THE FDA GROUP LLC

Insider Newsletter

Item #1 –

Considerations for Implementing ICH Q14's Enhanced Approach to Analytical Method Development

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Item #1: What is This About? Implementing ICH Q14's Enhanced Approach

In the first quarter of 2022, drafts of ICH Q2(R2) and Q14 were released for public comment. This is the first time there have been significant changes to the guidance for analytical methods since the release of Q2 in the 1990s. ICH is targeting finalization in May of 2023.

The key principles of these documents, as defined by ICH are the following:

- Together ICH Q14 and ICH Q2(R2) describe the development and validation activities suggested during the lifecycle of an analytical procedure used for the assessment of the quality of drug substances and drug products
- ICH Q2(R2) provides guidance for establishing, submitting, and maintaining evidence that an analytical procedure is fit for purpose (assuring drug quality)
- ICH Q14 describes the scientific principles for development, change management and submission requirements of analytical procedures for the minimal and enhanced approach

Item #1: What is This About? Implementing ICH Q14's Enhanced Approach

The new guideline in this pair, ICH Q14, describes science and risk-based approaches for the development and maintenance of analytical procedures in line with approaches suggested in previous ICH guidelines (e.g., ICH Q8 and Q11):

- For the first time in detail, two approaches to analytical procedure development are articulated, a minimal (or traditional) approach and an ***enhanced approach*** (originally mentioned at a high level in ICH Q12)
- There also is information for the development of multivariate analytical procedures and the use of these tests for real-time release testing (RTRT)
- In addition, principles are provided to facilitate change management of analytical procedures based on risk management, and a comprehensive understanding of the analytical procedure via adherence to predefined criteria for performance characteristics
- Lastly, there is guidance on the submission of analytical procedure development and related lifecycle information in the Common Technical Document (CTD)

Item #1: What is This About? Implementing ICH Q14's Enhanced Approach

In ICH Q14, the Minimal Approach to analytical procedure development is described as including the following elements:

- Identifying which attributes of the drug substance or drug product need to be tested by the analytical procedure.
- Selecting an appropriate analytical procedure technology and related instruments or suitable apparatus.
- Conducting appropriate development studies to evaluate analytical procedure performance characteristics such as specificity, accuracy and precision over the reportable range (including the calibration model, limits at lower and/or higher range ends) and robustness.
- Defining an appropriate analytical procedure description including the analytical procedure control strategy (e.g., parameter settings and system suitability).

Item #1: What is This About? Implementing ICH Q14's Enhanced Approach

ICH Q14 goes on to describe the benefits of using elements of the enhanced approach to analytical procedure development. The key elements of the enhanced approach are:

- Evaluation of the sample properties
- Defining an analytical target profile (ATP)
- Conducting risk assessment (ICH Q9) and evaluating prior knowledge
- Conducting uni- or multi-variate experiments
- Defining an analytical procedure control strategy
- Defining a lifecycle change management plan

Item #1: Implications or More Details of What's Happening

The benefits of this information-rich enhanced approach:

- A better understanding of which analytical procedure attributes are essential for robust procedure performance (e.g., Established Conditions (ECs))
- Also, by employing predefined performance characteristics and their associated acceptance criteria, there is a path that enables the evolution of the analytical procedure over its lifecycle

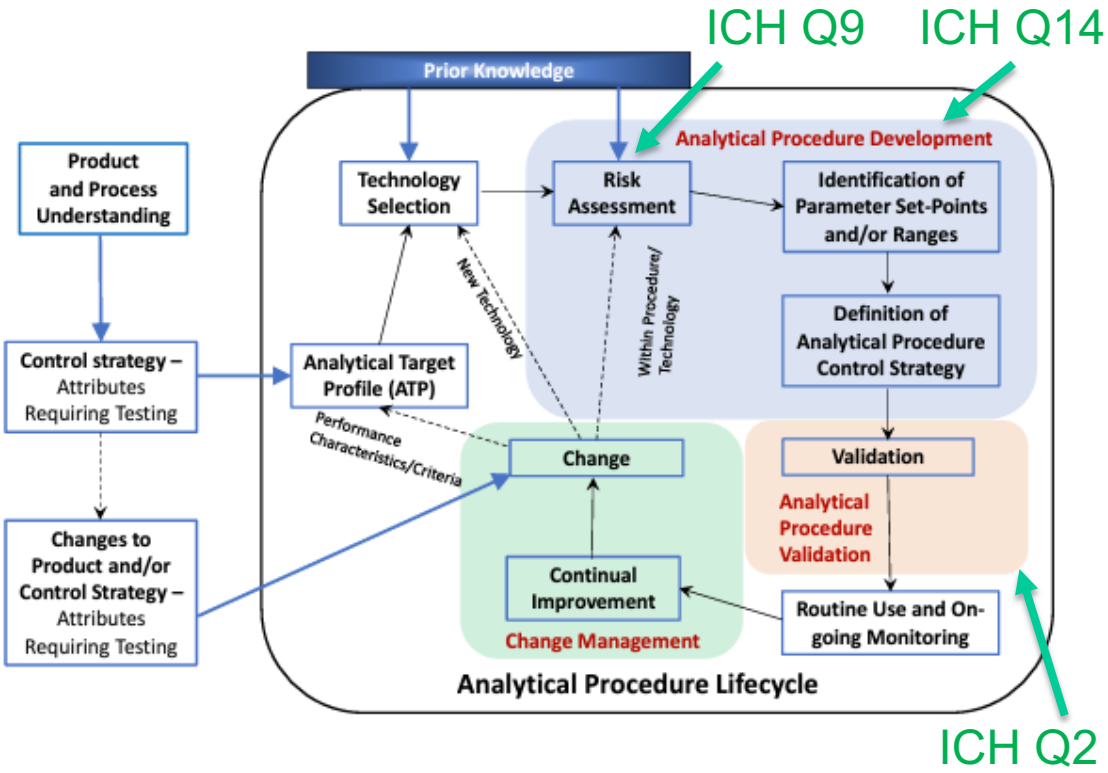
Taken together, these benefits of the enhanced approach should reduce the amount of effort required for analytical procedure lifecycle maintenance, including regulatory approval or notification (if required).

Item #1: Implications or More Details of What's Happening

However, it's important to note that these approaches aren't black and white; there is a continuum of options between the categories of minimal (traditional) and enhanced approaches for analytical procedure development.

- More specifically, it is possible to apply elements of the enhanced approach (e.g., Analytical Target Profile (ATP), ECs, risk assessment, prior knowledge, uni- or multi-variate experiments, analytical procedure control strategy or lifecycle change management plan) to minimal (traditional) analytical procedures.
- It's reasonable to expect that the benefits of using elements of the enhanced approach during development will be clarified as the documents are finalized, or through training information, as we have experienced with other ICH guidelines (e.g., ICH Q12).
    - One of those clarifications, hopefully, will be related to method qualification

Item #1: Implications or More Details of What's Happening



- Within ICH Q14 there is no specific mention of method "qualification"; missing a perfect opportunity to clarify this term/practice.
- The elements of method qualification are captured as part of Analytical Procedure Development with the Identification of Parameter Set-Points and/or Ranges through experimentation, risk assessment, and/or review of prior knowledge.
- And, correctly, these parameters are established prior to entering method validation.

Item #1: What organizations benefit? What organizations may find it infeasible to apply?

The short answer to the first question is – *all organizations*. In other words, for organizations well-suited to — and capable of taking — this approach, the upfront investment in implementing it pays dividends into the future.

To answer the second question - not all organizations are "well-suited to – and capable of taking – this approach".

Organizations with financial constraints, inexperienced analytical personnel, immature or non-existent quality systems, and ineffective vendor management (as applicable) are ill-positioned to implement this approach.

Item #1: Effective Implementation of the Enhanced Approach

What is involved in implementing the key elements of the enhanced approach? Practical guidance to implement the key elements of the enhanced approach are provided below and subsequent slides.

- Evaluation of the sample properties and the expected variability of the sample based on manufacturing process understanding
  - Capture process and formulation development activities in technical reports
  - Perform forced degradation studies
  - Using information from these activities, develop a Quality Target Product Profile (QTPP)
- Defining an analytical target profile (ATP)
  - Using the example from ICH Q14, capture the following information in an ATP document (note – this is not a thesis)
    - What you know about the molecule from the QTPP
    - Intended purpose of the analytical method
    - How the analytical method is linked to the critical quality attribute (CQA) of the molecule
    - Characteristics of the reportable results including desired or target acceptance criteria and associated rationale

Item #1: Effective Implementation of the Enhanced Approach - *continued*

- Conducting risk assessment (ICH Q9) and evaluating prior knowledge to identify the analytical procedure parameters that can impact performance of the procedure
  - With guidance from ICH Q9 and any number of risk assessment tools (e.g., Ishikawa), conduct a risk analysis.
  - Document it according to quality processes (Risk Assessment SOP)
  - Once analytical procedure parameters that can impact procedure performance have been identified, evaluate them experimentally
- Conducting uni- or multi-variate experiments to explore ranges and interactions between identified analytical procedure parameters
  - Once analytical procedure parameters have been identified evaluate them by conducting uni- or multi-variate experiments
  - Plan the experiments
  - Document the plan and properly record the results

Item #1: Effective Implementation of the Enhanced Approach - *continued*

- Defining an analytical procedure control strategy
  - Based on product and process understanding and considering the procedure development data and risk assessment, define the analytical procedure control strategy ensuring adherence to performance criteria. Include any of, or combination of, the following;
    - System suitability testing acceptance criteria
    - Positive and /or negative controls
    - Sample suitability acceptance criteria
- Defining a lifecycle change management plan
  - Develop a change management process within the quality systems to include the appropriate stakeholders in the assessment of any method or other changes that may impact the method
  - Develop a lifecycle change management plan that provides clear definitions and reporting categories of established conditions (ECs), proven acceptable ranges (PARs), or method operational design regions (MODRs) as appropriate.
    - Develop ECs based on product and process understanding and development data.
    - Justify reporting categories for changes including adherence to predefined acceptance criteria described in the ATP and additional performance controls (use the example in Annex A of ICH Q14 as a starting point)
  - For every change perform a structured risk assessment to evaluate potential impact on the performance characteristics and the link to CQA as defined in the respective ATP

Item #1: Concluding Thoughts - Implementing ICH Q14's Enhanced Approach

Overall, development of this guidance is a good first step towards defining a systematic approach toward analytical method development.

- It helps to establish industry and agency standards or expectations for analytical method development and to provide guidance for analytical and quality control scientists lacking the experience to develop robust analytical methods.
- Further, the detailed examples located in the Annexes are very useful tools. The same can be said for the addition of examples added to ICH Q2 (R2). These examples provide a starting point on which more customized approaches and documents can be developed.

The challenge is getting organizations to embrace the Enhanced Approach. Not all organizations are positioned to take this approach for the reasons stated earlier.

In most cases, hiring a consultant to lead this effort, internally, or manage external vendors responsible for these tasks is the best, most cost-effective solution and should be considered before taking a minimalistic approach because - as the saying goes - "you can pay now or later, but you will pay".

Item #1: References

- International Council for Harmonisation (ICH) Q2
- International Council for Harmonisation (ICH) Q8
- International Council for Harmonisation (ICH) Q9
- International Council for Harmonisation (ICH) Q10
- International Council for Harmonisation (ICH) Q11
- International Council for Harmonisation (ICH) Q12
- International Council for Harmonisation (ICH) Q14

FDA Proposes a Framework for Human Factors Information in Device Submissions

Item #2 —Revised Human Factors Guidance 2022

-On December 9, 2022, FDA issued a draft guidance outlining a risk-based framework about what human factors information should be included in marketing submissions for medical devices. This guidance is to complement the previous guidance of February 3, 2016, "Applying Human Factors and Usability Engineering to Medical Devices Guidance for Industry and Food and Drug Administration Staff "

- The FDA also decided after receiving stakeholder feedback on the guidance, "List of High Priority Devices for Human Factors Review" that it should issue another draft guidance regarding submission of Human Factors information for the purposes of premarket review, which will supersede the draft guidance, "List of High Priority Devices for Human Factors Review".

-The December 9, 2022 draft guidance framework explores how to determine the appropriate human factors submission category (1, 2, or 3) and what to include in a marketing submission based on that category.

Guidance for Submission of Human Factors Information to Replace "List of Highest Priority Devices for Human Factors Review

When finalized, this draft guidance is intended to be used to complement the FDA guidance **"Applying Human Factors and Usability Engineering to Medical Devices"** (hereafter referred to as the Human Factors Guidance). The purpose of the Human Factors Guidance is to recommend and guide manufacturers through human factors engineering processes during the development of new medical devices, focusing specifically on the user interface.

That guidance provides relevant human factors definitions and recommends useful preliminary analysis and evaluation tools and validation testing that will enable manufacturers to assess and reduce risks associated with medical device use. *The purpose of the current guidance is to help manufacturers apply a risk-based approach when considering what human factors information to include in a marketing submission.*

Human factors engineering and Human factors validation testing

Human factors engineering:

The application of knowledge about human behavior, abilities, limitations, and other characteristics of medical device users to the design of medical devices including mechanical and software driven user interfaces, systems, tasks, user documentation, and user training to enhance and demonstrate safe and effective use. Human factors engineering and usability engineering can be considered to be synonymous.

Human factors validation testing:

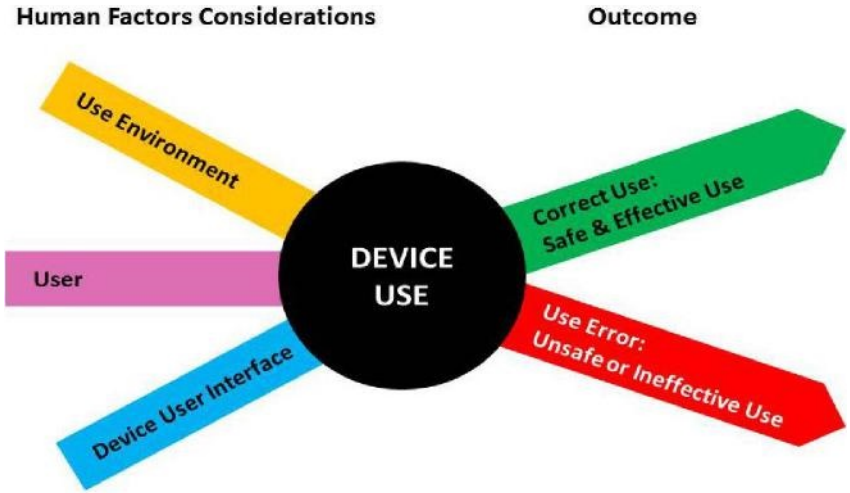
Testing conducted at the end of the device development process to assess user interactions with a device user interface to identify use errors that would or could result in serious harm to the patient or user. Human factors validation testing is also used to assess the effectiveness of risk management measures. Human factors validation testing represents one portion of design validation.

> *"The goal of the human factors assessment is to ensure that the device user interface has been designed such that use errors that occur during use of the device that could cause harm or degrade medical treatment are either eliminated or reduced to the extent possible."*

> *"The main factors to consider in a risk-based approach to human factors assessment, as described in this draft guidance, include the identification of (i.e., presence of or modification to) critical tasks and the elimination or reduction of use-related hazards."*

Common Human Factor mistakes/oversights companies make in submissions

For those use errors and problems that could result in serious harm, the test data should be analyzed to determine which part of the user interface was involved and how the user interaction could have resulted in the use error or problem. The primary purpose of the analysis is to determine whether that part of the user interface could and should be modified to reduce or eliminate the use problem and reduce the use-related risks to acceptable levels. An essential secondary purpose of the analysis is to develop a modified design that would not cause the same problem or a new problem.



Common errors and problems

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Even when the causes of the use errors and problems seem to be apparent from the test facilitators' observations, they should always be discussed as part of the post-use interview.

The test participant's perspective on use errors can provide helpful insights and reasons for the use error and sometimes includes suggestions for design improvements.

It is not uncommon for the user to explain exactly what caused them to do what they did but this is not always the case.

Sometimes users don't notice making errors, or cannot provide an explanation, or offer an explanation that is not helpful.

Design modifications made in response to human factors validation testing results to eliminate or reduce unacceptable use-related risks should be evaluated in a subsequent test to determine whether the design modifications were effective and whether they have introduced unacceptable new risks that need to be eliminated or reduced.

Common hazards traditionally considered in risk analysis:

Hazards traditionally considered in risk analysis include:

- Physical hazards (e.g., sharp corners or edges),
- Mechanical hazards (e.g., kinetic or potential energy from a moving object),
- Thermal hazards (e.g., high-temperature components),
- Electrical hazards (e.g., electrical current, electromagnetic interference (EMI)),
- Chemical hazards (e.g., toxic chemicals),
- Radiation hazards (e.g., ionizing and non-ionizing), and
- Biological hazards (e.g., allergens, bio-incompatible agents and infectious agents).

Medical device hazards associated with user interactions with devices should also be included in risk management. These hazards are referred to in this document as *use-related hazards* (see Figure 2). These hazards might result from aspects of the user interface design that cause the user to fail to adequately or correctly perceive, read, interpret, understand or act on information from the device. Some use-related hazards are more serious than others, depending on the severity of the potential harm to the user or patient encountering the hazard.

Optimizing Human Factors Validation

Analysis of Human Factors Validation Test Results:

The results of the human factors validation testing should be analyzed qualitatively to determine if the design of the device (or the labeling or user training) needs to be modified to reduce the use-related risks to acceptable levels. To do this, the observational data and knowledge task data should be aggregated with the interview data and analyzed carefully to determine the root cause of any use errors or problems (e.g. “close calls” and use difficulties) that occurred during the test.

The root causes of all use errors and problems should then be considered in relation to the associated risks to ascertain the potential for resulting harm and determine the priority for implementing additional risk management measures.

Risk Management

HFE/UE considerations and approaches should be incorporated into device design, development and risk management processes. Three steps are essential for performing a successful HFE/UE analysis:

- -Identify anticipated use-related hazards and initially unanticipated use-related hazards (derived through preliminary analyses and evaluations
- -Develop and apply measures to eliminate or reduce use-related hazards that could result in harm to the patient or the user
- -Demonstrate whether the final device user interface design supports safe and effective use by conducting human factors validation testing

Human factors validation testing is conducted to demonstrate that the device can be used by the intended users without serious use errors or problems, for the intended uses and under the expected use conditions.

The testing should be comprehensive in scope, adequately sensitive to capture use errors caused by the design of the user interface, and should be performed such that the results can be generalized to actual use.

The human factors validation testing should be designed as follows:
- The test participants represent the intended (actual) users of the device.
- All critical tasks are performed during the test.
- The device user interface represents the final design.
- The test conditions are sufficiently realistic to represent actual conditions of use.

Implications for Human Factors

When developing a new device, it is useful to identify use-related problems (if any) that have occurred with devices that are similar to the one under development with regard to use, the user interface or user interactions. When these types of problems are found, they should be considered during the design of the new device's user interface.

These devices might have been made by the same manufacturer or by other manufacturers.

Sources of information on use-related problems include customer complaint files, and the knowledge of training and sales staff familiar with use-related problems. Information can also be obtained from previous HFE/UE studies conducted, for example, on earlier versions of the device being developed or on similar existing devices.

Other sources of information on known use-related hazards are current device users, journal articles, proceedings of professional meetings, newsletters, and relevant internet sites, such as:

- FDA's Manufacturer and User Facility Device Experience (MAUDE) database;
- FDA's MedSun: Medical Product Safety Network;
- CDRH Medical Device Recalls;
- FDA Safety Communications;
- ECRI's Medical Device Safety Reports;
- The Institute of Safe Medical Practices (ISMP's) Medication Safety Alert

Newsletters; and The Joint Commission's Sentinel Events.

8 Device Marketing Submission Sections

Section 1: Conclusion and high-level summary

Section 2: Descriptions of intended device users, uses, use environments, and training

Section 3: Description of device-user interface

Section 4: Summary of known use problems

Section 5: Summary of preliminary analyses and evaluations

Section 6: Analysis of hazards and risks associated with use of the device

Section 7: Identification and description of critical tasks

Section 8: Details of the human factors validation testing of the final design

Section 1: Conclusion and high-level summary

Submitters should begin with a conclusion stating whether the user interface of the device has been found to be adequately designed for the intended users, uses, and use environments and whether new human factors testing was conducted to support this conclusion.

FDA recommends that submitters begin with a high-level summary of the human factors engineering assessment (e.g., use-related risks), including the underlying rationale for conducting the assessment, and a summary of the human factors engineering processes conducted (e.g., human factors engineering analyses and evaluations, device-user interface modifications and validation testing) and analysis of the results.

When applicable, this section should discuss any remaining residual use-related risks after human factors validation testing. Submitters should describe why further risk mitigation is not practicable based on a benefit-risk analysis for the device.

Risk-based approach to human factors engineering information in marketing submission

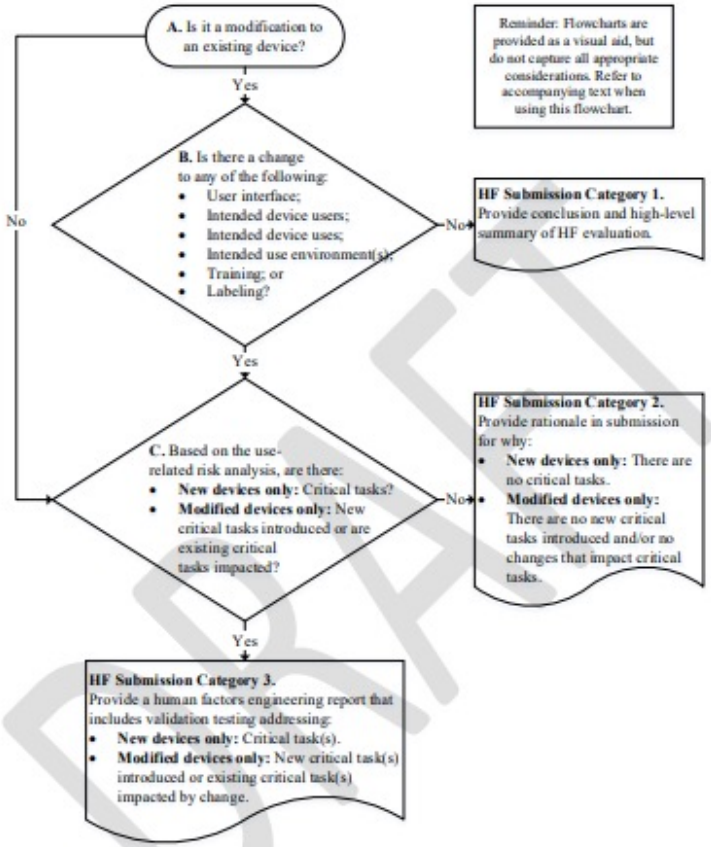


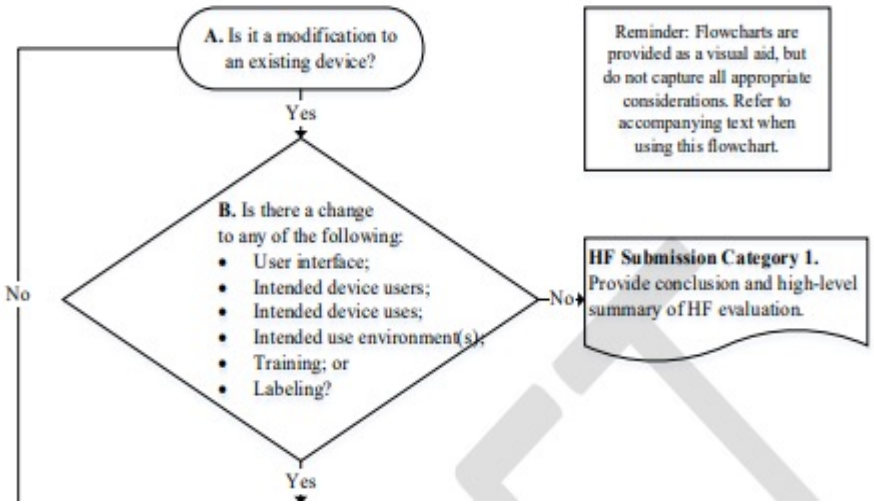
Figure 1. Flowchart illustrating a risk-based approach to determine the HF Submission Category. [22]

Human Factors Submission Category 1

- Human Factors Submission Category 1

1. A Human Factors Submission Category 1 is determined when device modifications are found to not affect human factors considerations of user interface, intended device users, intended device uses, intended use environments, training or labeling.

2. If applicable, use previous human factors engineering evaluations to provide a conclusion.



Human Factors Category 2

How to determine HF Submission Category

Decision Point A: Is it a modification to an existing device? Submitters should answer "Yes" to this question when their submission is for a change to a device that has already received marketing authorization from FDA through a 510(k), PMA, HDE application, or De Novo request. Submitters should generally answer "No" if their device is a completely new device that has not received marketing authorization from FDA. Depending on specific facts and circumstances, submitters may be able to answer "Yes" to this question when they are proposing to apply human factors information from one of their own legally marketed devices to a subject device that has the same or a similar user interface. Key "what's happening" point #1, my take on pt 1

HF Submission Category 1. Provide conclusion and high-level summary of HF evaluation: The submission should include a statement justifying that the device modifications do not affect the human factors considerations of the modified device and leverage, if applicable, previous human factors engineering evaluations to provide the conclusion and high level summary. See Table 1 (next slide) for the suggested submission content for devices that fall into HF Submission Category 1.

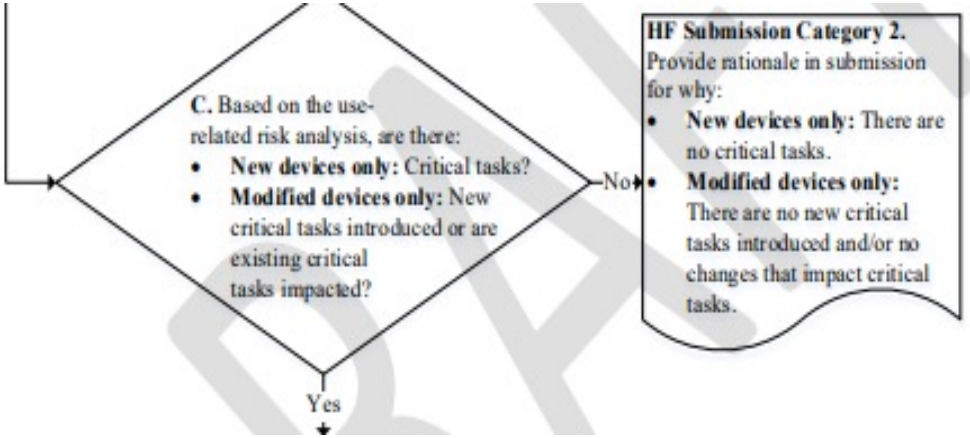


Table 1: Recommended minimum human factors information that should be provided for a marketing submission based on HF Submission Category

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Recommended information (Report section numbers from Section V below)	HF Submission Category		
	1	2	3
Conclusion and high-level summary (Section 1)	✓	✓	✓
Descriptions of: • Intended device users, uses, use environments, and training (Section 2) • Device-user interface (Section 3) • Summary of known use problems (Section 4)		✓	✓
Preliminary activities • Summary of preliminary analyses and evaluations (Section 5)			✓
Use-related risk analysis • Analysis of hazards and risks associated with use of the device (Section 6) • Identification and description of critical tasks (Section 7)			✓
Details of validation testing of final design (Section 8)			✓

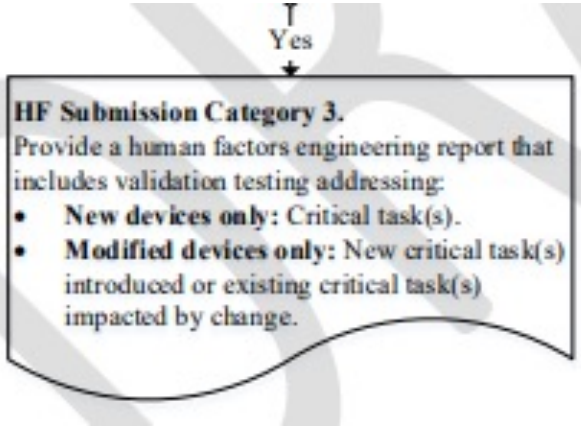
Human Factors Category #3

1. High-level summary of Human Factor Submission Category 3 evaluation:

- The submission should include a statement justifying that the device modifications do not affect the human factors considerations of the modified device and leverage, if applicable, previous human factors engineering evaluations to provide the conclusion and high level summary. Human Factors Submission Category 1

1. High-level summary of Human Factor Submission Category 1 evaluation:

The submission should include a statement justifying that the device modifications do not affect the human factors considerations of the modified device and leverage, if applicable, previous human factors engineering evaluations to provide the conclusion and high level summary.



Section 2: Descriptions of intended device users, uses, use environments, and training.

This section should include:
- A description of the intended user population. If there is more than one distinct user population, each population should be described.
-The description should include meaningful differences in capabilities or use responsibilities between user populations that could affect their interactions with the device. This includes lay and healthcare professional users who might use the same device to perform different tasks or different types of professionals who might perform different tasks on the device;
-A summary of the device's intended use;
-A summary of the device's operational context of use and critical aspects of device operation, including:
-Whether users should or must be trained by a healthcare professional prior to device use;
-How the device is used across clinical applications; and
- Set up, maintenance, cleaning, and reprocessing information.
-For the purposes of this guidance, FDA uses the term "benefit-risk analysis" consistent with ANSI/AAMI/ISO . 14971: 2019 Medical devices—Application of risk management to medical devices.
-A summary of the intended use environments (e.g., hospital, medevac vehicle, home use) and the characteristics of those environments (e.g., glare, vibration, ambient noise, high levels of activity) that could affect user interactions with the device; and
- A description of any training users would receive. A sample of the training materials such as a video, presentation slides, or a pamphlet may be appended.

Section 3: Description of device-user interface

Description of device-user interface

When applicable, this section should include:

- A graphical representation (e.g., photographs, illustrations, line drawings) of the device and its user interface. This should depict the overall device and all components of the user interface with which the user will interact (e.g., display and function screens, alarm speakers, controls, keypads, dedicated buttons, doors, components to be connected, retaining clips);
- A written description of the device user interface;
- A copy of the labeling that will be provided to the user with the device (e.g., instructions for use, user manual, quick-start guides, packaging);
- An overview of the operational sequence of the device and the user's expected interactions with the user interface. This should include the sequence of user actions performed to use the device and resulting device responses, when appropriate; and
- For modified devices, consider providing information comparing the subject and existing devices (see Table 4 for an example format).

Section 4: Summary of known use problems

-This section should describe all known use problems for previous models of the same device (as applicable) or with similar types of devices (e.g., predicate devices).

-FDA recommends that submitters state that there are no known use problems, if applicable.

-For a device that has been modified specifically in response to use problems in the field, this section should discuss those problems and the device modifications.

Section 5: Summary of preliminary analyses and evaluations

-This section should identify the preliminary analysis and evaluation methods used (e.g., specific analysis techniques, formative evaluations),

- summarize the key results of those analyses and evaluations, describe modifications made to the user interface design in response,

- and discuss the key findings that informed the protocol development for the human factors validation test.

Section 6: Analysis of hazards and risks associated with use of the device

-This section should include the use-related risk analysis document and/or comparative task analysis, as applicable.

-This is typically an excerpt from the comprehensive risk analysis that contains all use-related hazards and risks identified through the preliminary analyses and evaluations, including those associated with potential use errors.

-The use-related risk analysis document is intended to be a living document; updates should be made to identified risks and hazards throughout the device design process.

-FDA believes it can be useful to organize this information in a tabular format. An example tabular format is provided in Table 2. (see next slide)

-This example provides the recommended minimum information to evaluate the use-related risks associated with your device. For modified devices in HF Submission Category 3, the submitter should provide a comparative task analysis (see example tabular format in Table 3) comparing the modified device use-related risk analysis with the existing device use-related risk analysis.

- If you determine that a device change resulting in a modification to any task, associated harm, and/or risk mitigation measure does not merit new HF validation test data to support the device's use safety, (provide a rationale).-

Table 2 –Example Tabular Format for the use –related risk analysis

Table 2. Example tabular format for the use-related risk analysis

Use-related risk analysis Task #	User Task	Possible use error(s)	Potential hazards and clinical harm	Severity of harm	Critical Task (Y/N)	Risk Mitigation Measure(s)[25]	Validation method for effectiveness of risk mitigation measure[26]
Task #1							
Task #2							

Section 7: Identification and description of critical tasks

This section should: Explain the process followed to identify the critical tasks based on the use-related risk analysis document.

-Since critical tasks are determined by the severity of the potential harm, FDA recommends that the submitter describe the levels of severity being used and use a reference when appropriate. For example, if the submitter is using a qualitative five-level severity rating from a voluntary consensus standard (e.g., ISO 1497129 389), this section should include a table of severity levels with descriptions of each level and reference the applicable standard; and

- List and describe the critical tasks. For HF Submission Category 3, the submitter should provide a separate table highlighting the new critical tasks if relevant and rationale for why the task does not merit new HF validation test data to support the device's use safety. The submitter should also describe each use scenario included in the human factors validation testing and list the critical and non-critical tasks that constitute each use

–When modifying an existing device, FDA recommends that submitters compare the new device user interface to their own existing device in their marketing submission. FDA recommends completing this comparison in a tabular format. An example tabular format is provided in Table 4.

- In addition to the use-related risk analysis document for the entire device, submitters should include a subset of the use-related risk analysis that isolates tasks and risks associated with the proposed modifications made to the device.

-FDA recommends including photographic images of the device-user interface components that were modified, including modifications to labeling such as warning statements in an instructional manual. Submitters should list any critical tasks affected by the modification(s).

·-Submitters should also discuss whether the risk associated with the modification is acceptable and assess whether the proposed changes warranted human factors 29 ANSI/AAMI/ISO 14971: Medical devices—Application of risk management to medical devices.

- Contains Nonbinding Recommendations Draft – Not for Implementation validation testing. As stated in the Human Factors Guidance, the validation test may be limited to assessment of those aspects of users' interactions and tasks that were affected by the design modifications.

Section 8: Details of HF validation testing of final design

This section should summarize all HF validation activities conducted:

- In addition to test results, this section should have a comprehensive analysis of all use errors and problems that occurred that could have resulted in harm in real-world use,
- A description of all design modifications made to the user interface in response to the test results, and a benefit-risk discussion.
- A full test protocol and a sample of all scripts and forms used in the testing should be appended.
- Submitters should provide a residual risk analysis and the rationale for why existing mitigation controls are acceptable.
- While elimination of all residual risks may not be practicable, submitters should have evidence of a systematic analysis of use errors and mitigations of use-related risks.
-- Submitters should reevaluate risk control and mitigation measures to identify other means to reduce risk when it is determined that the residual risks are unacceptable.

Modification to an existing 510(k)cleared device- Example A.1

Example A.1.

- Scenario: A submitter currently has marketing authorization for a gastrointestinal lesion software detection system in a cleared 510(k). The device is a computer-assisted detection device used in conjunction with endoscopy for the detection of abnormal lesions in the gastrointestinal tract. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-andusability-engineering-medical-devices).
- For example, see Appendix C of "Applying Human Factors and Usability Engineering to Medical Devices."
- Gastrointestinal lesion software detection systems are classified under 21 CFR 876.1520 and are subject to the special controls established in the reclassification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200055.pdf. The publication of this classification in the Federal Register and codification in the Code of Federal Regulations is currently pending.
-The submitter has proposed to modify the computer-assisted detection algorithm such that a new 510(k) was submitted. The algorithm modifications improve the system's ability to assist in detection of lesions and does not change any aspects of the device-user interface:

Decision Point A: Is it a modification to an existing device?

Yes. The submitter is modifying their own existing 510(k)-cleared device and using that device as the predicate device

Decision Point B: Is there a change to any of the following:

· User interface;
· Intended device users;
· Intended device uses;
· Intended use environment(s);

Training; or

· Labeling? No. The changes to the algorithm do not impact any aspect of the device-user interface. The intended users, uses, and use environments remain the same and in this instance, changes to the algorithm do not include modifications to the labeling or training programs. **Analysis: The recommended HF information in this marketing submission is defined by HF Submission Category #1. The submitter should include a statement justifying that the device modifications do not affect the human factors considerations of the modified device and the conclusion and high level summary of HF evaluation.**

Modification to an existing 510(k)cleared device- Example A.2

Example A.2 Scenario**:** A submitter currently has marketing authorization for a gas machine for anesthesia in a cleared stand-alone device 510(k) submission.

-The gas machine for anesthesia is intended for use in the hospital environment and includes a touch screen graphical user interface (GUI) and control knobs to regulate gas flow.

-The submitter requests 510(k)- clearance for a modification to the internal gas valving system and included in their 510(k) labeling changes to reflect the modification. There are no changes to the apparent flow settings from this internal change.

-Any modifications regarding calculated flow rates are made in software settings.

-**Decision Point A:** Is it a modification to an existing device? Yes. The submitter is modifying their own existing 510(k)-cleared device and using that device as the predicate device.

-**Decision Point B**: Is there a change to any of the following: · User interface; · Intended device users; · Intended device uses;

· Intended use environment(s); · Training; or Contains Nonbinding Recommendations Draft – Not for Implementation

- Labeling? Yes:

The labeling (instructions manual) was changed to describe the modification to the internal gas valving system. This change does not impact any external user interface component on the device itself. There are no changes to the intended device users, uses, intended use environment, or training because there are no such changes to the indications for use.

Decision Point C: Based on the use-related risk analysis, are there:

· New devices only: Critical tasks? · Modified devices only: New critical tasks introduced or are existing critical tasks impacted? No. Even though the labeling (instructions manual) has changed, this change does not impact how the intended user is expected to interact with the device because the user is not intended to directly interact with the gas valving system, since it is an internal component.

-There are no changes that influence the cognitive and/or visual perception or the physical interaction between the user and the device. Therefore, there are no new critical tasks introduced, nor are existing critical tasks impacted.

- Analysis: The recommended HF information in this marketing submission is defined by HF Submission Category 2. The submitter should provide a rationale that clearly describes the basis of their decision that there are no new critical tasks introduced, and no impacted critical tasks for their modified device.

Modification to an existing 510(k)cleared device-Example A.3

Example A.3. Scenario: In addition to the change described in Example A.2, the submitter also requests 510(k) clearance to change the font size from 12 to 14 point on the text displayed on the graphical user interface (GUI) of the gas machine for anesthesia, along with a proportional increase in the screen's physical size. The submitter is also making associated software changes to address the proposed change in the font size. The GUI menu does not change in terms of selection layout and contains the same icons representing different intended actions.

Decision Point A: Is it a modification to an existing device**? Yes. The submitter is modifying their own existing 510(k)-cleared device and using that device as the predicate device.**

Decision Point B: Is there a change to any of the following: · User interface; · Intended device users; · Intended device uses; · Intended use environment(s); · Training; or · Labeling? **Yes. There are changes to the user interface from the software changes because the user is intended to directly interact visually with the words on the touch screen GUI, which the Contains Nonbinding Recommendations Draft – Not for Implementation 18 .** Which the submitter states is the only part of the device being modified. There are no changes to the intended device users, uses, intended use environment, training, or labeling.

Decision Point C: Based on the use-related risk analysis, are there: **New devices only: Critical tasks?**

- Modified devices only: New critical tasks introduced or are existing critical tasks impacted? No. Even though the user interface (GUI) was changed to include larger text font and a larger screen display, this change does not impact how the intended user is expected to interact with the device because the same textual information is being presented in the same layout and format.

-The text size change was assessed to introduce no negative influence on the cognitive and/or visual perception or the physical interaction between the user and the device. In this case, the submitter can choose to provide formative data and/or literature supporting this conclusion. Therefore, there are no new critical tasks introduced, nor are existing critical tasks impacted.

Analysis: The recommended HF information in this marketing submission is HF Submission Category 2. The submitter should provide a rationale (e.g., analysis of a literature review for acceptable font size) that clearly describes the basis of their decision that there are no new critical tasks introduced, and no impacted critical tasks for their modified device.

Modification to an existing 510(k)cleared device-Example A.4

Example A.4. Scenario: The submitter requests to change the GUI of the gas machine for anesthesia described in Example A.2.

The proposed changes consist of changing textual menu selection items to icons (i.e., graphics). In addition, the submitter requests a change from the physical knob interface with discrete values for gas flow control to a digital slider with continuous values within a pre-specified range that became an added feature to the touch screen GUI.

Based on these changes, the submitter updated the labeling, including the user manual and instructions for use, and training.

Decision Point A: Is it a modification to an existing device? **Yes. The submitter is modifying their own existing 510(k)-cleared device and using that device as the predicate device.**

Decision Point B: Is there a change to any of the following: · User interface; · Intended device users; · Intended device uses; · Intended use environment(s); · Training; or · Labeling? **Yes. There are changes to the user interface because the user directly interacts visually with the icons and controls on the touch screen GUI. There is also a change in the way the user controls the gas flow.** There are no changes to the intended device users, uses, or intended /Contains Nonbinding Recommendations Draft – Not for Implementation use environment. Both the submitter's training and labeling have changed based on the changes to the touch screen GUI.

Modification to an existing 510(k)cleared device-Example A.4 continued

Decision Point C: Based on the use-related risk analysis, are there:

· New devices only: Critical tasks? · Modified devices only: New critical tasks introduced or are existing critical tasks impacted? **Yes. There are several critical tasks associated with the main touch screen GUI of the gas machine for anesthesia, such as setting the ventilation mode, setting tidal volume and inspiratory pressure, and setting alarms.**

Changing the GUI to include only icons instead of text for menu selections may impact the ability of the user to comprehend the correct selection. There are also critical tasks associated with setting and controlling the gas flow to the patient. The interface for gas flow control changed from a physical knob to a digital slider on the touch screen interface, which impacts the physical interaction the user might have with the gas flow control. Although the same information is being conveyed, it is displayed in a different layout and format compared to the predicate.

Analysis: This requested change would be considered HF Submission Category 3. The submitter should submit test results and analysis from a new HF validation study for the subject device in an HF Report. The HF Report should include the use-related risk analysis, along with the information referenced in Table 3.

265 **Table 3. Example tabular format for the comparative use-related risk analysis**

Existing Device						Modified Device			Submitter's comparison comments
URRA Task #	User Task	Possible use error(s)	Potential hazards and clinical harm	Severity of harm	Critical task (Y/N)	Comparison of use task description to existing device	Labeling content and/or design change differences	Comparison of proposed risk mitigation measure to existing device	
Task #1									
Task #2									

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Modification to an existing PMA approved device, Example B.1

Example B.1. Scenario: An implantable infusion pump has a physician programmer and both have been approved as a standalone device through the PMA process. The approved physician programmer is a personal digital assistant (PDA) device, with a monochrome screen and physical buttons to control scrolling and menu selection. The submitter requests approval in a PMA Supplement for a modification to the reservoir volume of the infusion pump. This proposed change does not result in any change to medication concentration or dosing calculation. The software is being updated to allow for the proposed volume change. The proposed modifications, including the software changes, have no direct effect on the device with which a physician or patient directly interact.

Decision Point A: Is it a modification to an existing device? Yes. The submitter is modifying their own existing PMA-approved device.

Decision Point B: Is there a change to any of the following: User interface; · Intended device users; · Intended device uses; · Intended use environment(s); · Training; or · Labeling? Contains Nonbinding Recommendations Draft – Not for Implementation Yes. The labeling (instructions manual) was updated to specify the change in the reservoir volume

Decision Point C: Based on the use-related risk analysis, are there:

New devices only: Critical tasks? · Modified devices only: New critical tasks introduced or are existing critical tasks impacted? No. There are critical tasks that could in some circumstances be impacted by a change in the reservoir volume, including medication concentration and the dosing that are related to drug delivery to the patient. In this case, the medication concentration and dosing remained the same, even with the change in reservoir volume. Therefore, no critical tasks were impacted by the change in reservoir volume.

Analysis: The recommended HF information in this marketing submission is HF Submission Category 2. The submitter should provide a rationale (e.g., discussion of how the change in total reservoir volume does not affect critical tasks such as setting concentration or calculating dosage) that clearly describes the basis of their decision that there are no new critical tasks introduced, and no impacted critical tasks for their modified device.

Modification to an existing PMA approved device, Example B.2

Example B.2. Scenario: Like the previous example, an implantable infusion pump has a physician programmer and both have been approved through the PMA process. The approved physician programmer is a PDA device, with a monochrome screen and physical buttons to control scrolling and menu selection. The submitter requests approval in a PMA Supplement for a modification to the physician programmer from the approved monochrome PDA to a mini-tablet computer with a touch screen user interface. The display on the tablet computer will feature a full color display and new icons for menu functions.

Decision Point A: Is it a modification to an existing device?
Yes. The submitter is modifying their own existing PMA-approved device.

Decision Point B: Is there a change to any of the following:
· User interface; · Intended device users; · Intended device uses; · Intended use environment(s);· Training; or· Labeling**? Yes. The introduction of new icons, color selection and display, and new menu orientation, has changed the user interface. Due to these changes, the submitter is also proposing to change the relevant training and labeling (instructions manual).**

Decision Point C: Based on the use-related risk analysis, are there: · New devices only: Critical tasks? · Modified devices only: New critical tasks introduced or are existing critical tasks impacted**? Yes. In this case, the submitter evaluated the existing critical tasks, and some were impacted. Dose calculation function is impacted by additional (new) icon access on new home screen for unit selection and confirmation. Additional steps and workflow with new icon could cause user negative transfer of experience and lead to delay of therapy.**

Analysis: The recommended HF information in this marketing submission is HF Submission Category 3. The submitter should submit test results and analysis from a new HF validation study for the subject device in an HF Report. The HF Report should include the use-related risk analysis, along with the information referenced in Table 3.

265 **Table 3. Example tabular format for the comparative use-related risk analysis**

Existing Device						Modified Device			
URRA Task #	User Task	Possible use error(s)	Potential hazards and clinical harm	Severity of harm	Critical task (Y/N)	Comparison of use task description to existing device	Labeling content and/or design change differences	Comparison of proposed risk mitigation measure to existing device	**Submitter's comparison comments**
Task #1									
Task #2									

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Modification to an existing PMA approved device, Example B.3

Example B.3. Scenario: A submitter has an approved PMA for a stent with a balloon catheter delivery system. The submitter is requesting approval for a new stent under a new PMA that has a different stent design and coating. The new stent uses the same balloon catheter delivery system as the submitter's own PMA-approved stent. The submitter is proposing to leverage the previous HF validation test results for the balloon catheter delivery system.

Decision Point A: Is it a modification to an existing device **Yes. The submitter is using their own existing PMA-approved balloon catheter delivery system with a new stent.**

Decision Point B: Is there a change to any of the following:· User interface; Intended device users; · Intended device uses; · Intended use environment(s); · Training; or · Labeling? **No. Even though the submitter has submitted a new PMA, in this case, the user-interface of the balloon catheter delivery system is the same as that used in the approved PMA. The only changes to the product are the stent design and coating, which are not user-interfacing and are based on the submitter's approved PMA. The submitter evaluated the critical tasks, and none of them were impacted by the change in stent design and coating. The submitter can leverage the previous HF validation test results in their new PMA.**

Analysis: The recommended HF information in this marketing submission is HF Submission Category 1. The submitter should include a statement justifying that the device modifications do not affect the human factors considerations of the modified device and the conclusion and high level summary of HF evaluation.

C. New Devices, Example C.1

New devices Example C.1. Scenario: In an alternate scenario to Example B.3, the submitter is proposing to introduce the new stent as described above, along with a new balloon catheter delivery system that has a different design from the PMA-approved system.

Decision Point A: Is it a modification to an existing device**? No. The submitter is submitting a new PMA based on a new design of the catheter delivery system with a new stent**.

The submitter should proceed to **Decision Point B**: Based on the use-related risk analysis, are there: New devices only: Critical tasks? · Modified devices only: New critical tasks introduced or are existing critical tasks impacted? **Yes. The submitter has determined based on the use-related risk analysis that there are critical tasks associated with the subject device.**

Analysis: The recommended HF information in this marketing submission is HF Submission Category 3.

The submitter should submit test results and analysis from a new validation study for the subject device in an HF Report. The HF Report should include the use-related risk analysis, along with the information referenced in Table 3.

265 **Table 3. Example tabular format for the comparative use-related risk analysis**

Existing Device						Modified Device			
URRA Task #	User Task	Possible use error(s)	Potential hazards and clinical harm	Severity of harm	Critical task (Y/N)	Comparison of use task description to existing device	Labeling content and/or design change differences	Comparison of proposed risk mitigation measure to existing device	**Submitter's comparison comments**
Task #1									
Task #2									

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C. New Devices Example C.2

New Device. Example C.2.

Scenario: The submitter submits a 510(k) to request clearance for a new portable fingertip oximeter intended for spot checking oxygen saturation of arterial hemoglobin of adult patients in professional healthcare facilities and the home. This is the first portable oximeter device developed by the submitter. Therefore, the submitter uses a predicate device from a different submitter. The subject device does not include any alarms or additional information interpreting the oxygen saturation, nor is it intended for life supporting or life-sustaining functions. The user of the device places the sensor on a finger and then reads the oxygen saturation values calculated by the device. The submitter compares their device with the predicate device to show the indications for use, use environment, and users are the same between the two devices.

Decision Point A: Is it a modification to an existing device? No. The submitter has manufactured a new device. For purposes of demonstrating substantial equivalence, the submitter has identified as a predicate a device from another device manufacturer. The submitter should proceed to Decision Point C.

Decision Point C: Based on the use-related risk analysis, are there:· New devices only: Critical tasks? · Modified devices only: New critical tasks introduced or are existing critical tasks impacted? No. The submitter determined through their use-related risk analysis that the action of placing the sensor on a user's finger and reading the oxygen saturation values could not cause serious harm to the user/patient. The submitter further justifies this conclusion by stating the device is used as a spot-check and there are no alarms or additional information interpreting the results from the device.

Analysis: The recommended HF Submission Category in this marketing submission is HF Submission Category 2. The submitter should provide a rationale for why there are no critical tasks.

Item #2: Recommendations/Considerations

- Recommendation/Consideration #1- The device manufacturer must have an internal documentation of risk management, human factors engineering testing (when applicable), and design optimization processes which can help provide evidence, where appropriate, that the needs of the intended users were considered in the design and that the device is safe and effective for the intended users, uses, and use environments. The Quality System Regulation (21 CFR part 820) requires that manufacturers of certain finished devices verify and validate device design, review and approve changes to device design, and document changes and approvals in the design history file (21 CFR 820.30). FDA recommends that human factors information be maintained by the manufacturer regardless of whether it is submitted to FDA. The FDA Group can support a device manufacturer's internal risk documentation including human factors engineering testing and design optimization.

- Recommendation/Consideration #2-Submitters should begin with a conclusion stating whether the user interface of the device has been found to be adequately designed for the intended users, uses, and use environments and whether new human factors testing was conducted to support this conclusion. FDA recommends that submitters begin with a high-level summary of the human factors engineering assessment (e.g., use-related risks), including the underlying rationale for conducting the assessment, and a summary of the human factors engineering processes conducted (e.g., human factors engineering analyses and evaluations, device-user interface modifications and validation testing) and analysis of the results. The FDA Group can help support a conclusion where a device statement substantiates that the device user interface is adequately designed for its intended use.

Item #3: Recommendations/Considerations

- Recommendation/Consideration #3-When modifying an existing device, FDA recommends that submitters compare the new device user interface to their own existing device in their marketing submission. FDA recommends completing this comparison in a tabular format. An example tabular format is provided in Table 4. Submitters should list any critical tasks affected by the modification(s). Submitters should also discuss whether the risk associated with the modification is acceptable and assess whether the proposed changes warranted human factors 29 ANSI/AAMI/ISO 14971: Medical devices—Application of risk management to medical devices: " Contains Nonbinding Recommendations Draft – Not for Implementation validation testing. "

- **Table 4. Example tabular format for the comparison of the modified device user interface to the existing device**

Modification description	Image of existing device-user interface component	Image of modified device-user interface component	Description of the modification made to the modified device
Modification #1			
Modification #2			

Item #4: Recommendations/Considerations

Recommendation/Consideration #4- In addition to the use-related risk analysis document for the entire device, submitters should include a subset of the use-related risk analysis that isolates tasks and risks associated with the proposed modifications made to the device. FDA recommends including photographic images of the device-user interface components that were modified, including modifications to labeling such as warning statements in an instructional manual.

Recommendation/Consideration #5-Research – Research user needs to support design input.

-Analyze – Task analysis, know problem analysis and use-related risk analysis.
-Design – Develop designs that are intuitive, easy to use and that reduce the risk of use errors.
-Evaluate – Formative and summative evaluation support at each stage of product development.

- **Recommendation/Consideration #6-Consultative Services-**

Use consulting services to support needed Analysis, Design Research and Formative/Summative evaluation support to comply with FDA's new updated Human Factors Guidance to support 510k or PMA use-related risk analysis.

Optimizing device design through application of HFE/UE extend beyond improved safety

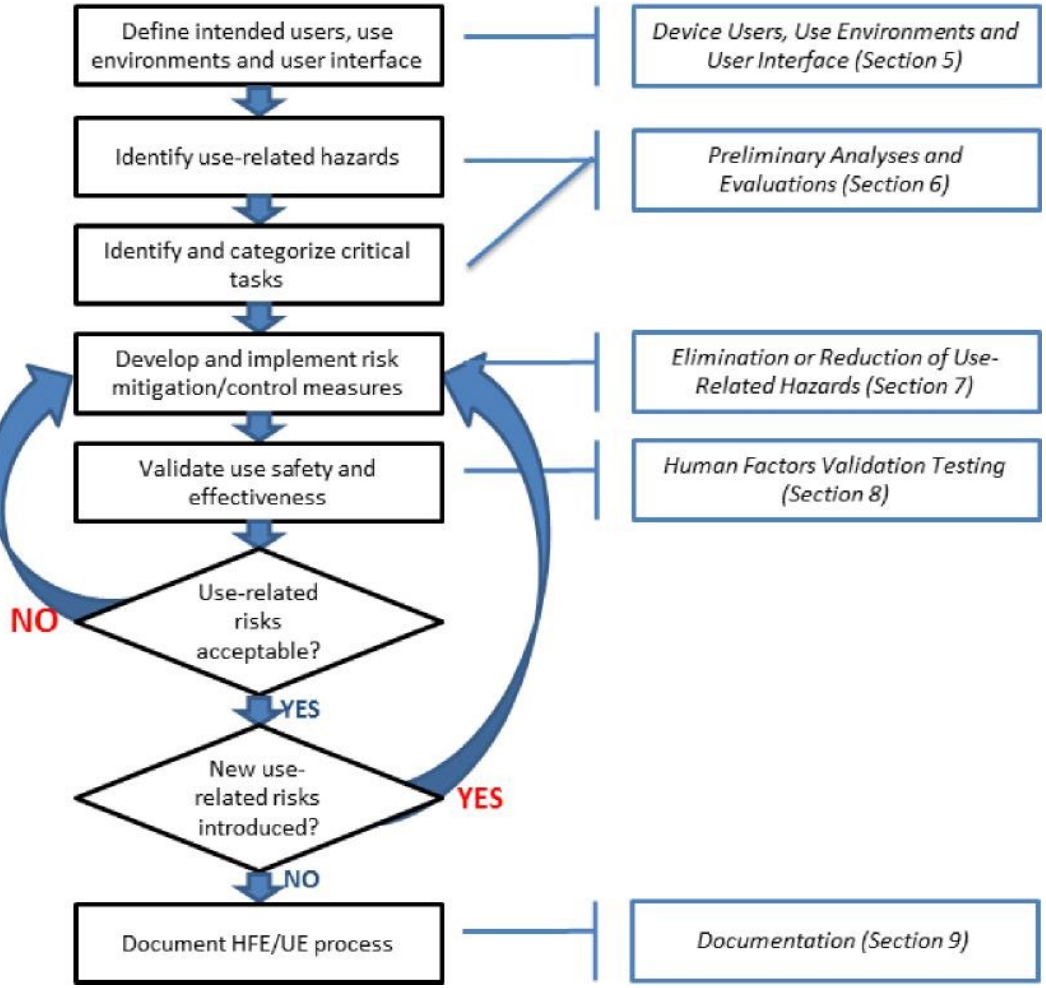
The advantages of optimizing device design through application of HFE/UE extend beyond improved safety. Many device manufacturers have found that the application of HFE/UE during the development of their products reduces the need for design modifications and costly updates after market introduction and offers competitive advantages.

With increased safety, the likelihood of incurring expenses associated with product recalls or liability is reduced; and when HFE/UE approaches are used during the design development process, particularly if the perspective of users is taken into account, the overall ease of use and appeal of a device can simultaneously be enhanced.

A HFE/UE report included in a premarket submission should provide information pertaining to device use safety and effectiveness in summary form. The report should discuss the safety-related HFE/UE considerations, issues, processes, resolutions, and conclusions.

The level of detail of documentation submitted should be sufficient to describe your identification, evaluation, and final assessment of all serious use-related hazards for the device. To facilitate FDA review, materials used directly in the HF/UE process, including portions of risk analyses focusing on user interactions with the device and specific risk analysis processes, results and conclusions should be included in the HFE/UE report.

Consulting support at any stage of HF analysis:



Consulting Support: Critical Task Identification and Categorization

An essential goal of the preliminary analysis and evaluation process is to identify critical tasks that users should perform correctly for their medical device to be safe and effective. Outside consultants such as the FDA Group can support the identification of critical medical device Human Factors' issues by performing a preliminary analysis and evaluation.

Consultants can also categorize critical user tasks based on the severity of the potential harm that could result from use errors, as identified in a risk analysis. The purpose is to identify the tasks that, if performed incorrectly or not performed at all, would or could cause serious harm.

Risk analysis approaches, such as failure modes effects analysis (FMEA) and fault tree analysis (FTA) can also be helpful tools for this purpose.

All risks associated with the warnings, cautions and contraindications in the labeling should be included in the risk assessment. Reasonably foreseeable misuse (including device use by unintended but foreseeable users) should be evaluated to the extent possible, and the labeling should include specific warnings describing that use and the potential consequences.

The results of the human factors validation testing should be analyzed qualitatively to determine if the design of the device (or the labeling or user training) needs to be modified to reduce the use-related risks to acceptable levels. To do this, the observational data and knowledge task data should be aggregated with the interview data and analyzed carefully to determine the root cause of any use errors or problems (e.g. "close calls" and use difficulties) that occurred during the test. Consultants can also address the root causes of all use errors and problems. These should then be considered in relation to the associated risks to ascertain the potential for resulting harm and determine the priority for implementing additional risk management measures.

Item #3: References

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Item #3 –

Anatomy of a Warning Letter-Glenmark Pharmaceuticals

Item #3: Background

- Glenmark Received an FDA Warning Letter (11/22) at its Goa, India facility.
  - **Four Major QMS Elements** Were Identified as Noncompliant
  - Product Found to be Adulterated, and Multiple Batches Recalled
- Glenmark is a Major Indian Pharma Manufacturer (About $1.5 USD Revenue)
- 13,000 Employees, 10 Formulation Facilities, and 4 R&D Centers (Global)
- Stock has Taken a 5% Hit Upon News of the Warning Letter Issuance
  - Typical for Public Healthcare Firms in Trouble

Q: What Went Wrong? A: Lots of Stuff.

Item #3: A Few Warning Letter Excerpts

- Although you attributed the content uniformity failure to the lack of defined [tablet] compression parameters for Desmopressin Acetate 0.1mg batch 20210776, you failed to test other batches/products that used same **(b)(4)** process & compression equipment.

- Your firm failed to adequately validate the manufacturing process for **(b)(4)** gel **(b)(4)**%. Specifically, your process validation lacks an evaluation of inter-batch and intra-batch variability for **(b)(4)** gel **(b)(4)**% [1 tube/each of the 3 validation batches tested].

- Your analyst manually modified the processing of chromatographic data of **(b)(4)** impurity peak for **(b)(4)** tablets batch **(b)(4)**. The impurity results would not have met release specification if the automatic integration processing had been applied in the same manner as they were to the standard and other peaks.

- Production operators acknowledged using default pre-set tablet rejection values in the recipes for tablet compression instead of calculating the batch specific rejection limits as required by your procedure … In each of the investigations, since the automatic weight control or compaction force control was turned on, the risk of finding tablets that did not meet specification was low.

Item #3: The Main Issues

Four Major QMS Systems Went Off the Rails in Goa:

1. OOS Investigation: Quarantine vs. Containment
2. Inadequate Process Validation
3. Chromatogram “Processing” to Pass/Ship Product
4. Breakdown in Mfg Procedures, sp. Equipment Setup

Item #3: The Consultant's View

#1 OOS Investigation: Quarantine vs. Containment

- Quarantine: Places a Suspect Lot or Product on Hold
- Containment: Places Product Brothers/Sister/Cousins on Hold
- A Rigorous Containment Action Would Probably Have Resulted in a Significantly Larger Recall

#2 Improper Validation

- 1 Tube Tested per PQ Lot for Viscosity
- No Defensible Statistical Rationale for Finished Drug PQ
- Either Process not Validation-Ready, or Corners Were Cut Due to Timeline/Cost Pressures

Item #3: The Consultant's View, Con't

#3 Chromatogram "Processing" to Pass/Ship Product

- Appears to be a Simple Case of Data Manipulation to Pass Product
- FDA has Zero Tolerance Regarding "Data Integrity" (Duhh…)
- Case of, "Do Whatever You Need to Do to Ship That Product"

#4 Breakdown in Mfg. SOP's, sp. Equipment Setup

- Equipment Setup SOP (Testing Machine) Deliberately Ignored
- Operators Were Aware That The Correct Settings Would Hit Yield
- Inadequate or Deliberate Oversight Confirming Machine Settings

Analysis of QMS Breakdown

- Looking at the Firm as a Whole, Seems Successful ($1.5B Revenue)
- 13,000 Employees & 10 Sites, No Shortage of Talent/Resources
  - These are Bush-League, Low-Hanging Fruit Problems
  - This Stuff Should Have Been Caught During an Internal Audit

- The Real Question is, “Where is Quality”? Who is Signing Off On:
  - Inadequate OOS Investigations?
  - Validation Protocols w/Zero Statistical Rationale?
  - Manipulated Chromatograms?
  - Incorrect Machine Setups?

Let's Apply a 5 Why's Methodology

- Why 1: Why did the Goa Facility QMS go off the rails?
  - Lack of Quality/Independent Oversight
- Why 2: Why was There a Lack Quality/Independent Oversight?
  - Inadequate Quality Resources, Capabilities, or Oversight Mandate
- Why 3: Why was There a Lack of Quality Resources/Oversight?
  - Failure to Adequately Manage Product & Compliance Risk at Goa
- Why 4: Why did was There a Failure to Adequately Manage Risk?
  - Lack of Site-Level or Corporate-Level Leadership
- Why 5: Why was There Such a Leadership Loss?
  - How Could Boeing Ship the Most Successful Plane in Aviation History, and end up Killing 346 People & Costing the Firm $20B?

The Aftermath and its Root Cause(s)

- Glenmark's Credibility is now Suspect with FDA, as well as with the EU, AUS/NZ & Other Lucrative Markets Glenmark Depends Upon
- The 5% Stock Hit, Probable Suspension of Pending NDA/ANDA Reviews, and a Very Costly Site Remediation is their New Reality
- Any "Savings" from Cutting Corners Essentially Evaporated
- Goa Site Ops & Quality Management Will End Up Being Blamed
- Possible Root Causes for a Firm in "Regulatory Distress" Include:
  - Lack of Management or Technical Competency
  - Lack of Resources
  - Lack of Oversight
  - Lack of Management Integrity/Commitment

Key Lessons & Takeaways

- Corporate Governance in a Multi-Site/Multinational Healthcare Firm Must Be Laser-Focused on Uniform QMS Processes & Oversight
  - New Product Development
  - Validation and Verification (V&V)
  - Internal Audits
  - OOS Investigations
  - CAPA
- Especially Crucial to Apply the Above Governance With Recent Acquisitions, Site Expansions, Implementation of New Technology, etc.

"At the End of the Day, It's Much Smarter for YOU to First Find the Problem, and not the FDA"

Thank you