CPC – Injector Systems Human Factors Topics

Topic	Overview	Examples	CPC Position	Support for CPC Position
1. Intended Users	CDER has recommended validation studies include specific numbers of trained vs. untrained and injection experienced vs. injection naïve participants. The CDRH draft guidance does not specify experience as a criterion for a distinct user group nor suggest that a summative study include different training levels, only that training be consistent with that expected in commercial use.	• A proposed validation study protocol required a minimum of 15 participants per distinct user group with the objective of including a mixture of trained and untrained participants spread across all user groups (without specifying a recruiting target). ○ CDER recommended that each user group in the validation study include a minimum of 15 trained and 15 untrained users which resulted in a minimum of 30 participants per user group; thus, doubling the size of the study. Feedback from DMEPA has indicated a worst case –i.e. real world where no or inadequate/ inconsistent training is provided should be considered in the summative as an additional untrained arm. CDER recommended the validation study include a minimum of 15 injection	• It's not necessary to include health care practitioners ("HCPs") as participants in a validation study of a product intended for self-administration. If it's helpful to elicit feedback from HCPs on the device and IFU, this group can be included in formative studies. If this group in NOT determined to be one that would use the device in commercial use, they need not be included in the summative study. • If the company has determined that users must be trained in order to safely use the device (possibly through the formative testing process) then untrained users need not be included in a summative study. Only if it is anticipated that some users will receive no training, then the test participants in the validation testing should include a corresponding subset of untrained users. Thus, untrained users would be a subset of the minimum 15 participants per distinct user group instead of requiring both 15 trained and 15 untrained per distinct user group.	• Formative studies and risk analysis are used to determine if mitigations such as training are necessary to address unacceptable use errors. • The draft HF guidance appropriately states that training provided to participants in validation studies should approximate the actual training that users will receive. If potential study participants have experience with the specific device that is being tested, then there will be a potential difference in performance and these individuals should be excluded. Injection experienced and injection naïve participants should only be required in summative studies if these groups have use characteristics that are distinct from other user groups.

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		experienced and 15 injection naïve participants per distinct user group.
		• Feedback from a CDER protocol review included a requirement to add a physician user group to an injection device study when the company had proposed trained and untrained nurses.
		  ○ The company provided evidence that physicians, while qualified, almost never performed the injection. CDER insisted on adding a physician arm in equal numbers to the nurse group, doubling the size of the study.
		• In another example, CDER recommended the validation study include participants with specific health impairments (e.g. vision impairment, hand impairment); however, the CDRH draft human factors ("HF") guidance states that the selected user groups must be defined based on critical differences in capabilities without specifying health impairments which must
			• While the current CDRH guidance provides factors to consider when selecting specific user groups, it appears that FDA may not agree with how these factors are applied. Therefore, it would be helpful for FDA to provide additional guidance on how it applies these factors when evaluating the selection of specific user groups for HF studies.
			  ○ This may include providing additional factors that should be analyzed or providing examples of how FDA has analyzed these factors in certain instances.
			• In addition to providing general guidance regarding how to analyze whether individuals with specific impairments should be included in the user group, it would be helpful if FDA provides feedback in its comments on summative HF protocols as to why it has determined that specific impairments should be included and criteria for inclusion in the user group with respect to a specific protocol.	

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		be evaluated. Guidance was not provided on whether participants must be screened for the impairments or if the participants can self-identify.		
2. Labeling	During review, FDA has requested modification of labeling that has been successfully validated in the summative HF study.	• Less than one month before the PDUFA approval date, CDER comments on a patient IFU for an injection device included significant wording revisions to all instruction steps, and required the addition of two new figures and revisions to two additional figures. The IFU had been validated in two HF studies and was aligned with a user FMEA. All comments and figures except one were incorporated after an urgent design review meeting. CDER's remaining revision instruction was appealed based on HF study results, but the appeal was denied.	• Manufacturers should not be required to implement changes to an IFU which meets regulatory requirements and which has been appropriately validated in HF studies unless FDA provides a scientific basis for its determination that the wording of the IFU, as submitted, would be reasonably likely to cause patient harm. Otherwise, FDA may request the change but should allow manufacturers to utilize the labeling as submitted. • CDER review of IFUs should preferably occur early in the development process (e.g. during CDER review of the summative HF protocols) so that IFU wording and figures can be finalized with complete review of justifications and consideration of alternative options. If CDER is unable to provide a review during the development process or it feels it is necessary to re-review the IFU during the review cycle, it would be preferable to receive CDER's IFU comments early in the	• The design of device labels and instructions begins early in the device development process. The labels and instructions are iterated during device development as the device concept evolves and as a result of device prototype testing, human factors testing, and design risk evaluation. The final validation as to the acceptability and adequacy of the labeling for device labels and instructions occurs during the validation study, which is completed before submission. • Some FDA requested IFU changes could negate the HF validation and could require a new validation study. Some requested IFU changes may be adequately evaluated by a risk analysis or an IFU comprehension study without the need for a subsequent HF validation study.

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			review cycle so that there is sufficient time to prepare and submit a response without causing extensive delays in the review cycle.	
3. "Actual use" Studies	CDER has requested collection of usability information during clinical trials in addition to conducting separate human factors validation studies.	• CDER has requested "real-life actual use data to support marketing approval" [clinical trial] and "usability of your product presentations during the clinical trial" but has not provided examples of how to do this or the outcomes it will require/agree with. These requests were made without reviewing the planned summative HF study plan (simulated use). • Also, during an End of Phase 2 meeting with CDER and CDRH, CDRH expressed concern with assessing clinical and simulated use endpoints in the same study because it could overly complicate study. CDRH recommended that simulated use testing be separated from clinical trials.	• Human factors studies are the most rigorous means to assess usability as they are conducted with experienced, human factors specialists that are experts at identifying use errors. Simulated use human factors studies are structured to allow qualified personnel to observe and document device use and use errors. • Manufacturers should not be required to collect usability information during clinical trials as this information will be collected in separate human factors validation studies • Documentation of a gap analysis of adequacy of simulation compared to actual use will ensure all anticipated use-related risks can be validated without the need for an actual use data collection.	• Clinical trials are not normally necessary to establish the reliability or usability of injection devices. As the safety and effectiveness of the drug have already been established during the Phase III studies, possibly supplemented by BE studies with the device, drug effectiveness is not a required outcome of HF studies. The CPC considers bench testing along with simulated use summative usability studies as sufficient to establish the reliability and usability of the delivery device. If an open label extension of the Phase III trial is required due to a unique element specific to the delivery device, the objective of the study should be to collect and investigate any device related adverse events. Although some of these investigations may establish use error as the cause or contributing to the failure, this is not and should not be considered a HF study. Any information

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				gathered during the investigation will be analyzed and considered for mitigation based on a risk as is done with any events collected during clinical investigations. Most importantly, the identification of use errors during clinical use will not be considered as evidence that the simulated use studies were not effective in validating the usability of the product. • Clinical trials for injection devices are conducted in a controlled manner such that clinical outcomes are the result of normal intended device use. It's typically not appropriate to allow patients in clinical trials to complete tasks that could result in use errors. Adverse events and complaints from clinical trials are evaluated for potential relationship to the injection device; however, patterns of use failure or use difficulties usually cannot be identified by adverse event or complaint reports alone. It's necessary to conduct separate HF evaluations where trained observers watch the participants completing specific tasks with the

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				device to uncover patterns of use failure and use difficulties. We agree with CDRH that simulated use testing should be separated from clinical trials.
4. Actual Use vs. Injection Pads	CDER requested placebo injection for a HF validation study	• CDER requested the autoinjector summative HF study involve placebo injection and not the use of injection pads. • Another review division asked for justification as to why the use of injection pads instead of placebo injections would be appropriate for a summative autoinjector HF study.	• Actual use in patients should not be a general requirement. It only should be required when the device use or use environment are poorly understood or if injection pad study participants exhibit behaviors which indicate the study is not an adequate simulation.	• Injection pad studies have historically provided adequate realism to allow discovery of use errors and evaluation of risk mitigations. Since there are no planned injections, these studies have the added benefit of minimizing the risk to subjects. • According to the CDRH draft guidance, injection devices typically should not require placebo injection during the HF validation study because they generally don't have particularly challenging or poorly understood use or use environments. • The CDRH draft guidance states: "Due to the nature of some types of device use or use environments that may be particularly challenging or poorly understood, it might be necessary to validate a device under conditions of actual use in a clinical study."

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5. Formative vs. Summative Study Objectives	CDER recommended evaluating complete device failure in the summative HF study.	• CDER recommended including a task to simulate complete device failure in the summative HF study.	• If the IFU includes specific risk mitigation tasks, then it may be appropriate to evaluate them in summative studies.	• User reactions to non-standard scenarios (broken device, empty device, piece missing, etc.) are evaluated in studies during development in order to enhance the design and/or user interface and create user instructions. The final instruction can be evaluated in formative studies to establish that they are readable and understandable (comprehension studies). However, the summative study is conducted to establish that the device can be used without patterns of preventable use errors, and requires the device to operate normally.
6. Injection Device Changes	CDER expects risk assessments to determine the need for subsequent HF studies, but has not provided a decision framework.	• CDER has stated consistently that devices used in validation studies should represent the final design which includes instructions for use and any other labeling materials. • CDER expects risk assessments to be conducted for any device modifications to determine if new functional and/or simulated use risks are identified. If so, CDER agreed that subsequent	• The evaluation of proposed changes to marketed injectors or the development of new devices based on a previous platform should include a risk assessment. • CPC believes that the design change assessment should be consistent with the FDA Guidance, Deciding When to Submit a 510(k) for a Change to an Existing Device (1997). Specifically, topics B6 and B8.3 provide a good framework for this evaluation:	• Injection devices are iterated for various reasons including consumer preferences, manufacturing productivity improvements, device feature improvements, and mitigation of customer complaints. • It's common for new injection devices to be based upon a previous device "platform" which incorporates device modifications to adapt it to a new dose or intended user group.

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		bench testing and/ or HF validation studies might be needed. However, a decision framework for evaluating changes to the device, intended users or use environment has not been provided.	○ B6 - Is it a change in ergonomics of the patient/user interface? ○ B8.3 - Do results of design validation raise new issues of safety and effectiveness? • If the above assessment indicates the potential for new use errors, then those use aspects should be evaluated via HF studies. Aspects of the previous device version or platform that were not changed should not require another HF evaluation.	• It's common to limit the testing to the change implemented and not revert to a full evaluation if change impact and risk analysis are documented.
7. Human Factors study results supporting a delivery device change in a NDA/BLA supplement, should not be considered "clinical data" with respect to PDUFA V review goals and fees	A prior approval supplement for a design modification to a prefilled injector may be supported by design validation studies including HF studies. These studies may involve "subjects" for the purposes of confirming usability of the device but typically do not include active drug or injections into subjects, or raise new questions as to the safety or effectiveness of the drug itself.	• No examples to date	• Post approval changes involving device changes which are supported by HF studies should be viewed as manufacturing changes consistent with device design changes reviewed as Special 510(k)s.	• While these HF studies support the device constituent part of the combination product, they do not constitute clinical data in the context of drug safety and efficacy as assessed in human subjects. Therefore, these data should not be viewed as supporting an efficacy supplement that includes clinical data. Rather the classification of the submission should be as a manufacturing (and potentially labeling) supplement.