Integrating FDA's new cybersecurity guidance into medical device human factors engineering processes

Bold Insight

Kaitlin Stinson

How does a manufacturer ***demonstrate compliance*** with the HFE-related recommendations in this new guidance?

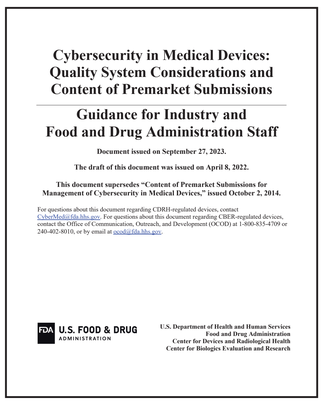
The guidance covers labeling requirements and testing cybersecurity risks but **lacks implementation steps.**

Based on our experience, we recommend integrating the following steps into design controls to ensure compliance.

The steps below follow an ideal early-stage implementation but can be adjusted based on the device's development stage, circumstances, and constraints.

BACKGROUND

Integrating connected medical devices into healthcare introduces cybersecurity risks. The growing use of networked technologies in medical devices highlights the **need for strong cybersecurity to ensure safety and functionality.**



Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 27, 2023.

The draft of this document was issued on April 8, 2022.

This document supersedes "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices," issued October 2, 2014.

For questions about this document regarding CDRH-regulated devices, contact CyberMed@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

In response, the FDA has issued a final guidance, **Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions**, intended to:

1. Promote consistency
2. Facilitate efficient premarket review
3. Help ensure that marketed medical devices are sufficiently resilient to cybersecurity threats.

In the guidance, the FDA provides recommendations to the industry regarding cybersecurity device design, labeling, testing, and the documentation they recommend be included in premarket submissions for devices with cybersecurity risk.

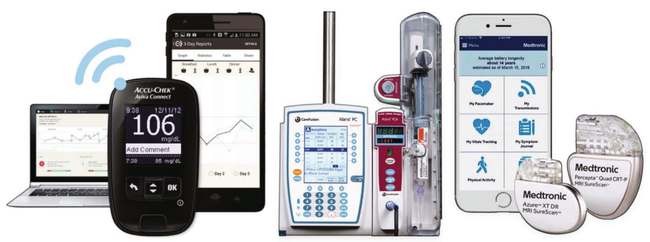


Fig. 1: Three examples of software-driven medical devices.

Gordon, W.J., Stern, A.D. Challenges and opportunities in software-driven medical devices. Nat Biomed Eng 3, 493–497 (2019). https://doi.org/10.1038/s41551-019-0426-z

This guidance document applies to devices with cybersecurity considerations, including devices with a device software function or that contain software (including firmware) or programmable logic.

1 DESIGN & DEVELOPMENT PLANNING

☐ Risk Management Plan:

Include content in the Risk Management plan that specifies:

- The process to identify use-related cybersecurity risks.
- How to mitigate these risks in, at a minimum, the product's labeling.
- Mitigations must be tested via human factors (HF) methods to ensure their effectiveness.

☐ HFE Plan:

Include content in the HF Plan about:

- The process to ensure use-related cybersecurity risks are identified through the use-related risk analysis (URRA) process.
- How risks will be evaluated via analytical and empirical usability testing methods.
- Which of these risks (i.e., all or only those associated with critical tasks or serious harm) must be tested in HF Summative Validation.

2 DESIGN INPUT

☐ Cybersecurity Risk Assessment:

Identify use-related cybersecurity risks during the Cybersecurity Risk Assessment.

- To help manage traceability and enhance the visibility of adherence to the guidance, employ a categorization scheme to label each risk type to easily identify which risks are use-related and specify the labeling requirement(s) used to mitigate each risk.

☐ Task analysis:

Ensure that task analysis covers all use-related cybersecurity use scenarios, workflows, and tasks associated with device use.

☐ Use/Application FMEA & URRA:

Evaluate use-related cybersecurity risks in the Use/Application Failure Mode and Effects Analysis (FMEA) to ensure adequate mitigation measures are implemented in the user interface's design and labeling. Document these risks in the Use-Related Risk Assessment (URRA).

☐ User interface requirements & specifications:

Develop user interface requirements and specifications with the input of HF team members.

3 DESIGN OUTPUT

☐ User interface design:

Product labeling (e.g., device labels or markings, IFU, training) must be implemented to adequately mitigate use-related cybersecurity risks in addition to other user interface design mitigations implemented based on the output of the u/aFMEA.

The labeling should be designed to communicate to users the relevant device security information so that users can take appropriate actions to manage those types of risks that may enable their ongoing security posture or an organization's overall state of cybersecurity readiness, thereby helping ensure a device remains safe and effective throughout its lifecycle.

To ensure that labeling is implemented effectively, consider the following when developing labeling strategies:

- Review the examples in the guidance document to determine applicability to the medical device under development.
- The depth of detail, the exact location in the labeling for specific types of information (e.g., operator's manual, security implementation guide), and the method to provide this information should account for the intended user of the information (e.g., is the user a patient or caregiver with limited technical knowledge? or is the user a hospital technician with significant technical knowledge and experience?).

☐ Usability test plans/protocols:

Include tasks associated with use-related cybersecurity risks in formative usability studies to ensure risk-mitigating controls are designed effectively, that labeling controls are understandable, and that users have the information they need to take appropriate actions to manage these risks.

4 HF VALIDATION

☐ HF Summative Validation study:

Include use-related cybersecurity critical tasks in the HF Summative Validation study to validate the controls mitigating these types of risks. Performance-based and knowledge-task evaluation methods should include labeling implemented to control for use-related cybersecurity risks.

☐ HFE report:

Document the process used to appropriately identify, mitigate, and test use-related cybersecurity risks during the HFE process throughout the device's development lifecycle in the HFE report.

CONCLUSIONS

Although the FDA's guidance focuses specifically on the recommendation to implement and test labeling controls to mitigate use-related cybersecurity risks, the steps listed above go beyond this type of control strategy to include non-labeling-based controls within the medical device's user interface design.

This recommendation is based on the 2016 FDA HFE guidance document, which indicates that labeling, or information for safety, is the least effective risk mitigation control strategy when used alone and based on HFE best practices. Furthermore, since the FDA has released guidance on this topic, they will likely have use-related cybersecurity risks at the top of their minds when reviewing HF submissions for devices with these types of risks. The plan we've outlined maximizes mitigating these types of risks to reduce them to be as low as possible. Lastly, the approach presented here provides a comprehensive strategy that ensures cybersecurity risk management is embedded into the design-controls process and that human factors engineering is part of the process.

Practical applications of an IFU scorecard

James Kershner | Allison Paul | Hailey Fehrenbach

70%

of HF practitioners cite **IFU design & content** as one of the **most common drivers of FDA requests.**

10+

Guidance sources that may be referenced throughout IFU scorecard reviews

1

IFU-related guidance is **all in one spot** to ensure everything is captured

What is an IFU Scorecard?

A **framework** for HF practitioners to **evaluate their IFU** and understand **areas to improve** based off regulatory guidance. This work includes **prescriptive and directional recommendations** on the content and format, and identifies **where guidance is or is not met.**

IFU scorecard process

Review IFU against guidance in scorecard

Letter of the Law

The extent to which the labeling adheres to the **literal text** of the requirement in the reference documents.

Spirit of the Law

The extent to which the labeling adheres to the **intent of the requirement** (e.g. best practices in user-centered design).

Compile scores from all reviewers

Analyze findings between reviewers

Implement changes to IFU

Example #1

Step 8 **Close one (1) nostril.**

- With your free hand, use a finger to gently press on one (1) nostril to close it (see ***Figure 8***).
- Continue to breathe normally through your mouth.

Figure 8

Step heading label
Step headings should be noted as "Step 1, Step 2, etc."

intent: Clarity
(CDER/CBER 2019)

Figures use numeric labels
Visuals should be labeled alphabetically in bold type (such as Figure A, Figure B, etc.)

(CDER/CBER 2019)

Example #2

Step 12 **Confirm dosing is complete.**

- You have successfully received a full 24-hour extended release dose if you have:
  - » Used one (1) device.
  - » Sprayed device one (1) time into one (1) nostril (see ***Figure 13***).

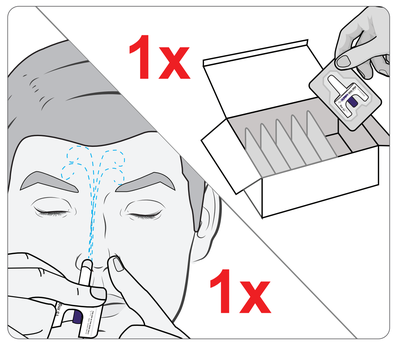


Figure 13

Appropriate font used
Sans-serif font should be used for all text in the IFU, with font size no smaller than 10 points.

Intent: Clarity
(CDER/CBER 2019)

Disposal info not present
IFU ends at Step 12. Disposal info should be described under: Disposing of [Drug Name].

Intent: Safety
(CDER/CBER 2019)

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> **This would never happen in my hospital**

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THE IMPORTANCE OF ADJUSTING YOUR SIMULATED-USE ENVIRONMENT BASED ON HCP PARTICIPANT FEEDBACK

Kaitlin Carter, Director • Coleen Long, Director • Jonathan Carlson, Collaborator

Early formative studies, although they usually involve smaller sample sizes, can reveal important indications of study artifacts. These indications may be amplified in larger validation studies that include health care practitioners.

Considerations for study design and simulated-use setup can help decrease the incidence of study artifacts. This approach increases the validation study's acceptability during FDA submission by ensuring that the usability data produced is both complete and accurate.

Test plan
Build a usability test plan starting with a base of best practices and prior experience.

Formative studies
Conduct formative studies and monitor for trends in study artifact, asking for participant feedback as time allows.

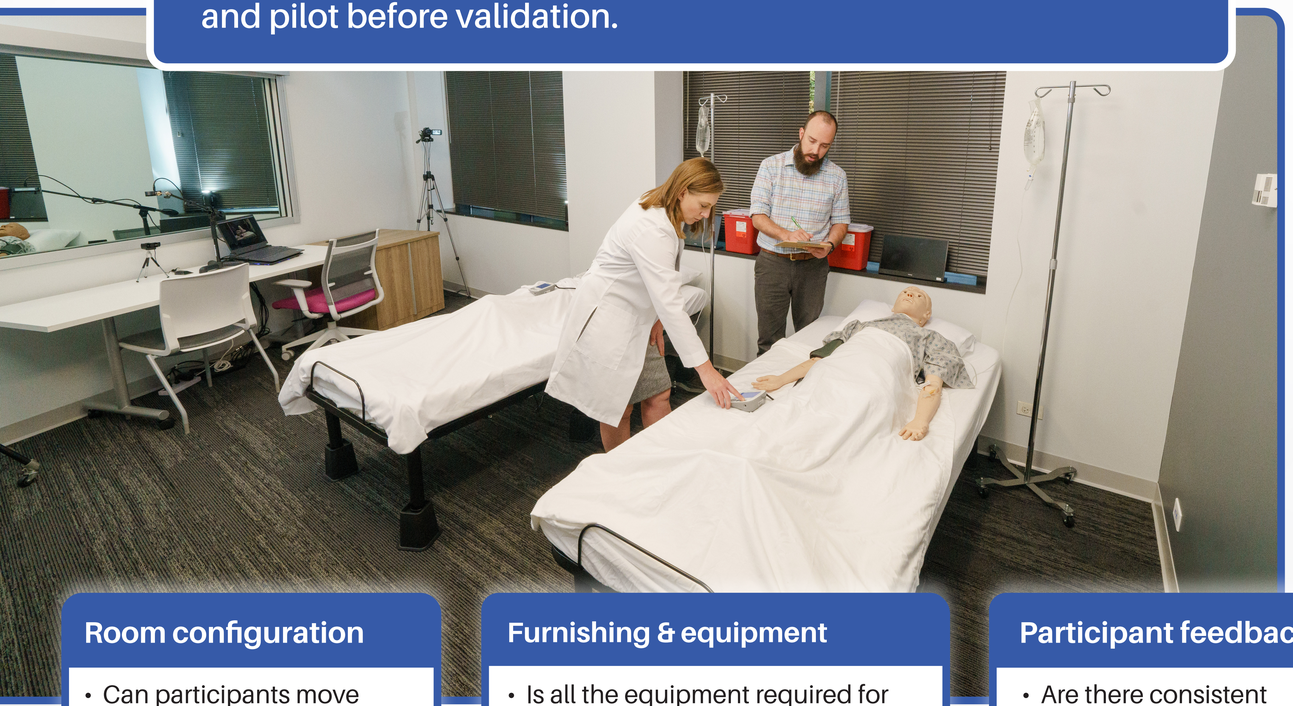
Validation plan
Integrate observations of study artifact and and feedback while planning the validation study.

Live pilots and pre-validation
Evaluate study changes based on identified study artifacts prior to formal validation.

Validation studies
Conduct validation studies informed by the findings surrounding study artifacts.

Repeat
Compile all learnings from the completed studies to build on existing best practices to support future product validation.

In our 20 year history of usability study participant feedback, there are key components of simulated use to listen for, update, and pilot before validation.



Room configuration
- Can participants move freely?
- Is there too much or too little space in between furniture?
- Is it distractingly different from their normal work set up?

Furnishing & equipment
- Is all the equipment required for the workflow present (i.e., sinks for handwashing)?
- Can participants access telephones to call for support?
- Are furnishings consistent with the intended-use environment (i.e., home environment)?

Participant feedback
- Are there consistent themes on what needs to be updated?
- Is there variation depending on facility type?

CASE STUDY

What happens when you need to test multiple variations of device use within one session?

Pre-summative testing revealed a high incidence of test artifacts due to our attempt to evaluate multiple modes and alarm states of a medical device in a way that did not align with its actual use with a single patient. Participant feedback during follow-up questioning and root-cause probing helped us better understand these test artifacts.

Based on the findings from pre-summative, the following changes were made for summative:

- The concept of caring for multiple patients was introduced.
- Additional personal and clinical context was provided with each simulated-use scenario to fully flesh out the test environment and reduce the pressure of feeling tested.
- Bedside simulated environment fidelity was increased.

- A **30% reduction** in test artifacts when evaluating alarm states.
- A **50% reduction** in test artifacts related to room configuration.

PLANNING AND OPERATIONAL CONSIDERATIONS FOR CONDUCTING

Human factors studies with cadavers and tissue samples

Patrick McCormack
Ryan Carney

Bold Insight

INTRODUCTION

A primary goal when executing a simulated use human factors study is to **create an environment that is as realistic as possible.**

For certain stimuli (e.g., surgical tools), **to achieve the necessary level of realism**, it may be necessary to **involve human or animal tissue samples.**

This poster addresses the **complexities of conducting realistic human factors research with cadaveric and animal tissue samples**, highlighting key logistical, ethical, and technical challenges.

PREPARATION

Choose the right facility

- Traditional market research facility can work for studies involving animal tissue but often lack accommodations needed for cadaver studies.
- "Wet" labs are designed specifically for conducting research and training involving human cadavers.
- They have proper processes and accommodations for receiving, storing, and handling cadaver specimens.
- They are also likely to provide changing rooms and personal protective equipment (PPE).

Logistics of acquiring tissue samples

- Coordinate with your client and/or external vendor to ensure sufficient time is budgeted for acquiring and receiving samples.
- Coordinate to ensure that as few cadavers are required as possible.

  Example: If conducting an orthopedic procedure, use both of the specimen's knees.
- Work with the facility on how tissue samples should be stored.
- Keep in mind that some types of tissue samples have a short shelf life.

  Example: Pig eyes may only be usable for a few days.

Ethical consideration

If working with an external vendor to source human cadavers, ensure they have the necessary license or certification, which vary by location. You want to be certain that any cadavers used in your studies are ethically sourced.

Add realism to the session

- Consider what elements can be added to simulated use setup simulate living bodily functions with your tissue samples.

  Example: Manually pumping blood through a pig heart when testing a cardiac surgical tool.

  Example: Creating negative pressure behind pig eyeballs when testing an ophthalmologic injector.

  Example: Using a CPAP machine to inflate human lungs when testing a bronchoscopy tool.

Prepare your team

- Ensure all team members complete any client, facility, or quality system training.

  Example: Bloodborne pathogen training, hazardous material training, and radiation exposure training.
- Assign and document what roles each team member (internal team and client team) that will be acting as members of surgical team will have.
- Review with the team what they can and cannot do during sessions and ensure that they are not interfering with any critical use tasks.

DATA COLLECTION

Account for time needed to prepare the specimen

- With minimal training, human factors researchers can handle and prepare animal tissue samples.
- Be sure a trained expert is on-site to handle and prepare human cadaver samples.
- Mishandling could impact validity of data.
- Cadavers can take days to thaw and hours to prep before a session.
- Ensure proper placement, positioning, and securing of the tissue, cadaver, or organ.

  Example: If using a pig heart, ensure it is correctly oriented in the manikin chest cavity.

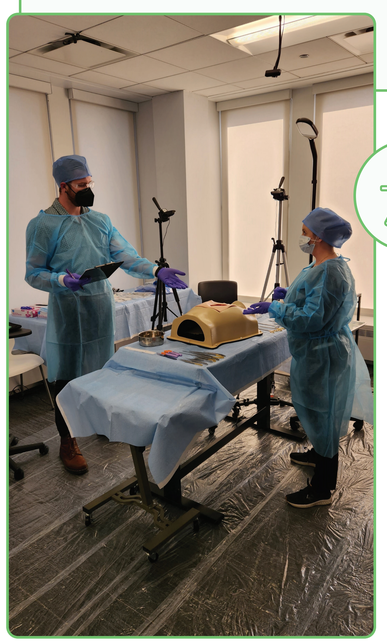
  Example: If using portions of a cadaver, consider that only a portion of the cadaver may be used and will not have the same weight as a living patient.

Ethical consideration

Make sure the use of cadaver and animal specimens is clearly detailed in all recruiting and consent documents.

Wear the proper gear

- When working with cadavers, the proper PPE is necessary to protect you, your research team, and your participant.
- At a minimum:
  - Scrubs (top and bottom)
  - Foot/shoe covers
  - Mask
- Depending on the facility or procedure, head covers and surgical gowns may be required.
- Depending on the situation, you may also need:
  - Gloves (for those directly interacting with the cadaver)
  - Lead vest (if x-rays/imaging being used)
  - Safety glasses (if aerosolized biological matter is possible)
  - Vick's VapoRub under the nose (if specimen odor is present)



Set up your study equipment

- Position your cameras and other study equipment to not interfere with the surgeon's task-completion.

Ethical consideration

Remind the participant that the cadaver was once a living person and should be treated with the same care and expertise that they would use with a living patient.

ANALYSIS AND REPORTING

Acknowledge any specimen limitations or artifacts

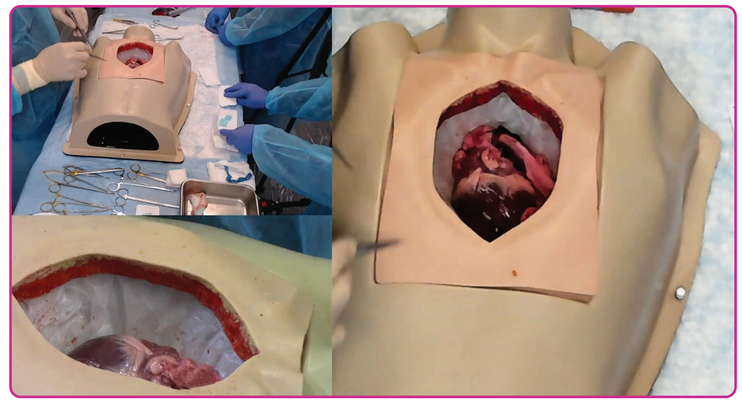
- While animal and cadaveric tissue brings a greater level of realism to a study than using a manikin, it introduces certain test artifacts.
- Be sure to identify if there were any traits or conditions with the cadaver that could impact your test results.

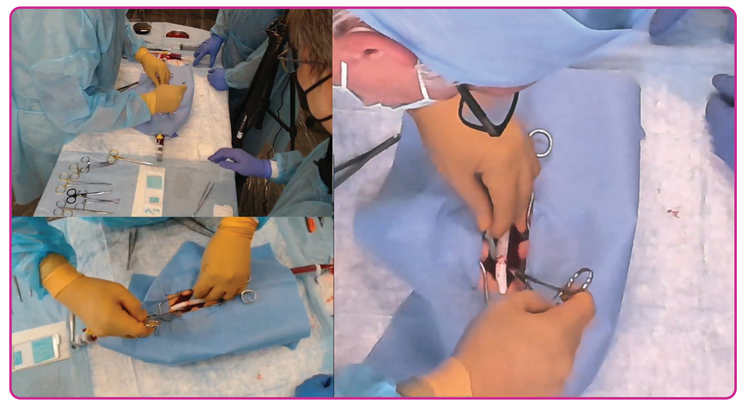
  Example: The age of specimen.

  Example: If the specimen had an illness that could overly impact the specimen tissue quality.
- Be sure to identify ways in which cadaver/animal tissue is different from living tissue and how they may impact your test results.

  Example: Tissue may not be as elastic and may damage easier than regular tissue.

  Example: Refrigerated tissue will be colder than warm living tissue, which could impact participant's dexterity and performance.





Ethical consideration

Be very judicious of omitting data. While it is unavoidable at times, keep in mind that the remains of a human or animal were part of your data collection.

If using a human cadaver, this was their final wish. The families of the deceased may ultimately receive a letter with a list of how their loved one's remains were used for scientific research.

As such, every effort should be made to ensure the specimen is not wasted and is, in fact, used for research purposes.

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Navigating Sensitive Health Topics and Tasks in Human Factors Testing:

STRATEGIES FOR RESEARCH VALIDITY AND PARTICIPANT WELL-BEING

Bold Insight
Kaitlin Stinson

Genentech
Chris Valek

HIGH LEVEL SUMMARY

This poster presentation offers strategies for Human Factors (HF) researchers approaching sensitive research topics, emphasizing the balance between normalizing the process and acknowledging the stigmas that may accompany them.

INTRODUCTION

Sensitive health topics are topics that could hurt participants' reputation or cause negative repercussions if their data were released.

However, guidance is limited on working with user groups with:

- stigmatized identities,
- medical conditions, or
- other vulnerable populations.

Heightened importance should be taken when these characteristics are part of the objectives of the study.

Before conducting research, researchers must understand what additional considerations they should follow to ensure participant comfort, respect for the subject matter, and assuring data quality.

CONCLUSIONS

Conducting HF testing on sensitive health topics requires a nuanced approach to effectively and empathetically work with stigmatized or vulnerable populations.

Given the limited guidance available, researchers must take extra precautions to prioritize participant comfort, respect the sensitive subject matter, and ensure the integrity of collected data.

STRATEGIES

Strategy 1

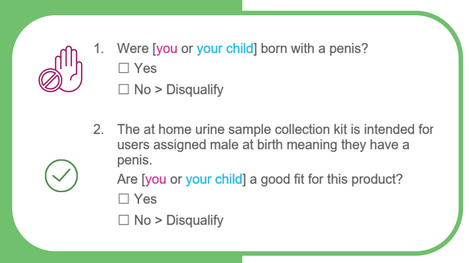
Engage in **thorough background research relevant to the study focus.**

For example, if testing a product intended for individuals living with HIV, gaining a solid understanding of contemporary experiences and challenges faced by this community is essential.

This knowledge **enables researchers to approach sensitive topics with empathy and authenticity**, enhancing participant comfort and improving the overall quality of the data collected.

Strategy 2

Considerations when engaging and recruiting participants.



Above is an example of insensitive vs. sensitive framing of a question.

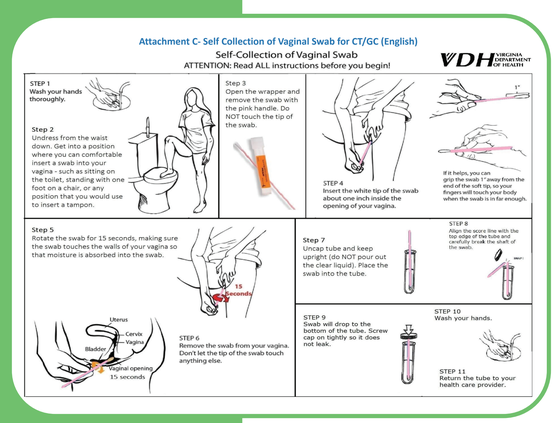
A carefully worded screener utilizing clear, yet gentle language can effectively inform participants about the session's nature while empowering those who may be uncomfortable to decline.

Investigate **what words / phrases that you should and should not be using** to avoid offending potential participants.

When it comes to screening eligibility for studies on sensitive health topics, the best practice to only ask for information necessary to determine eligibility is of increased importance to avoid unnecessary disclosure of private sensitive information.

Strategy 3

Treat the topic **seriously but know when to take a lighthearted approach** to set participants at ease.



For example, during the consent process in which participants read that they will simulate providing a urine sample during the test session, the moderator can take a more humorous approach to the consent process by acknowledging what may be perceived as a funny task to perform during testing.

Also, **be upfront and talk directly about how the test stimuli may be confronting and cause feelings of embarrassment or awkwardness.** This will set the tone for the test session; build rapport between the participant and the moderator, and help to reduce awkward moments during testing.

The dilemma of task prompt wording in HF validation:

HISTORY, CHALLENGES, AND STRATEGIES FOR SUCCESS

INTRODUCTION

Designing effective task prompts for usability testing is a critical yet challenging aspect of medical device evaluation.

Regulatory guidance and industry best practices emphasize the importance of prompts that reflect real-world scenarios without leading participants toward specific actions. However, **the balance between avoiding leading language and maintaining clarity can be difficult to achieve.**

This presentation will explore the history, challenges, and best practices for task prompt phrasing, highlighting the implications for medical device safety and usability.

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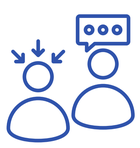
HISTORY



The FDA has identified **overly leading task prompts as a recurring issue with manufactures.**

Manufacturers either:

1. Go straight into validation, don't discuss this with FDA ahead of time, and get comments in the submission period.
   or
2. They follow FDA strict guidance and end up with overly vague task prompts.

CHALLENGES

Overly leading task wording results in an unrealistic task for participants in which they are directed to a specific feature or function to address the simulated scenario.

Using exact FDA language may be overly vague.

Overly vague task wording results in participants being tested on **medical knowledge**,

rather than on

specific **features or functions of the device.**

STRATEGIES FOR SUCCESS

1 Determine the sweet spot to ensure adequate real-life context & applicability to the device

Clearly articulate the scenario that the participant is walking into with enough granularity or detail to ensure that a specific feature or function is required to address it and/or is being evaluated. Example: "I'd like you to imagine that..."

2 Negotiate & collaborate with regulatory authorities

- **2a:** **Propose** language with rationale for specific task prompt phrasing.
- **2b:** **Negotiate** final task prompt phrasing to address regulatory concerns.
- **2c:** **Set expectations** for results regarding artifacts and/or other suboptimal outcomes.

3 Detailed HFE report

- **3a:** Include a detailed discussion of the development of task prompt wording.
- **3b:** Analyze and discuss the extent to which the study results match the expectations from 2c.

Note: These strategies do not account for internal FDA initiatives in respect to consistency among similar products. (First to file sets precedent. Then, the FDA mandates it for all others in that space.)

	Too leading	Too Vague	Balanced
Case Study 1: Rescue Autoinjector	"Demonstrate how to administer the medication using the autoinjector." **(Assumes the correct action.)**	"You encounter someone having an allergic reaction. Show what you would do." **(Scenario not tied to device.)**	"Imagine your friend is having a severe allergic reaction and needs your help to take their medicine. Please proceed as you would in real life to help them." **(Provides context without being overly directive, allows natural decision-making.)**
Case Study 2: Insulin Pump	"Imagine you need to suspend insulin delivery for 2 hours. Please show how you would do that." **(Lacks real-world context, overly directive.)**	"Imagine you will have increased physical activity for the next two hours. Please show what you would do in this situation." **(Not tied to the device, could lead to unrelated responses.)**	"Imagine you are going to a 2-hour exercise class. Please show on this pump how you would account for your increased activity level." **(Provides relevant context while focusing on device interaction.)**
Case Study 3: Electronic Health Record (EHR) System	"Demonstrate how to review and update a patient's medication list in the EHR system." **(Too task-specific, assumes correct action.)**	"A patient has been admitted. Show what you would do in the EHR." **(Lacks real-world context, overly broad.)**	"A patient has been admitted from another facility. Upon reviewing the chart, you notice potential discrepancies in their medications. Show how you would proceed in the EHR system." **(Scenario-driven, supports usability focus.)**

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Warm Up to Clarity:

ICONOGRAPHY IN TEMPERATURE COMMUNICATION ON COMBINATION PRODUCTS AND MEDICAL DEVICES

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This study was funded by AbbVie, Inc. AbbVie participated in the study design, research, data collection, analysis and interpretation of data, as well as writing, reviewing, and approving the publication. Jordan Hilgers, Jim Kershner and Christina Ambrose are employees at Bold Insight and have no conflicts of interest to report. Ashley Morris, and Amrish Chourasia, are AbbVie employees and may own AbbVie stock/options.

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HIGH-LEVEL SUMMARY

Relevant standards and on-market pharmaceutical product IFU's seldom specify guidance related to communicating warm-up time for temperature-sensitive medications.

This presentation strives to discuss this existing gap, present relevant background information, and demonstrate a step forward in this space by showcasing a case study in which warm-up compliance labels were tested with n=45 representative users.

Set users up for success by clearly communicating warm-up time with effective iconography.

Adding labeling to pharmaceutical products that require refrigeration, and subsequent warm up periods can:

- Enhance product usability, and
- Improve users' mental models of product readiness

INTRODUCTION

Some medications, like insulin for example, are refrigerated prior to use and are then required to be left out at room temperature to "warm up" prior to drug delivery.

- This process is done to ensure the medication works most effectively and the injection causes the patient the least amount of pain possible.

Communicating warm-up time and temperature of a product prior to use is an important topic for:

Pharmaceutical manufacturers who are developing medications that need to be warmed up prior to use, to support users in complying with instructions to warm a product prior to use.

+

Users (patients, caregivers, healthcare providers) that need to warm a product prior to use.

One potential method of communicating warm-up time is to use **temperature-sensitive labels** on the packaging to indicate when the product has reached room temperature.

- These labels are small, so **iconography** is typically used to communicate temperature information.

For illustrative purposes, example icons that represent temperature were sourced from The Noun Project online design resource database.

Example Temperature Icons from The Noun Project

	Warm /Too Warm			Cold / Too Cold	
Term Searched	"Sun"	"Warmth"	"Thermometer"	"Frost"	"Thermometer"
Icon Example					

An assessment is needed, of:

- Standards and regulations that provide guidance on communicating warm-up time and temperature of a product related to its use, and
- Existing temperature-sensitivity iconography and temperature-indicator labels in on-market products.

Learnings from this research may inform the design of device labeling and instructional materials related to warming up medication.

OBJECTIVES

1. Present an evaluation of notable temperature-sensitivity symbols and icons, and ways of communicating warm-up time to users from:
   - Standards and regulations, and
   - On-market combination products.
2. Share user insights and lessons learned from a usability testing case study on a set of temperature-sensitive labels.

METHODS

The standards and regulations listed in the below table were reviewed to identify applicable guidance related to iconography and "warm-up time" communication.

International Standards	Regulations (US)
• ANSI/AAMI HE75 • ANSI Z535.4 • IEC 60601-1-6:2010/AMD1:2013 • IEC 60417 • IEC 62304:2006/A1:2015 • IEC 62366-1:2015 • IEEE 11073-10417 • ISO 15223-1:2021 • ISO 14971:2019 and ISO/TR 24971:2020 • ISO 11607-1:2019	• 21 CFR Part 201 Labeling • 21 CFR Part 801 Labeling • 21 CFR Part 820 Quality System Regulation • FDA, "Applying Human Factors and Usability Engineering to Medical Devices" • FDA, "Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products — Content and Format" • FDA, "Human Factors Implications of the New GMP Rule Overall Requirements of the New Quality System Regulation" • FDA, "Application of Human Factors Engineering Principles for Combination Products: Questions and Answers" • USP <659> Packaging and Storage Requirements • USP <1079> Good Storage and Distribution Practices for Drug Products

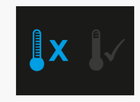
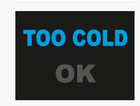
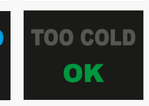
The labeling for notable on-market medicinal products that communicate information about the temperature of a product prior to use were reviewed to explore how warm-up is communicated to users (text instructions or using icons, symbols or labels):

- Lantus (insulin product),
- Pfizer-BioNTech Covid-19 (mRNA vaccine),
- Enbrel (biologic; tumor necrosis factor blocker),
- Humira (biologic; tumor necrosis factor blocker),
- Avonex (biologic; interferon beta- 1a),
- Orencia (biologic for autoimmune conditions), &
- Taltz (biologic for autoimmune conditions).

A CASE STUDY

A formative usability test was conducted to evaluate four design concepts for temperature sensitive warm-up compliance labels that are intended to visually indicate that the product has or has not reached room temperature.

- A total of n=45 participants completed testing, including 18 adult patients, 17 adolescent patients, and 10 healthcare providers (HCPs).
- Each of the four design concept prototypes each contained two sets of temperature-sensitive labels, one that was visible when the product was below room temperature and one that was visible when the product had reached room temperature.

Concept	<15°C	≥15°C
A "thermometers"		
B "stop sign/check mark"		
C "not ready/ready"		
D "too cold/ok"		

RESULTS

0/11 Of the 11 international standards reviewed, none provided standard guidance for communicating warm-up time or temperature-sensitivity of the product.

- Focus of existing standards is on designing for safe and effective use, which includes storage and handling prior to use of the product.

0/9 Of the 9 U.S. regulations reviewed, none prescribed specific icons or methods for conveying temperature sensitivity or warm-up time information.

- The regulations generally mandate that any critical information for safe use (including instructions such as "warm-up time") be clearly communicated (see 21 CFR 201, 801, 820).

0 to 1/7 Of the 7 on-market products that were reviewed to explore how warm-up time is communicated to users, none utilized temperature-sensitivity labels and only 1 used an icon to communicate warm up instructions (excerpt from Taltz IFU below).

Step 1a

- **Take the TALTZ autoinjector from the refrigerator.**
- Remove the autoinjector from the package. Put the original package with any unused autoinjectors back in the refrigerator.
- Leave the base cap on until you are ready to inject.
- **Wait 30 minutes** to let the autoinjector warm to room temperature before you use it.
- **Do not** microwave the autoinjector, run hot water over it, or leave it in direct sunlight.
- **Do not** shake the autoinjector.

Case Study User Insights

- Symbol-based labels were more frequently scored "best" when compared to text-based labels.
- The thermometer symbol was found to be more understandable to users.
- The words "OK" or "ready" lacked temperature-specific context, when presented on their own.
- Color primarily conveys meaning (i.e., green = go, red = stop). Red "ready" text was confusing to participants.

CONCLUSIONS

- With limited standards and regulations to guide pharmaceutical manufacturers on communicating warm-up time for medical products prior to use, manufacturers often rely on text-based instructions.
- There are a variety of icons available to users in the public that manufacturers could leverage to communicate temperature sensitivity of a product, but without guidance and standards for such communication, it is difficult for manufacturers to be consistent, which can be confusing for users.
- Contextual factors play a role in iconography development (e.g., heating pad or fire symbol is not appropriate for warming at room temperature).
- **Ultimately, icons must be:**
  Clear,
  Consistent,
  Culturally sensitive, and
  Compliant.

Implications for Practice

- **Adoption of standardized temperature icons across the industry through regulatory alignment can reduce confusion and enhance consistency in instructions, benefiting users, manufacturers, and regulators.**
- Insights from this work can inform the design of future device labeling and instructional materials, making them more user-friendly and effective in communicating critical information.

Bold Insight

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