Combination Products Coalition

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March 12, 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Re: Comments to "FDA Draft Guidance for Industry and Food and Drug Administration Staff: Design Considerations for Devices Intended for Home Use"
Docket No. FDA-2012-D-1161-0001

Dear Sir or Madam:

On behalf of the Combination Products Coalition ("CPC"), we welcome the opportunity to comment on FDA's Draft Guidance regarding Design Considerations for Devices Intended for Home Use ("Draft Guidance"). The CPC appreciates the Agency's emphasis on device design to reduce or minimize product risk. We view this guidance from the perspective of combination product design and many of which are intended for home use.

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 the Office of Combination Products 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Our comments on the Draft Guidance center around four issues. First, FDA has issued multiple guidance documents addressing the need to incorporate human factors into product design. However, these guidance documents do not explain the roles and responsibilities of the

various divisions, offices, and centers with jurisdiction over combination product review and approval. For example, the Draft Guidance was issued by CDRH and CBER but indicates it is applicable to all devices designed for use in the home. Therefore, it is unclear to what extent this guidance is applicable to combination products containing a drug constituent part. Second, the Agency states that some Human Factor ("HF") testing is subject to investigational device exemption ("IDE") regulations and requirements. However, neither the Draft Guidance nor any other Agency guidance specifically describes how a manufacturer should evaluate whether HF testing would be subject to an IDE, especially as it relates to combination products. Third, the Agency discusses labeling in the Draft Guidance and notes the central importance of effective labeling for home use devices. The Draft Guidance specifically mentions that checklists may be a useful way to present instructions for use. We agree with this premise, but also believe that it may be helpful to incorporate a user checklist that focuses on communicating only the most critical aspects of proper use so that experienced users are more apt to refer back to the checklist. Finally, we describe various points where additional clarification and/or revision would be beneficial.

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 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.[1] This lack of coordination has not only resulted in confusion regarding which guidance document(s) apply to which products, and how they apply

[1] 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).

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, and other organizations within the Agency will play in review.

B. Application of the Draft Guidance to Home Use Combination Products Containing a Drug Constituent Part Should be Clarified

It is unclear whether this Guidance applies to device-drug or drug-device combination products that are or are likely to be used in the home. The Draft Guidance states that it applies to "both prescription and over-the-counter medical devices that are intended for home use." As the Draft Guidance was developed by CDRH and CBER there is reason to believe that the guidance is applicable to combination products. However, as CDER did not participate in the development of the Draft Guidance, it would be strange for the information contained in the guidance document to be understood as reflecting CDER's current thinking on this topic. Therefore we request that the final guidance clarify this document is applicable to combination products. If so, we believe it is important that as CDRH and CBER develop the final guidance document they seek input from CDER and the Office of Combination products to ensure issues unique to combination products are taken into account. This also will help ensure that there are no conflicts with the other recent guidance documents that address similar issues (e.g., CDER's Draft Guidance on Safety Considerations for Product Design to Minimize Medication Errors and CDRH's Draft Guidance on Applying Human Factors and Usability Engineering to Optimize Medical Device Design).

II. The Guidance Should Clarify in What Situations Human Factor Testing May be Subject to IDE Requirements

The Draft Guidance states that HF testing "may be subject to IDE requirements"[2] (*see* 21 U.S.C. § 360j(g) and 21 C.F.R. Part 812) as well as human subject protection requirements (*see* 21 C.F.R. Parts 50, 56). However, neither the Draft Guidance nor any other FDA guidance documents provide detailed information regarding the factors for determining whether HF testing is subject to IDE requirements, especially with respect to combination products. Although we acknowledge that some HF testing is subject to the IDE requirements, we believe most HF testing is not. Specifically, simulated use studies, e.g., a study in which a material is not injected or delivered/administered to the subject, should not be subject to IDE requirements. In addition to providing factors for determining whether HF testing is subject to IDE requirements, it is important for FDA to provide parameters for when HF testing would be considered a significant risk study and when it would be considered a non-significant risk study.

[2] Draft Guidance § 6, fn. 4

III. User Checklists that Include Only the Most Critical Steps Necessary to Ensure Safe Use of Combination Products Should be Implemented as Part of the Draft Guidance

The Draft Guidance makes the assumption that users will either remember how to use a device or will refer back to the IFU. At the same time, the Draft Guidance states that lengthy labeling tends to be ignored by the end user, because it can be confusing.[3] While we agree that lengthy labeling tends to be ignored by the end user, novice users likely need more extensive instructions than experience users. Therefore, experienced users are more apt to ignore the instructions than novice users.

We agree that instructions should not be used as a substitute for important design features, with respect to controlling risks, but instructions are useful to reinforce safe use. Additionally, the level of instruction needed to reinforce safe use may vary by the user's experience level which may make it difficult to create a set of instructions that provide sufficient information for a novice, while at the same time being short enough such that experienced users will be more apt to use them as reinforcement. Although user checklists may present instructions in a more concise and less confusing format, we believe that it is still difficult to design a checklist that is useful to both novice and experienced users. Therefore, a condensed version of the IFU, possibly in the form of an abbreviated checklist that focuses on the most critical steps that may be overlooked by experienced uses, may be the an effective means of reinforcing safe use even among those that are reluctant to refer back to the instructions. At the same time, such a condensed IFU may not be sufficient for novice users. Therefore we believe a user checklist can be used to present an abbreviated IFU that highlights critical steps that may be easily overlooked by an experienced user but are important to reinforcing the safe use of the combination product.

IV. Other Recommendations

A. FDA Should Clarify What it Considers to be a "Device Design Flaw" and Recognize that Labeling might Mitigate Some Risks

The Draft Guidance states that "labeling should never be used to mitigate risks associated with *device design flaws*."[4] However, it is unclear what the Agency considers "device design flaws," or how these would be distinguished from design or technological *limitations* more generally, recognizing that such distinctions may be somewhat subjective. Because the appropriate manner for mitigating risk depends on the particular risks, technologies, and other factors it is unclear how an arguably "flawed" design might be used safely and effectively with appropriate labeling (e.g., changes in operating conditions), especially when risks are inherently low and the manufacturer has strong evidence demonstrating the labeling would adequately address risk concerns.

To recognize that there *may* be instances in which labeling is a solution for any design issue, we believe that the Agency should revise the clause to read "... labeling should ~~never~~

[3] *See* Draft Guidance § 2.1.

[4] Draft Guidance, § 3.

generally not be used to mitigate risks associated with device design flaws." Further, we believe the final guidance should adopt a definition of "device design flaw" which includes examples that clarify both its meaning and its distinction from technical or design *limitations* that are encountered with all devices (and where labeling to mitigate risk is generally appropriate).

B. Additional Comments and Recommendations

Attachment A to this letter contains a number of additional comments and recommendations that we believe would add clarity to the final guidance, such as changes that would emphasize the steps taken in human factor evaluations depend upon a products intended user (or "indicated") patient population.

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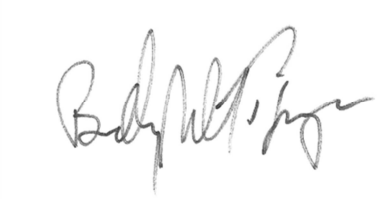
Again, we commend the Agency for emphasis on device design to reduce or minimize product risk. However, we also believe there are several areas in which the final guidance would benefit from clarifications and revisions. By addressing these issues as recommended in our comments, we believe the Agency will further both product innovation and patient safety.

Kindest regards,



Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Attachment A: Additional Comments and Recommendations

Page/ Paragraph/ Sentence **(Line Numbers)**	**COMMENT**	**RECOMMENDATION** **(Suggested Text in Bold)**
1. Introduction		
1.1 Scope		
Page 5, 2nd paragraph, 1st sentence (Lines 136-138)	The Statement of Scope in the guidance should be revised to clarify that it applies to combination products with device constituents.	Revise the sentence to read: "This draft guidance provides recommendations for minimizing the risks associated with home use devices**, and combination products with device constituents,** by considering the user, the use environment, the device or system, human factors, and labeling.
2. Background		
2.1 Design Controls for Home Use Devices under the Quality System regulation		
Page 7, 2nd paragraph, last sentence (Lines 232-34)	The cited standard, ANSI/AAMI HE74:2001, has been superseded by HE75:2009, *Human Factors Engineering – Design of Medical Devices*. This current standard, which is referenced in other FDA guidance documents, should be included here. Further, this standard has been incorporated as an annex of the FDA-recognized consensus standard AAMI/ANSI/IEC 62366:2007 *Medical Devices - Application of Usability Engineering to Medical Devices*, and is no longer a stand-alone standard.	Revise the 5th sentence to read: "… We also recommend that you refer to ANSI/AAMI ~~HE74-2001~~**HE75:2009, *Human Factors Engineering – Design of Medical Devices,* now an Annex of AAMI/ANSI/IEC 62366:2007 *Medical Devices - Application of Usability Engineering to Medical Devices*,** for a process-oriented approach to user interface design, which is especially relevant in developing safe and effective home use devices."
3. Environmental Considerations		
Page 9, 1st paragraph, last sentence (Lines 306-308)	The guidance should reflect that efforts in a premarket submission to account for environmental considerations should be made with reference to the device's intended use.	Revise the last sentence to read: "You should include in your premarket submissions a description of the efforts you took to account for the environmental considerations outlined below in your device design **based on the intended use of the device**."

Page/ Paragraph/ Sentence (Line Numbers)	COMMENT	RECOMMENDATION (Suggested Text in **Bold**)
Page 9, 2nd paragraph, last sentence (Lines 314-18)	The bullet point about location-related environmental considerations should be expanded to include sources of EMI interference that are commonly encountered in the home.	Revise the last sentence to read: "You should also note possible sources of electromagnetic interference (EMI) for electric powered medical devices in the use location(s) that may be near or in contact with other objects that would interfere with their functioning, such as large electric motors or amateur radio transmitters, radio and TV transmitters, radar, ~~and~~ high tension power lines, **as well as commonly encountered objects such as refrigerator magnets, metal detectors, and de-magnetizers used in retail security systems.**"
Page 10, 5th full paragraph, last sentence (Lines 358-60)	Recommendations on childproofing should reference 16 C.F.R. Part 1501, as it addresses the standards for assessing choking hazards.	Revise the last sentence to read: Devices should have a minimal number of parts that can be manipulated easily as well as a minimal number of detachable parts that could fall off the device, presenting an inhalation or swallowing hazard **(see 16 C.F.R. Part 1501)**.
Page 10, after the 7th full paragraph (Line 375)	Product disposal should be added to the list of environmental considerations. Appropriate disposal of medical devices is an important element of using products outside of a health care setting and should be highlighted as an area to consider in this section.	Add the following after the last bullet on the page: **"Disposal: The design of home use devices should consider the manner in which home users will dispose of devices once used or no longer needed."**
4. User Considerations		
Page 11, 5th full paragraph (Lines 416-17)	The guidance should clarify that physical considerations should be limited to those which are relevant to intended (indicated) users.	"**Physical:** You should design for **intended (indicated)** users ~~with~~ **of the device considering as appropriate** a range of physical sizes, mobility, dexterity, coordination, flexibility, strength, and stamina."

Page/ Paragraph/ Sentence (Line Numbers)	COMMENT	RECOMMENDATION (Suggested Text in **Bold**)
Page 12, 1st full paragraph, first sentence (Lines 428-431)	The guidance should clarify that cognitive considerations should be limited to those which are relevant to intended (indicated) users.	Revise the sentence to read: "**Cognitive:** You should design for users**, representative of your intended (indicated) user population** with a range of abilities to process information and literacy levels, and consider the potential that users might have some type of cognitive impairment that could affect how they interact with the home use device."
5. Device Considerations		
Page 12, 3rd full paragraph (Lines 443-45)	The guidance should clarify device-specific considerations should be determined based on the intended (indicated) user population.	Revise the paragraph to read: "Home use devices should be simple for users to understand, operate, and maintain safely and effectively. Below are some of the device-specific considerations that you should take into account when designing a home use device. **The considerations should be based on the intended (indicated) user population**"
5.1 Lock-Out Mechanisms		
Page 12, 4th full paragraph, second sentence (Lines 451-52)	Risk analysis of the design and effectiveness or impact to functionality should be the criteria to demonstrate features in addition to lock-out should it be included or excluded.	Revise the sentence to read: "Before using a lock-out mechanism as the only mechanism to reduce or prevent patient harm, you should first rule out other design solutions **through a risk analysis.**"
5.2 Calibration		
Page 12, 5th full paragraph (Lines 457-462)	Due to form factors (ergonomic design) there may not be available space to have a visual display of step-by-step calibration functions. However, a confirmatory "in" or "out" of calibration signal should be	Revise the paragraph to read: "Home use devices should be designed without the need for calibration, but if that is not

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	sufficient. Additionally, based on the intended (indicated) user, this can be an auditory signal instead of a visual.	possible, the device should be designed to require minimal calibration by the user. Calibration instructions on the device display should be step-by-step and preferably provide the user with any feedback necessary to complete the calibration process. This **may** also include a visual indicator on the device that states when it was last calibrated and when the next calibration is needed. **Instructions do not have to be on a display but a confirmation of correct calibration should be present.**"
Pages 12-13, split paragraph (Line 466)	The reference to a "quality management system" is ambiguous.	Please clarify whether the "quality management system" is referring to design controls or a design assurance case that calibration values are controlled through the life of the device either by design considerations (CRC, instructions, labeling) or external service.
5.3 Mechanical Strength		
Page 13, 2nd full paragraph, 3rd sentence (Lines 480-83)	Per IEC 60601-1, 3rd edition, the option to 'fail safe' (i.e., do no secondary harm) is important to ensure with respect to both mechanical and electrical functionality. As 'normal conditions of use' cannot be completely defined due to changing transport/portable conditions, the minimum device requirement is the 'fail safe'.	Revise the third sentence to read: "If the device will be used while the user is in transit, the device should have adequate mechanical strength and durability to withstand normal transport conditions on trains, road vehicles, cycles, ships, and aircraft **or fail safe per design**."
Page 13. 2nd full paragraph, 4th sentence (Lines 483-84)	The section on Mechanical Strength makes reference to testing to, "see how they function after impact with the ground or other objects". In addition to IEC 60601-1-11:2010, the guidance should make reference to ASTM D4169-09, Standard Practice for Performance Testing of Shipping Containers and Systems. This, too is an FDA-recognized consensus standard.	Revise the sentence to read: "FDA recommends you follow IEC 60601-1-11:2010 **and ASTM D4169-09** for mechanical strength in the design of medical devices, including those devices that are not electrical equipment."
5.4 Electrical Issues		

Page/ Paragraph/ Sentence (Line Numbers)	COMMENT	RECOMMENDATION (Suggested Text in **Bold**)
Pages 13-14 (Lines 501-506)	Expiry dating is presented on the package label and includes electrical, mechanical, and compatibility considerations (e.g., drug expiry). Instructions for use must be consistent with the package label, and presented at the appropriate education/age level with enough detail that the user is aware of error and/or action to take.	Revise the last paragraph on Page 13 (Lines 501-506) to read: "**Internal electrical power source:** If the safe performance of a device is dependent on an internal electrical power source (e.g., batteries), the IFU should describe the typical operation time or number of procedures and the typical service life of the power source **and be consistent with the information presented on the package label, e.g., use by date (expiry).** If the device uses a rechargeable power source, the IFU should explain whether the device can be used while it is charging. If the internal power source is replaceable, the IFU should explain the replacement process."
(Lines 538-39)	If the power source is not user serviceable or by design is single use and not accessible by the user, information on the service life of the device as oppose to the expiry date will cause confusion to the user.	Revise the 4th paragraph on page 14 (Lines 538-39)to read: "**Battery life:** If a device operates on battery power, you should inform the user how long he or she can expect the device to work on a fully charged battery. **For single use devices, an expiry date is adequate notification.**"
5.5 Electromagnetic Compatibility (EMC)		
Page 15, 2nd full paragraph (Lines 562-565)	The guidance should clarify that the use of labeling can be used to address precautionary steps that reduce hazards. Also, it should be noted that through use case analysis the manufacture shall identify the use environments and the limits that the device shall be subjected to. This in addition to risk analysis (likelihood of the event) determines the level of exposure and	Revise the paragraph to read: "Lay users should not be expected to understand how to avoid electrostatic discharge (ESD) or how to take proper ESD precautions. You should consider that the standard ESD test levels are often exceeded in the home environment and home use devices

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	the mitigations need in place to either operate or fail safe or inform the user operating outside of defined parameters (i.e. in a cell tower, or within a static chamber).	should be designed to reduce this increased risk to an acceptable level. **Labeling may be used to explain and emphasize precautionary steps to reduce the likelihood of a specific hazard.**"
5.6 Wireless Technology		
Page 15, 3rd full paragraph, 3rd sentence (Lines 573-75)	The points which should be addressed in the development of wireless technology depend upon the intend use of the data that are being transmitted by the device. Also, it is unclear whether the Agency believes *FDA's Draft Guidance for Industry and FDA Staff: Radio-Frequency Wireless Technology in Medical Devices* should be followed here.	Revise the third sentence to read: "Particular points to address include quality of service needed, data integrity, coexistence, security, and EMC of the wireless signals, **based on intended use of the data by the manufacturer**." Also, clarify in the final guidance with FDA's *Wireless* guidance referenced in the comment should be followed.
5.7 Alarm Systems		
Page 15, last paragraph, first sentence (Lines 592-93)	There may be situations in which design data and circumstances support use of a single alarm mode.	The first sentence of the paragraph should be revised to read: "FDA recommends you provide alarm signals for home use devices in at least two of the three following modes: visual, auditory, and tactile**, unless use of only one mode is appropriately validated (e.g., by clinical or simulated clinical usability testing).**"
6. Human Factors		
6.1 User Training and Certification		
Pg. 17, Paragraphs 1-3 (Lines 631-651)	We understand that depending on the risk level of the device certification and/or training might or might not be appropriate. However additional clarification on this point is needed.	Please provide clarification on what types of devices require certification and training, including examples. Additionally, please provide clarification on how the FDA defines "certification."