Recent FDA Requests to Validate User Interface Specifications for Drug and Biologic-led Combination Products

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1. BACKGROUND

Human Factors Engineering is an essential part of the combination product development process with a goal of delivering a product user interface that can be used safely and effectively by the intended users in the expected use environments. International and US regulations, standards and health authority guidance documents[1,2,3,4,5] provide a roadmap for design considerations and best practices in the development process of a combination product, including establishment of user requirements and design requirements, and methods for formative usability testing, use-related risk management, and human factors (summative) validation studies.

One aspect of this work is prospectively defining design input requirements to ensure the product will be able to be used as intended. User interaction-based design requirements for injection devices (intended to deliver a drug or biologic) can include attributes like cap removal forces, dose dialing torques, and plunger depression forces. These requirement limits are typically based on user capabilities and are established through user testing or analysis of published literature. Verification testing subsequently confirms the design performs within these limits when tested in the lab. Design outputs such as user interface specifications are established for manufacturing based on these design input requirements as well as an understanding of the final design, sources of manufacturing variability, and required controls.

2. RECENT AGENCY QUESTIONS ON SPECIFICATION VALIDATION

CPC member companies have recently experienced FDA requesting that combination product manufacturers demonstrate how they have "validated" device user interface specifications in the intended user population(s). In some cases, these requests included validation of specifications in users at the extreme end of the labeled use range (e.g., 5th percentile of the youngest pediatric users). The timing of receipt of such requests by CPC member companies has varied from IND phase through midway through review of a marketing application and/or supplement.

3. PROBLEM STATEMENT

CPC member companies are not aware of any Agency guidance or recognized consensus standards that describe this expectation to "validate" device user interface specifications. Further, FDA requests for evidence of how specifications have been validated appear to be a new request for the premarket review of both combination products and traditional medical devices.

According to ANSI/AAMI HE75 and current industry best practice, anthropometric design considerations for medical devices should accommodate users from a 5th percentile female to a 95th percentile male, which theoretically covers more than 90% of the entire user population (this design guidance is provided primarily to accommodate the physical size of people in the dimensional design of devices). Notably, the

[1]Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (FDA, CDER/CBER/CDRH/OCP, 2016).
[2] Applying Human Factors and Usability Engineering to Medical Devices (FDA, CDRH, 2016)
[3]IEC 62366-1:2015, Application of usability engineering to medical devices
[4] ANSI/AAMI HE75:2009/(R)2018, Human factors engineering - Design of medical devices
[5] 21 CFR Part 820.30 Design Controls

guidance recognizes that although designers ought to accommodate the widest possible range of users, it is generally infeasible to consider the entire user population. Consequently, ANSI/AAMI HE75 implies that manufacturers should understand their users' capabilities and have a user-based justification for their product user interface requirements and associated specifications; however, the standard does not mention "validating" user interface specifications once the design space / anthropometric range has been selected and supported.

CPC member companies are concerned with the recent Agency questions on validation of specifications for combination products. Specifically, we are concerned that:

- The Agency has not fully defined their expectations for how combination product manufacturers should demonstrate that specifications have been "validated."

- These requests appear to be new and not associated with any Agency regulation, guidance, or policy statement.

- These requests appear to be specific to CDER-led combination product reviews and not asked as part of traditional CDRH-led medical device premarket reviews (e.g., 510(k), de novo)

- The text of the requests received seems in some cases to imply that combination product manufacturers should use usability testing to "validate" specifications across the full user population capability range. This implication is particularly problematic because usability testing is not intended to "validate" specifications across the entire range of possible performance for each product attribute; rather it is intended, during development, to identify and aid in the identification and control of use-related risks associated with critical product use tasks and then to validate the product use interface with people who are representative of the intended users.

- The text of the requests received seems in some cases to ask that sponsors design devices to accommodate a subpopulation of a subpopulation of the intended users instead of setting device specifications broadly to suit the entire intended user population. Specifically, multiple Agency requests in the case studies noted below have been to set specifications based on the capabilities of 95% of 12-year-old female users, which represents a subpopulation of adolescent patients, who are already a subpopulation of the entire user population.

The case studies below provide four specific examples of recent Agency feedback received by CPC members on this topic.

4. CASE STUDIES HIGHLIGHTING A RANGE OF EXPERIENCES

- Case study 1:

    - For one CPC member company, FDA requested *'verification that the indicated specifications are appropriate for adolescent use'*. Supportive data from user studies and strength data from published literature were provided by the company. FDA then requested justification based on the strength of the weakest patients of the population, defined by FDA as the 5th percentile of 12-year-old patients. Ultimately, the review by CDRH identified deficiencies in that the data from literature studies did not validate some of the device specifications. The

product was approved with labeling prohibiting product use by pediatrics, allowing administration of the product to pediatrics by adult caregivers and HCPs only.

- Case study 2:
    - A second company received the following request from FDA: "*From the device validation perspective, you should provide a justification or data validating the limits of the proposed device specifications to ensure that a majority of the intended user group (adults and pediatric patients) can meet the proposed specification. In accordance with HE75:2009 this evaluation would include considering the weakest 5th percentile user group when establishing the specification.*" The CPC member company interpreted this request to refer to the "weakest 5th percentile" of the entire user population rather than "5th percentile of the weakest" user group, as noted in Case Study 1.
- Case study 3:
    - A third CPC member company received the following request from FDA: *"You provided a statement of justification for each EPR in your meeting package. From the information provided, we cannot yet determine if the proposed EPR specifications for cap removal force, actuation force and needle cover lock override force are appropriate for the intended user group. While your justifications point to Human Factors studies and literature sources, they do not provide enough detail to make a determination. The data used to validate your specifications should ensure the postures and motions are representative of each EPR and analyze that data assuming your weakest (5th percentile pediatric females of the youngest age you identify as appropriate to self-administer) users per HE 75 to validate upper limit specifications. Please ensure you clearly indicate the age limit for self-administration with your device and use data on the weakest 5th percentile females of that age to validate your EPR specifications."*
- Case study 4:
    - A fourth CPC member company was requested by FDA to provide data validating the specifications across the entire intended user population with no requirements on weakest user groups or what fraction of the population should be accommodated.

5. CPC REQUESTS FOR FDA

After consideration of the questions that the combination products industry has recently received related to validation of specifications, CPC respectfully requests that the Agency:

- Clarify expectations for how combination product manufacturers "validate" product user interface specifications as part of the design control process.
- Confirm that the Agency's expectations relate only to the process of selecting design input requirements and the practice of using published or self-generated human performance data for the entire intended user population as part of that selection process.

- Confirm that the Agency is not expecting combination product manufacturers to use Human Factors Validation testing to “validate” the selection of product user interface design specifications across the range of capabilities existing in the intended user population.