available as a 100 mg vial. If 3 vials are needed to make up the full dose rather than a single vial, the product may be prone to dosing and administration errors. Multiple units (e.g., tablets, capsules, vials, syringes) required to achieve a usual single dose have led to dosing errors because of users making miscalculations or forgetting how many units have already been administered.

- Dosing devices should be appropriate to the dosages to be measured.[20] The principles outlined in this guidance should also be applied to oral liquids specific for prescription 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. An example of a dosing error related to dosing device markings is an oral syringe that is calibrated in mg rather than mL.

- Intravenous Products

[20] FDA guidance to industry, *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products*, May 2011, addresses issues concerning dosing devices for OTC liquid drug 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 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. Additionally, 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 container closure system that allows for the drug and diluent to be physically linked or packaged in a ready-for-infusion solution.

2. Commonly Reported Problems and Errors with 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 is the physical device.

Factors influencing the choice of a container closure system for commercial distribution of the finished product should go beyond stability or ease of manufacturing. The design should protect against improper use.

The best container closure designs do not require extensive end-user training and should make sense for the dose, route, and method of administration. Improper container closure system designs have contributed to medication errors resulting in 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 of products previously marketed with the same type of closure. These types of container closure systems should be redesigned because they cannot be remedied with additive 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; this 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.

- Ensure container closures do not look similar within a product line or across a different product line. Distinguish container closures by size, shape, color, tactile features, or some other means. Drug products packaged in container closures that have a similar appearance has led to product selection errors in which the wrong drug and 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.
  - Blister packaging using similar graphic designs for all strengths or for products within a company's entire product line.
  - Syringes that are 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 for such a product 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 administration of the contents of one compartment without proper mixing of the two ingredients.

- 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.

- Sponsors should avoid transdermal systems that have a large reservoir of drug that is not depleted prior to removal of the system. This has the potential to lead to overdose from dose dumping and, when disposed of in the trash, can lead to accidental ingestion by children and pets.[21]

- Drug-device combination products (such as inhalers and prefilled pens) that have an unusual or unexpected device operation lack protection against incorrect use, have confusing or complex controls, labeling, operation, or defeatable or ignorable safety features have led to wrong-dose errors and errors in administration, and should be avoided.

[21] See FDA guidance for industry, *Residual Drug in Transdermal and Related Drug Delivery Systems*, August 2011.

- 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. Container closures that provide poor visual contrast between the container closure material and the color used to print the 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 (LDPE) vial, are difficult to read, and should be avoided. These have led to incorrect doses and wrong-drug errors.

IV. PROACTIVE RISK ASSESSMENTS

Proactive risk assessments considering human and environmental factors in drug product design help manufacturers anticipate potential use errors, identify the need for implementing iterative design modifications, ensure that any design modification minimizes unintended consequences (i.e., does not introduce new hazards) and the recurrence of use errors.

Ideally, proactive risk assessments that employ analytical approaches (e.g., exploratory or formative evaluations and simulated use testing) should occur early in the drug product design development process, before the product design is finalized, so that the results of the risk assessments can be used to modify the drug product design to minimize use-related risks prior to implementing phase 2 clinical trials or product marketing. Considering the end user's needs, environment of use, and contexts of use in the development and design of a drug product alongside commercialization aspects can reduce postapproval safety issues.

Many tools exist to support proactive risk assessments that can help identify use-related errors and potential harm.[22] For products that are drug/device combinations, we refer you to the CDRH guidance for industry and FDA Premarket and Design Control Reviewers, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, July 18, 2000, and CDRH draft guidance for industry and Food and Drug Administration staff - *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, June 22, 2011.

Two tools routinely employed by the CDER medication error prevention staff include failure mode and effects analysis (FMEA) and simulated use testing (i.e., human factors or usability or user testing). We recommend that sponsors use these tools in the development of their drug product.[23]

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

[22] See draft guidance, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*. When final, this guidance will represent FDA's current thinking on this topic.

[23] If sponsors have questions regarding the use of FMEA and simulated use testing, please consult the Division of Medication Error Prevention and Analysis for guidance.

affect use error and prioritization of risk. FMEA also provides for a multidisciplinary review that considers everyone in the medication use process. This systematic evaluation includes:

- An analysis of all steps involved in user interactions with the drug product within the anticipated environments of use
- Identification of the potential use errors and system failures that could occur at each step of the medication use process
- An estimate of the probability of occurrence of each use error and failure
- Identification of the potential effects and severity of consequences of each use error and failure

This technique can be expanded to include:

- Identification of mitigation strategies that can address problems or use error.
- Evaluation of the success of the mitigation strategies at reducing risks to acceptable levels, either by reducing the probability of the occurrence of the problem or by reducing the severity of the potential consequences of the problem.

  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-error Failure Mode and Effects Analysis.[24]

B. Simulated Use Testing

Simulated use testing involves systematic collection of data from representative participants using early drug product designs or final product designs and their labels and labeling in realistic situations. Data are obtained in a variety of ways, including direct observation, and subjective user feedback, including a discussion of the reasons for any use errors or failures that were observed from the user perspective, and using manual and automated measures of user performance.

Simulated use testing is helpful in determining whether the intended users can safely and effectively perform the critical tasks involved in the use of the drug product or whether they will make errors, have difficulty, or be unable to use the product at all. 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.

[24] *Handbook of Human Factors and Ergonomics in Health Care and Patient Safety*, Second Edition; Edited by Pascale Carayon, 2012, Chapter 29 – Human Factors Risk Management for Medical Products, Failure Mode and Effects Analysis - pgs.479-486

In addition to conducting proactive risk assessments before the initial approval of a medication, these assessments should also be conducted prior to subsequent product modifications such as additions to a product line (e.g., adding an extended-release formulation) or making changes to a currently marketed product (e.g., new strength, new dosage form, new packaging configuration, new indication of use, new delivery system) or prior to a revision made to address a known problem or error. To make an effective design modification based on a known problem or error, it is essential that a root cause analysis (RCA) be conducted to understand the causes (i.e., the how and why) of the problem or error. RCA, although retrospective, is another tool that the CDER medication error staff use when evaluating postmarking problems or errors and when evaluating proposed remedies for those problems or errors. The knowledge gained from the evaluation of the RCA of a known postmarketing error can be applied to the premarket safety assessments of other products. FDA recommends that industry also conduct an RCA in the design process. Understanding how and why errors occur is an essential piece in any proactive risk assessment.

For drug-device combinations there are additional considerations that should be evaluated before approval. We refer you to the following guidances that describe risk management relating to medical devices and premarket design when developing a drug-device combination product.

- ANSI/AAMI/ISO 14971:2007, *Medical devices – Application of risk management to medical devices,* provides guidance on the risk management process. It identifies the two components of risk as being (1) the probability of occurrence of harm and (2) the severity of the potential consequences of that harm. The standard also identifies six steps in the risk management process: (1) risk analysis, (2) risk evaluation (these two steps constitute risk assessment), (3) risk control, (4) evaluation of overall residual risk acceptability, (5) risk management report, and (6) production and postproduction information.

- CDRH guidance for industry and FDA Premarket and Design Control Reviewers, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, July 18, 2000, and CDRH draft guidance for industry and Food and Drug Administration staff on *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, June 22, 2011.

V. CONCLUSION

To avoid safety issues and costly redesigns post-approval, it is important to consider the end user(s) in their environment of use during the development and design of a drug product. FDA recommends using proactive risk assessments at the early stages of drug product development and when changes or additions to an already marketed drug product occur throughout the drug product's life-cycle to produce products with minimal error potential.