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CPC Injector Systems Working Group – Labeling Q&A

Ref #	Topic	Overview	Examples	CPC Position	Support for CPC Position
1	The timing of the feedback provided to companies resulting from BLA/NDA reviews of instructions for use (IFU), product and secondary packaging labeling (e.g., injector dose indicators, graduations, symbols, colors and other user interface mechanisms) that accompany new pre-filled injectors	Companies conduct Human Factors (HF) studies in accordance with Design Control requirements, CDRH Human Factors and Usability guidance and widely accepted standards (e.g., ISO standards) to validate the content, graphics and presentation of labeling and instructions for use for injector systems. FDA's practice of providing comments or requesting changes to a product's IFU, product or secondary packaging that relate to the function and use of the injector system device constituent part and have been validated as described above can result in delays to marketing the product, which impedes patients' ability to access these combination products. These delays could be significant if the proposed revisions to the statements must be revalidated. These delays can be avoided by FDA providing comments earlier in the review process.	Less than one month before the PDUFA approval date, CDER provided a company with comments on a patient IFU for an injection device. These comments recommended significant changes including: 1. Significantly revising to the wording for all instruction steps 2. Revising to two figures; and 3. Adding two new figures. These comments were made in spite of the fact that the patient IFU had been validated in two HF studies and was aligned with a user FMEA. However, after an internal design review meeting the Company confirmed that for the most part these changes had no impact on the risk analysis and incorporated all of the changes except for one of the figures. The Company's analysis was documented in a review memo.	CPC requests that FDA provide feedback on patient IFU's and product and secondary packaging early in the BLA/NDA review cycle, at least with respect to those aspects related to the injector system's device constituent part. In addition, the CPC requests that FDA provide timely comments on any proposed statements (including the proposed IFU) that accompany the proposed human factors study protocol when submitted for FDA review prior to validation testing.	The CPC appreciates the feedback it receives from FDA as a result of the FDA labeling experts' detailed reviews. Many of these comments and wording and formatting recommendations are excellent and contribute significantly to the creation of instructions that are easily understood by patients. Examples of these contributions include suggested rewording of instructions in order to simplify the statements (e.g., 7th grade level) and converting statements from passive to active voice. However, these recommendations would be more valuable if they were provided earlier in the process. Ideally, each of the relevant centers and offices that will be involved in the BLA/NDA review would not only conduct such a review early in the BLA/NDA review process, but they would also provide timely comments to proposed IFUs submitted with proposed HF testing study protocols when FDA review is requested. Such a review will permit the companies to

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					incorporate this feedback into IFU before it undergoes validation testing in the HF study. Even if such early review was not feasible, the review should take place early in the BLA/NDA review process and can be conducted well before the final label review occurs. We understand that the final label review must occur late in the review cycle because of the focus on clinical data included in the BLA/NDA and statements included in the USPI. However, the label review of the device constituent part aspects generally will focuses on the HF testing used to validate these aspects of the labeling.
1a	FDA requests changes to IFUs that have been validated in HF Studies conducted in accordance with Design Controls pursuant to 21 CFR §820.30; Human Factors and Usability guidance issued by CDRH and widely accepted Standards.	In addition to the validation requirements described above, certain steps and precautionary statements may be included as partial mitigations to risks identified in Usability Failure Modes and Effects Analysis HF studies provide solid scientific evidence that verify	Less than one month before the PDUFA approval date, CDER provided a company with comments on a patient IFU for an injection device. These comments recommended significant changes including: 1. Significantly revising to the wording for all	CPC requests that all Centers rely on information from usability studies conducted in compliance with Design Controls, CDRH Human Factors and Usability guidance and widely accepted standards when reviewing the content, graphics and presentation of labeling and instructions for use	As stated above, many of the requests for changes are excellent and significantly contribute to ensuring the product can be used safely by the user population. However, the value of these changes diminishes if they are provided after the content has

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		and validate that the information to be provided with the commercial product is sufficient to ensure the product can be used safely by the user population. However, as either CDER or CBER generally is the lead center in reviewing these products and these Centers are less familiar with HF testing, it is not uncommon for FDA to request that sponsors make substantive revisions to labeling and instructions for use that have been validated in this manner. In addition, FDA does not always provide justification or other support for these requests.	instruction steps 2. Revising to two figures; and 3. Adding two new figures. These comments were made in spite of the fact that the patient IFU had been validated in two HF studies and was aligned with a user FMEA. However, after an internal design review meeting the Company confirmed that for the most part these changes had no impact on the risk analysis and incorporated all of the changes except for one of the figures. The Company's analysis was documented in a review memo.	for the injector system device constituent parts. CPC also requests that FDA provide justification or support for all requests for changes to content, graphics or the presentation of product labeling or instructions for use that have been validated through appropriate HF studies conducted in accordance Design Controls, FDA Guidance or industry standards. To the extent FDA does not provide justification, manufacturers should not be required to implement changes to appropriately validated content, graphics or the presentation of product labeling or instructions for use. However, manufacturers should be permitted to implement these changes if they choose.	been validated in accordance with the standards set forth in FDA guidance and regulations. The value diminishes even more if FDA fails to provide justification or support for the request. Without any justification or support for a request, the manufacturer has very little information from which to evaluate whether the changes would alter the meaning of an instruction step resulting in user confusion, or would impact the validity of prior HF studies. Also, without adequate justification or support manufacturers have very little information from which to craft an adequate response with justifications and data as to why the original wording or alternative wording is preferred. This generally results in many of the revisions being adopted without an assessment as robust as used to validate the original content which is contrary to the intent of HF principles.

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2	It is not always clear what information related to the "use" of an injector should be provided in a Medication Guide Patient IFU (PIFU) versus specified sections in the Prescribing Information (PI) under the regulations in 21 CFR § 201.	There is lack of clarity with respect to instructional information required to be located in the mandated prescribing information format for "How Supplied Storage and Handling" (PI Section 16) and "Patient counseling information (PI Section 17) compared to what is provided in patient IFUs located in a patient Medication Guide. Under 21 CFR 201.57, PI Section #17 "must contain information necessary for patients to use the drug safely and effectively" but, short of reproducing the Medication Guide's entire IFU, this PI section can never be complete. Likewise, certain handling information must be in both the PI section 16 and in the Patient IFU. FDA took the position, in January 2006, that the labeling final rule: Requirements on the Content and Format of Labeling for Human Prescription Drug and Biological Products (issued January 24, 2006) [PDF - 780KB] , applied to combination products approved under an NDA or BLA, as specifically stated in Draft Guidance Labeling for Human Prescription Drug and Biological Products —	Below are examples of FDA comments on PIs/Medication Guide IFUs: • "There is no instruction in the PI to discard after the expiration date, or where the expiration date is found. Healthcare providers should know to look… ; however, patients should be instructed to look… This information should be added to the PI, such as in section 16.0 How Supplied/Storage and Handling, or the information must be deleted from the PIFU. The information in the PIFU must be consistent with the information in the PI." • "There are no instructions in the PI directing patients to take the product out of the refrigerator XX minutes prior to injection, and no information about warming or avoiding other methods of warming. If you wish to include this information in the PIFU, it must be added to the PI. The information in the PIFU must be consistent with the information in the PI."	IFU's for HCPs are best presented in PI Section 2 "Dosage and Administration" per 21 CFR 201.57(c). Patient IFU's are best presented in a dedicated section (e.g., Medication Guide). CPC would like FDA to consider developing a guidance document specific to PIFUs for delivery devices that provides additional details on its requirements on formatting and content elements, both for PIFUs and relevant PI sections. Appendix A contains a list of current FDA Guidance documents on labeling format that impact combination products. However, these documents do not provide a means to understand the content required in a medication guide for an injector system or Agency interpretation of applicable regulations and guidance as they pertain to injector systems. CPC believes additional guidance should be developed that addresses these issues.	In these examples, FDA has asked that certain, specific, but not all instructions be added to the PI. It is unclear when information in the PI and PIFU is redundant, when it is duplicative, or to what degree the must be worded consistently for the different audience. Sponsors would benefit in understanding FDA's expectations regarding labeling and IFUs (i.e., format, content and figure requirements, and what needs to appear in both the PI and PIFU/Medication guide.)

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		Implementing the New Content and Format Requirements, Q&A # 5 (2006) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf. However, the FDA's position was also that OCP would inform manufacturers if their combination product that is subject to *device* standards would be subject to the requirements described in the final rule. It is unclear whether this remains FDA's position. Therefore, OCP should clarify and provide guidance, in the interest of transparency, as to when combination products that are subject to device regulations also would be subject to the final rule requirements.	Also, FDA has sometimes made very specific formatting requirements to PIFUs: • "Do not use all capital letters in figure call-outs. Re-label the syringe parts to use combined upper case and lower case letters" • " Add a figure showing all of the injection supplies."		
3	FDA has not encouraged or allowed, in some cases, the development of abbreviated/reference IFUs or "quick start guides" or "reminder cards" for medical devices. PIFUs can be overly detailed and obscure the few critical or key tasks required for a user to perform a safe and effective injection.	A quick start guide outlining the four to five key steps necessary to properly use an injector device would reinforce prior detailed training and could be validated in Human Factors studies. However, FDA has not allowed any abbreviation of the full IFU in many cases, even for medical information training materials reviewed by OPDP	In one review of a bulleted IFU reminder list, FDA commented: "Providing the bulleted list of information could mislead the patient to think that this is the most relevant information and preclude them from referencing the Medication Guide. Patients should refer to the Medication Guide for all relevant product information, including instruction	CPC believes that patients often follow detailed written directions when first using an injector system but subsequently ignore these written directions when they become comfortable using the device. In some cases, patients may forget or misremember necessary steps in the proper operation of the injector system.	Reminder cards for critical tasks can be an effective means to ensure that patients follow key instructions for use for an injector and avoid use errors.

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		(formerly DDMAC).	for use."	An abbreviated version of the IFU that outlines critical steps necessary to ensure safe use could avoid some instances of user error and thereby reduce harm to patients. CPC requests FDA provide guidance as to when it would permit the use of reminder cards that reinforce prior detailed training if their use is validated in Human Factors studies.	
4	FDA expectations regarding validation of minor changes to a PIFU, either after Human Factors studies or after product approval are not transparent.	In many cases Human Factors studies can identify certain IFU statements that cause hesitation or were found to be confusing in subject interviews. In most cases, wording changes can be made and justified without conducting a summative human factors re-study.	None	CPC requests that FDA provide additional guidance beyond that provided in the CDRH Human Factors and Usability guidance describing FDA's expectations regarding when it expects manufacturers to validate minor changes to IFUs.	
5	What level of evidence / evidentiary standard is required for drug delivery device-related labeling (including promotional) claims such as 'ease of use'/'simplicity of use', convenience, user preference, reduction of accidental needle-stick claims?	Drugs and devices are held to different regulatory standards for labeling statements regarding and promotional claims, such as those that describe safety and effectiveness. These different standards also apply to the evaluation of other promotional claims.	A promotional claim (e.g., a statement on a product website) stating, "The drug delivery device is easy to use" could be adequately supported by data from a questionnaire employed in a simulated use summative HF study. The questionnaire would include affirmative statements about whether	Promotional claims that relate solely to performance characteristics of the injector system constituent part should only need to be supported by valid scientific evidence as described in 21 CFR § 860.7. These performance characteristic claims should not be limited to only those claims	There are two separate standards for the data necessary for supporting claims related to drugs and devices. The standards applicable to drugs should not automatically apply to claims related to device constituent parts solely because the product contains a drug constituent part. There will be

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		Drug promotional claims that relate to "safety or effectiveness must [be] supported by substantial evidence derived from adequate and well-controlled studies" (21 CFR 202.1(e)(6)). Whereas the safety and effectiveness of a device must be supported by "valid scientific evidence" which includes "well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts and reports of significant human experience with a marketed device." (21 CFR § 860.7) For injector systems, performance features of the device constituent part such as those aiding usability or convenience that are present as a *matter of fact* may be described in promotional materials. Although it seems intuitive that such promotional claims should be evaluated using the standard applicable to devices, FDA has not made this clear.	specific features on the device are easy to use. Study participants would be asked to indicate their relative agreement with the statements based on a 7-point Likert scale after simulated use of the device.	describing *matter of fact* device features (e.g., "large injector button"), but should also include comparison claims (e.g., "large injector button makes it easier to use than Product X's injector system"), if they do not compare the safety and effectiveness of the drug. Also, it would be helpful if FDA could provide guidance regarding how companies should evaluate whether a promotional claim regarding the functional characteristics of the device constituent part impacts the safety and effectiveness of the drug constituent part.	occasions where a combination product's labeling contains promotional claims that do not affect the safety and effectiveness of the drug constituent part. For example, claims relating to the performance characteristics of the device constituent part such as its "ease of use" or durability, generally will not impact the safety or effectiveness of the device. If the device constituent part was not part of combination product, such claims could be supported by evidence other than well-controlled controlled studies. In particular, the safety and effectiveness of a device may be supported by substantial evidence derived from bench/non-clinical methods, including simulated use summative HF studies. (reference *Draft Guidance for Industry and FDA Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design,* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuida

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					nce/GuidanceDocuments/ucm259748.htm). Therefore, claims that relate to the performance characteristics of a device constituent part should not be held to a higher standard solely because the device is a constituent part of a combination product and should be able to be supported by valid scientific evidence including results from HF studies.
6	What is FDA's current stance on use of internationally accepted symbols (without text definitions) on primary and secondary package labels; while providing definitions in the user instructions? Our understanding is that although FDA has accepted use of symbols (with text definitions) for IVD labels and instructions, they haven't publicly acknowledged acceptance of symbols for combination product labeling (or device labeling for that matter) instead of text.	Our understanding is that FDA recognizes ISO 15223-1 Second Edition 2012-07-01, Medical devices - Symbols to be used with medical device labels, labeling, and information to be supplied - Part 1: General requirements. (General). However, FDA recognizes selected symbols in this standard only for use on the label and in the labeling of medical devices intended for professional use. FDA does not recognize these or any symbols for use in the labels and labeling of over-the-counter or prescription home-use devices unless accompanied by	Appendix B lists examples of ISO standards currently accepted by FDA.	The CPC requests that FDA consider broader applicability of ISO 15223-1 Second Edition 2012-07-01 with regard to use of symbols and permit the use of internationally recognized and clearly understood symbols on primary and secondary package labels without text definitions. The CPC also asks FDA to issue guidance on this topic.	CPC believes that while symbols should be optional and never mandatory, internationally recognized and clearly understood symbols should also be acceptable on product labeling (including over the counter or prescription home use devices) without text definition, e.g. the symbols can be defined in the IFU instead of on package labeling. This will go a long way to help companies assure labels are consistent across regions and will require less text to be translated, which can lead to inconsistencies or misunderstanding by users. In

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		equivalent text in English (CDRH website).			addition, it affords companies the ability to convey important information when dealing within a limited space (e.g. primary labels on prefilled syringes or autoinjectors).

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Appendix A: FDA Guidance Documents Regarding Device Labeling

(*see* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/)

Labeling: Regulatory Requirements for Medical Devices; CDRH, August 1989 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095308.pdf)

Write it Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care; CDRH, August 1993 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070771.pdf)

Device Labeling Guidance #G91-1 (blue book memo); ODE, March 1991 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081368.htm)

Guidance on Medical Device Patient Labeling; CDRH, April 2001 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070801.pdf)

Human Factors Principles for Medical Device Labeling; CDRH, September 1993 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095300.pdf)

Section 206 of the Medical Device User Fee and Modernization Act (MDUFMA) (New section 502(f) of the Federal Food, Drug, and Cosmetic Act) Electronic Labeling for Prescription Devices Intended for Use in Health Care Facilities; ODE, March 2003 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109203.pdf)

Alternative to Certain Prescription Device Labeling Requirements; CDRH, January 2000 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072748.pdf)

Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products; CDRH / CDER / CBER / OCP, April 2009 (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf)

Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion; CDER / CBER / CVM / CDRH, May 2009 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf)

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Appendix B: Examples of ISO Standards Accepted by FDA

Number	Product Area	Title of Standard	Reference Number and Date	Publication Date	Standards Development Organization
2-181	Biocomp	Clinical investigation of medical devices for human subjects - Good clinical practice	14155:2011	03/16/2012	AAMI ANSI ISO
2-182	Biocomp	Clinical investigation of medical devices for human subjects - Good clinical practice	14155 Second edition 2011-02-01	03/16/2012	ISO
5-36	General	Technical Information Report: Medical devices - Guidances on the selection of standards in support of recognized essential principles of safety and performance of medical devices, second edition	TR 16142:2006	09/08/2009	ISO
5-40	General	Medical devices - Application of risk management to medical devices	14971 Second edition 2007-03-01	08/20/2012	ISO
5-70	General	Medical devices - Applications of risk management to medical devices	14971:2007/(R)2010 (Corrected 4 October 2007)	03/16/2012	AAMI ANSI ISO
5-73	General	Medical devices - Symbols to be used with medical device labels, labelling, and information to be supplied - Part 1: General requirements	15223-1 Second Edition 2012-07-01	01/15/2013	ISO