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February 11, 2013

VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Comments to FDA Draft Guidance for Industry:  
Safety Considerations for Product Design to  
Minimize Medication Errors;  
Docket Number: FDA-2012-D-1005

Dear Sir or Madam:

On behalf of the Combination Products Coalition (“CPC”), we welcome the opportunity to comment on FDA’s Draft Guidance regarding Safety Considerations for Product Design to Minimize Medication Errors (“Draft Guidance”). The CPC commends the Agency for providing greater clarity regarding minimizing medication error risks through product design. We view this guidance from the perspective of combination product design and development and thereby focus our comments specifically on the area of drug-device combination products.

By way of background, the CPC is a diverse group of drug, biological product, and medical device manufacturers with substantial experience in the combination products area. Our members range in size from small start-ups to multi-billion dollar manufacturers. These companies all share an intense interest in policy issues affecting combination products. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

One of our principal goals is to work with FDA on such issues in order to advance our common mission of providing the best possible health care for patients. In this regard, the CPC has had frequent dialogue with FDA on regulations, guidance documents, and other policy issues that affect combination products and how best to serve patient needs with respect to such products. For example, we have submitted dozens of written comments, policy documents, proposed guidance documents, and other materials to the Agency on these issues for nearly a decade. If you are interested, you can find several of these materials on our website: <http://www.combinationproducts.com/>.

Our comments center around two issues. First, FDA has issued multiple guidance documents addressing the need to incorporate human factors into product design. However, these guidance documents do not spell out each of the roles and responsibilities of the various offices with jurisdictional oversight of combination product review and approval. Further clarification of

these roles and responsibilities is necessary to improve product design in order to minimize the risk of medication errors and enhance product safety overall. Second, we commend FDA's Division of Medication Error Prevention and Analysis ("DMEPA") for referencing the Center for Devices and Radiological Health ("CDRH") Human Factors Draft Guidance. However, it is unclear to what extent that guidance, or other guidances touching on human factors, would be relied upon by DMEPA and whether it would defer to CDRH with respect to the human factors as it relates to the device function of a drug-device combination product. We elaborate on these issues below and provide recommendations on how the allocation of responsibilities could be handled with respect to certain types of combination products.

## **I. General Comments Regarding the Need to Establish Roles and Responsibilities with Respect to the Review of Combination Products**

### **A. Clarity is Needed Regarding the Reviewing Roles of the Different Centers and Divisions, and How the Various Guidance Documents Addressing Human Factors Will Be Applied**

In 1991, CDRH, the Center for Drug Evaluation and Research ("CDER"), and Center for Biological Evaluation and Research ("CBER") entered into three separate Intercenter Agreements outlining how combination products and single entity products were to be classified and assigned. These Intercenter Agreements also outlined each Center's roles and responsibilities with respect to the oversight of combination products. In 2006, after reviewing the agreements as required by 21 U.S.C. § 353(g)(4)(F), the Agency proposed to keep them in effect, with the understanding that they should not be independently relied upon as the Agency's most current, complete jurisdictional statements. 71 Fed. Reg. 56,988 (Sept. 28, 2006). The publication of the *Draft Guidance for Industry and FDA Staff: Classification of Products as Drugs and Devices and Additional Product Classifications Issues* in June 2011 further eroded the value of these agreements by creating more doubt about their reliability.

This lack of clarity has resulted in Centers and Divisions taking on responsibilities for issues outside of their areas of expertise. We believe in large part this was due to the absence of a current document that clearly assigns roles and responsibilities, especially when it comes to combination products. This is particularly clear with respect to human factors-related issues. Within the past year, at least three guidance documents impacting human factors were released without any apparent coordination between the Centers.<sup>1</sup> This lack of coordination has not only resulted in confusion regarding which guidance document(s) apply to which products, and how they apply to those products; it has resulted in a significant duplication of efforts between the Centers. Understanding that Agency resources are already stretched thin and additional budget cuts may be on the horizon, until the Agency updates the Intercenter Agreements, it is important that the final guidance clearly spell out how manufacturers should apply this guidance in conjunction with the other guidance documents that touch on human factors issues, and also the roles that CDRH, DMEPA, and other organizations within the Agency will play in review.

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<sup>1</sup> Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design (June 22, 2011); Draft Guidance for Industry and FDA Staff - Design Considerations for Devices Intended for Home Use (December 12, 2012); Draft Guidance - Safety Considerations for Product Design to Minimize Medication Errors (December 2012).

## B. Recommendations as to the Roles of DMEPA and CDRH to Reduce Medication Errors Associated with the Use of Drug-Device Combination Products

With respect to drug-device combination products, DMEPA's responsibility should be limited to evaluating the "accuracy" of the dose whereas CDRH should be responsible for evaluating the "precision" of the dose. Specifically, DMEPA should limit its review where the various interactions with the combination product are likely to impact the accuracy of the drug administration (e.g., distinguishing between different doses the drug-device combination product is intended to deliver, or distinguishing between different products). Given DMEPA's mandate to address "any preventable event" that may lead to the inappropriate use or some other harm with a given drug product, they have a broad role to play in drug product design, development, and review and approval. However, they do not have sufficient expertise in the technical aspects of device constituent parts of drug-device combination products to be able to examine whether human factors are likely to cause medication errors with respect to the device constituent part.

CDRH should be responsible for reviewing whether the end users of the product are likely to administer an wrong (or imprecise) dose or drug because of misuse of the product (e.g., where the end user is provided the correct product with the correct dose, and the question is whether the wrong dose could still be administered due to the improper use by the end user). The use of both Failure Mode and Effects Analysis ("FMEA") and simulated use testing, both recommended in the Draft Guidance, can be used effectively to carry out risk assessment of the device constituent of a drug-device combination product. However, in order to use these tools, one must have sufficient technical expertise to evaluate whether the inputs to the problem have been adequately characterized in order to have a robust analysis of risks and the effects of a design change on risk. As FMEA and simulated use testing have been applied to devices for many years, CDRH is best suited to take the lead in reviewing these issues.

We provide examples in three areas of drug-device combination products – injector systems, transdermal systems, and infusion pumps – to illustrate how DMEPA and CDRH would allocate responsibilities with respect to medication error risk assessment under our proposal.

### 1. Injector Systems

Injector systems are generally grouped into two categories: variable-dose and fixed-dose systems. In variable-dose injector systems, the user can select the dose administered. In fixed-dose systems, there are separate systems for each dosing level. With respect to variable-dose injector systems, potential sources of medication errors include: confusing one product for another, setting the wrong injection volume, failing to inject the full volume, or injecting more than the set volume either by accidentally administering multiple injections or because the device allows more than the set volume to be injected. With respect to fixed-dose injection systems, potential sources of medication errors include: confusing one product for another, failing to inject the full volume, or injecting more than the set volume either by accidentally administering multiple injections or because the device allows more than the set volume to be injected.

While we understand that it can be difficult to draw bright lines regarding roles and responsibilities, below is our attempt to draw such lines:

- a) Variable-dose injector systems:

- (1) DMEPA should be responsible for evaluating the likelihood that
    - (A) The injector system could be confused with another injector system
    - (B) The user sets an improper injection volume
  - (2) CDRH should be responsible for evaluating the likelihood that
    - (A) The actual injection volume administered is greater than or less than the injection volume the patient believes that he or she had set
    - (B) Multiple injections can result from mishandling the device
- b) Fixed-dose injector systems
- (1) DMEPA should be responsible for evaluating the likelihood that
    - (A) The injector system can be confused with another injector system (i.e., a different medication or between injection volumes of the same medication)
  - (2) CDRH should be responsible for evaluating the likelihood that
    - (A) The dose administered is different from the fixed dose set to be administered
    - (B) Multiple injections can result from mishandling the device

## 2. Transdermal Systems

The Draft Guidance specifically references certain considerations that should be evaluated with respect to transdermal drug delivery products. However, as these products are combination products, it is important that DMEPA and CDRH delineate their respective responsibilities with respect to the potential for medication errors involving transdermal drug delivery systems. As discussed in the Draft Guidance, potential sources of medication errors include: inadvertent contact with excess drug in the reservoir, the inability to locate the patch to ensure its removal, the inability to distinguish between dosage sizes or other medications, the improper application to the skin resulting in less than the full dose being administered, or the ability to receive excess dose if left on the body for too long.

For these issues, we suggest the following delineation of roles and responsibilities:

- a) DMEPA should be responsible for evaluating the likelihood of medication errors resulting from:
  - (1) Excess drug in the reservoir
  - (2) Inability to find the patch to remove
  - (3) The inability to distinguish dosages
  - (4) The product's similarity with other transdermal products
- b) CDRH should be responsible for evaluating the likelihood of medication errors resulting from:
  - (1) Improper application to the skin resulting in partial dose being administered

- (2) Ability to result in excess dose if left on body too long

### 3. Infusion Pumps

We understand that not all infusion pumps are combination products, as many are designed to be used with multiple drug or biologic products. There are infusion pump combination products that are designed and labeled for use with specific drugs or biologics. In general, CDRH will be solely responsible for potential medication errors related to non-combination product infusion pumps. However, DMEPA may have some responsibility with respect to infusion pump combination products.

Where combination product infusion pumps are concerned, we suggest the following delineation of roles and responsibilities:

- a) DMEPA should be responsible for evaluating the likelihood of medication errors resulting from:
  - (1) The wrong drug being administered to patient
  - (2) The wrong concentration to be administered because the wrong concentration is incorporated into infusion pump or the wrong dilution being set by user
  - (3) The wrong infusion rate being set by user
- b) CDRH should be responsible for evaluating the likelihood of medication errors resulting from:
  - (1) The dose or concentration administered, or infusion rate differing from that intended to be set by the user

## II. **Key Terms should be Defined**

The introductory section of the Draft Guidance contains several terms that have particular meanings either because they have been defined in regulations or are used as terms of art in the industry. In order to avoid ambiguity, key terms used in the Draft Guidance should be defined in the final Guidance to ensure the intended meaning is clear to industry.

***Proposed solution:*** Add a “Definitions” section for key terms that are already included in the body of the text (e.g., end user, container).

## III. **The Timing and the Scope of the Initial Risk Assessment Should be Revised**

The Draft Guidance states on Lines 93-95 that “[medication] 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.” While prospective risk assessment is critical to identifying and minimizing the risk associated with drug, device, and combination drug-device products, the timing and scope of human factor assessments and risk minimization efforts prior to marketing should balance the cost of undertaking such assessments, the benefits to the ultimate drug-device product that reaches the consumer, and the burden on industry to implement such risk assessments before sufficient confidence exists that the product will reach the market.

Additionally, we are concerned about the feasibility of and the cost of eliminating a new product's risk of leading to medication errors. Not only is the complete elimination of medication error risk impossible, any attempt to eliminate all such risk will drastically increase the costs of developing new products and thereby hinder innovation and its associated benefits to patients. Therefore, FDA should instead emphasize eliminating the obvious, the most likely and the most serious risks as opposed to requiring manufacturers to accomplish the impossible goal of eliminating *all* risks. Although FDA discusses *minimizing* unintended consequences (see e.g., Lines 488-495, "... ensure that any design modification minimizes unintended consequences (i.e., does not introduce new hazards) and the recurrence of use errors ... so that the results of the risk assessments can be used to modify the drug product design to minimize use-related risks ...") (Emphasis added)) the Draft Guidance also discusses the *elimination* of risk factors (see e.g., Lines 91-92 "it is therefore preferable to eliminate these risk factors from the drug product design to reduce the risk of medication errors." (Emphasis added)).

**Proposed solution:** The final guidance should reflect a practical approach to risk assessment during the development of a drug-device combination product. Specifically, we recommend the language in Section II.B, Lines 90-96, be revised as follows:

"Drug product design features that predispose end users to errors may not always be overcome by product labeling and health care provider or patient education; it is therefore preferable to ~~eliminate~~ **minimize** 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 **design** 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."

#### **IV. Expand the Timing of Proactive Risk Assessments**

The Draft Guidance states on Lines 492-495 that proactive risk assessment "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." We fully support the purpose of the Draft Guidance and proactive risk assessment that aims to minimize use-related risks as early as possible in the drug product design. However, the work to implement product design changes occurs iteratively and at multiple points prior to product marketing. A phase 2 clinical trial is only one of those possible points, and often the manufacturer may not anticipate incorporating the drug into a combination product until after the completion of a phase 2 clinical trial.

**Proposed solution:** The final guidance should reflect that risk assessment should be conducted proactively and before the drug-device combination product reaches the market, but not necessarily before the start of phase 2 clinical trials. We recommend the reference to phase 2 clinical trials be deleted from Line 495 and lines be revised as follows:

“Ideally, proactive risk assessments that employ analytical approaches (e.g., exploratory or formative evaluations and simulated use testing) should occur **throughout** ~~early in~~ the drug product **or drug-device combination** product design development process, **but should begin early in the process and** 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.”

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Again, we commend the Agency for providing greater clarity about minimizing medication error risks through product design. However, we believe it is important for the final guidance to clarify the roles and responsibilities of the various offices with jurisdictional oversight of combination product review and approval. Further clarification of these roles and responsibilities is necessary to improve product design in order to minimize the risk of medication errors and enhance product safety overall. Also, it is important for the final guidance to clarify how DMEPA will rely on other Agency guidance documents that touch on human factor issues. By addressing these issues as recommended in our comments, we believe the Agency will further both product innovation and patient safety.

Kindest regards,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, with a large initial "B" and "M".

Bradley Merrill Thompson,  
On behalf of the Combination Products Coalition