BUILDING EQUITY

IN MEDICAL DEVICE DESIGN CONTROL

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INTRODUCTION

Across the United States, there are major disparities in health outcomes across different demographics. While there are many contributing factors to this public health problem, medical devices have the potential to either exacerbate or aid in outcomes. Unfortunately, medical devices continue to be designed and developed without consideration of the diverse user population across the United States (US). For example, products are predominately tested on the White, male demographic, yet Latino and Black communities comprise 30% of the United States' population. In fact, the US Census Bureau predicts that within 30 years, the nonwhite proportion of the American population will shift to more than 50%. However, these communities make up a mere 6% of all participants in federally funded clinical trials (Konkel, 2015).

The severity of health inequity in America has recently been highlighted by the COVID-19 pandemic. This can be seen, for example, through racial biases exposed in current pulse oximeters, which are integral to diagnosing and treating respiratory conditions such as hypoxemia (often linked with COVID-19). Research has shown that occult hypoxemia is more prevalent in patients with darker skin colors due to the inaccuracy of current over-the-counter *and* hospital-grade pulse oximeters. (Cabanas, 2022) and (Fawzy, 2022).

A study conducted by the University of Michigan in December 2020 revealed that patients with darker skin tones are at a significantly higher risk of pulse oximeters missing low oxygen saturation (SpO_2) levels; in fact, Black patients are three times more susceptible (Wallis, 2021). Yet despite being aware of this and similar disparities found throughout medicine, medical device developers continue to report data for specific subpopulations that rarely meet regulatory guidance (Richardson, 2021). As a result, developers often are not held sufficiently accountable for issues of bias and transparency in their algorithms, resulting in a market of at-risk and unaware customers.

To ensure medical devices are equitable to diverse consumers across the population, an intentional process to build equity into medical device design control must be undertaken. Currently, the mitigation of bias is predominantly accomplished through equitable clinical studies during the design validation stage. However, opportunities for bias to enter devices **exist at every stage of the medical device development process**: design planning, design inputs, design outputs, design verification, design validation, design changes, design reviews and design transfer, along with the risk management process. Design requirements that do not account for user diversity lead to biased products; insufficient diversity in sampled populations taints data collection; failure to implement anti-bias mitigations causes issues during model development; a lack of developer awareness about bias and equity results in inadequate model evaluation; and insufficient regulations and

regulatory guidance related to equity prevents FDA review and approval from being an effective guard against inequality. However, by identifying discrete stages to prevent bias during the medical device development workflow, one can identify specific processes that need greater scrutiny and target where methods can be introduced for ensuring equity. This allows for experts in the field to propose concrete means for addressing systemic bias and introducing equity for developed devices and their users (Vokinger, 2021). Through a case study of MelanOxi, an updated calibrated pulse oximeter design created by the Cornell University Biomedical Device (CUBMD) team, this paper will discuss ways to create, standardize, and control an equitable medical design development process for all types of devices.

1. SCOPE

1.1. Field of Application

The scope of this paper is for products that are classified as medical devices. This includes, but is not limited to medical device hardware, software as a medical device (SaMD) and artificial intelligence/machine learning software (AI/ML), medical device hardware with software integration, biologic medical devices, and combination products that include a medical device constituent.

1.2. Relation to other Standards

For the purposes of this paper, the scope is limited to the US FDA regulatory requirements, specifically 21 CFR Part 820 – Quality System Regulation. Any product classified as a medical device or that has a medical device component and is intended for sale in the United States requires compliance with the FDA's quality system regulations. Class II and Class III devices require implementation of the medical device design control requirements under 21 CFR Part 820.30. It is important to note that the FDA issued a proposed rule to adopt the ISO 13485:2016 Medical Device Quality Management Systems Standard. References to this standard will also be included in this paper.

2. KEY DEFINITIONS[1]

2.1. **AI/ML (Artificial intelligence/machine learning)-** the science and engineering of making intelligent machines, especially intelligent computer programs (McCarthy, 2007).

[1] Refer to 21 CFR 820 and ISO 13485:2016 for a comprehensive set of definitions.

2.2. **Bias** – Perception of a social group that influences the understanding of that group, and the actions and decisions towards them (NIH).

2.3. **DHF (Design History File)-** "a compilation of records which describes the design history of a finished device" A DHF should include information necessary to demonstrate "that the design was developed in accordance with the Design Plan and Quality System requirements" (FDA).

2.4. **Health Equity-** Having equal and fair opportunities to attain the highest level of health for everybody, which requires addressing the social determinants of health, health disparities, and historically unethical practices (CDC)**.**

2.5. **Medical Device** – "An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: (A) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section *520(o).*" (Section 201(h) of the Food, Drug and Cosmetic)**.**

2.6. **Pulse Oximeter -** "A noninvasive medical device that utilizes spectrophotometry to measure the oxygen saturation of circulating arterial blood in an individual by determining the percentage of oxygenated hemoglobin pulsating through a network of blood capillaries by way of a sensory attached typically to a finger, toe or earlobe" (Merriam-Webster).

2.7. **QMS (Quality Management System)-** "A formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives. A QMS helps coordinate and direct an organization's activities to meet customer and regulatory requirements and improve its effectiveness and efficiency on a continuous basis" (ASQ).

2.8. **QSR (Quality System Regulation)-** "The quality system regulation includes requirements related to the methods used in, and the facilities and controls used for, designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use" (FDA).

2.9. **Residual Risk-** Risk remaining after risk control measures have been implemented (ISO 14971: 2019E, 3.17).

2.10. **SaMD (Software as a Medical Device)-** "Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device." (International Medical Device Regulators Forum).

2.11. **Supplier-** "A person, organization, or other entity that provides something that another person, organization, or entity needs. Suppliers provide or supply products or services" (Market Business News).

2.12. **Traceability Matrix-** "A self-documenting verification method is the traceability matrix. This method is particularly useful when the design input and output are both documents; it also has great utility in software development. In the most common form of the traceability matrix, the input requirements are enumerated in a table, and references are provided to each section in the output documents (or software modules) which address or satisfy each input requirement. (FDA, 1997) Then the verification and validation reports that satisfied the design input requirements are also referenced in the table.

3. BUILDING EQUITY INTO MEDICAL DEVICE DESIGN CONTROL

3.1. DESIGN AND DEVELOPMENT PLANNING

Regulatory References: 21 CFR 820.30 (b); ISO 13485:2016 7.3.2

3.1.1. Design Development Plan (DDP)

The Design Development Planning process is the first step of medical device development. A DDP should be established and include an overall project plan with deliverables and goals that reflect all phases of the development process and be kept up to date as the design progresses. This ensures that the medical device development process is controlled and compliant with the regulatory requirements of the country it will be launched in. The DDP can be an all-inclusive plan that covers the entire development process or an overarching plan that sub-plans flow into. For the purposes of this paper, we recommend **how equity can be realized for each subsection planning of a medical device, whose scope includes hardware and software including artificial intelligence (AI) and machine learning (ML)**.

DDPs include an outline of the development phases, a list of team members and their qualifications, and establish critical decision-making points in the development process. The organizational structure of the team, their responsibilities, and their interrelationships should be clearly defined and documented (FDA, March 1997).

Equity can be operationalized in this phase of Design and Development Planning as follows:

- Establishing a team of experts to design and develop a medical device is the first critical step in the development process. The following principle is an example of how to reduce algorithmic bias on a team but can be applied to any team of experts that is developing a medical device. To address algorithmic bias, the team working on the product should be diverse:

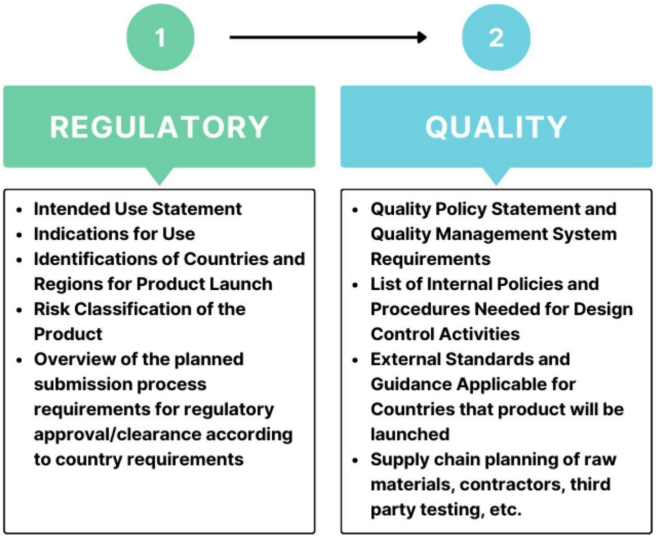
  "Therefore, combating algorithmic bias means that data science teams should include professionals from a diversity of backgrounds and perspectives, not simply data scientists who have a technical understanding of AI. In the Journal of Global Health paper, Panch and Mattie suggested that clinicians should be part of these teams, as they can provide a deep understanding of the clinical context that will improve modeling." - (Igoe, 2021).

- A diversity of not only expertise, but backgrounds is essential to ensuring proper vetting and equity from the beginning of the design process. Studies have shown that even if teams consist of experts with the same technical background, those with members from diverse racial, religious, socioeconomic, etc. backgrounds tend to be more successful at combating bias in their designs (Gomez, 2019).

The following plans are recommended subsections of the overall DDP with recommendations on how to incorporate planning for building equity in design control:

3.1.1.1. Quality and Regulatory Plan

Regulatory Planning outlines the regulatory strategy of how the product will be submitted for FDA approval or clearance into the market, along with any other intended market strategies. This drives Quality Planning, starting with what type of quality management system (QMS) is required for the development, production, and post market monitoring of the final product. Below is a diagram that lists some important attributes that should be included in the Regulatory and Quality Planning document(s).



Equity can be operationalized in this phase of Design and Development Planning as follows:

- The Quality Policy should include a **"Fairness Statement"** (Wallis 2021) promising that equity principles are established downstream throughout the Quality Management System. This would drive company policies and procedures to incorporate principles of equity from the design control process through post market monitoring of the product.

- Manufacturers should include subject matter expert(s) in health equity as a resource on the design development team. They can be an in-house resource or contracted out and qualified as a supplier. Table 1 represents recommendations based on company size:

TABLE 1: Recommendations on Resourcing Equity Specialists in the Organization

Small Sized Company	Medium Sized Company	Large Sized Company
In-house Product Developer trained and certified in Health Equity principles and receives annual training.	Contract Health Equity subject matter expert trained in Design Control Principles.	Embedded Health Equity organization to support product development and post market surveillance.

- Regarding the acquisition of data sets used for AI/ML training: if the data is acquired through a third-party resource, the supplier evaluation process should include a way to verify the data sets provided are not biased. One way is to require the supplier to provide a Fairness Statement for the data

provided. Another way is for suppliers to provide equivalent documentation that demonstrates equity across the user population in the data.

- Regulatory Plans should consider if the submission process inadvertently reinforces inequalities when using in vitro methods to show equivalence to a product that was developed, clinically tested and cleared in the past. Are there ways to prevent carrying forward inequity into the new product design?
- External Standards and Guidance applicable for countries that products will be launched in are typically included in the DDP. They should also include a list of regulatory standards and guidance documents related to implementation of equity for the medical device development process.[2]

3.1.1.2. Design Health Equity Plan

The Design Health Equity Planning document should provide an overall strategy on how to implement equity principles throughout the design control process. This is not yet required by the FDA regulations or proposed in any guidance documents and is therefore a new concept introduced in this paper. However, in 2022, the White House released a Blueprint for an AI Bill of Rights which speaks to Algorithmic Discrimination Protections and states the following:

"Designers, developers, and deployers of automated systems should take proactive and continuous measures to protect individuals and communities from algorithmic discrimination and to use and design systems in an equitable way. This protection should include proactive equity assessments as part of the system design, use of representative data and protection against proxies for demographic features, ensuring accessibility for people with disabilities in design and development, pre-deployment and ongoing disparity testing and mitigation, and clear organizational oversight. Independent evaluation and plain language reporting in the form of an ***algorithmic impact assessment, including disparity testing results and mitigation information,*** *should be performed and made public whenever possible to confirm these protections."*

Although this is centered on AI models, the underlying concept of this blueprint can be applied to the development of any type of medical device. The design development team members should include a subject matter expert in health equity whose purpose is to ensure that devices are designed equitably and can perform independent assessments through every step of the development process.

Another resource that can be used to develop a Health Equity Plan is the Health Equity-Oriented Strategy Selection, Design and Implementation guidance released by the Centers for Disease Control and Prevention (CDC). This contains excellent points that can be built into the Design and Development Planning stage and executed throughout the development process:

[2] This paper has compiled a list of references that can assist companies in initiating this process. See Regulatory References and Guidance.

- Balance community input & available evidence.
- Ensure design strategies can identify inequalities.
- Generate a comprehensive approach of strategies.
- Establish processes to identify and address implementation challenges.
- Account for diversity.

The Health Equity experts should also provide and/or facilitate DEI (Diversity, Equity, Inclusion) training to the entire design team. The training should be tailored to the role of the team participants. This effort will help support the Fairness Statement in the Quality Policy.

3.1.1.3. Design Verification Plan

The Design Verification Planning Document provides an outline of the activities needed to provide evidence that the design input requirements have been met. This can be achieved through objective evidence, typically through testing and inspection of the production builds that were manufactured according to design output requirements. This also includes an analysis of the results to ensure that the product passes established verification testing. Plans for verification testing include the overall verification strategy, along with worst-case analysis of critical and major design points to ensure that the product is reliable (FDA, March 1997).

Equity can be operationalized in this phase of Design and Development Planning as follows:

- Manufacturers should make strides in determining worst-case scenarios and potential scenarios of inequities and bias when they generate their Design Verification Planning document.
    - Using the pulse oximeter as an example, design verification activities should include the requirement to use a validated/certified scale for skin tone during testing for SpO_2 levels. In this example, the Verification Plan or associated verification protocol(s) should include acceptance criteria using the scale.
- A feedback system built into the Risk Management Plan is imperative so that if unexpected failures occur, they can be assessed and mitigated through the risk management process.

3.1.1.4. Design Validation Plan

The Design Validation Planning document should outline the process of how the user needs and intended use of the device can be verified under actual or simulated conditions. Along with Human Factors Summative Testing, this is the stage where the end-user can test the device before it goes to market.

The Design Validation Plan should outline the processes needed to achieve the product's intended use: "the performance characteristics that are to be assessed should be identified, and validation methods and acceptance criteria should be established" (FDA, March 1997). Design Validation Planning should ensure that outputs from the Human Factors Summative Studies and Clinical Investigations are tied into the Risk Management process and are evaluated under the umbrella of the Design Validation Planning process.

If the device requires clinical evaluation, the Design Validation Plan should include (or refer to a separate document that outlines) clinical investigation planning requirements to establish or verify the safety and/or performance of the medical device in a clinical environment.

Equity can be operationalized in this phase of Design and Development Planning as follows:

- When it comes to developing a clinical plan, the FDA recommends that "a plan to address inclusion of clinically relevant subpopulations should be submitted for discussion to the Agency at the earliest phase of development." (FDA, October 2016)
    - The FDA recommends the development of a "Race and Ethnicity Diversity Plan…to enroll representative numbers of participants from underrepresented 19 racial and ethnic populations in the United States, such as Black or African American, 20 Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific 21 Islanders, and other persons of color, in clinical trials" (FDA, April 2022).
    - The "Race and Diversity Plan" can be integrated into or referenced as a standalone to the Clinical Plan.

- The Clinical Plan under the DDP should include statistically sound criteria to ensure population demographics are fairly represented. This will lead to enhanced safety and effectiveness of the final product.
- Data collection methods should include adequate race and ethnicity data (FDA, October 2016).
    - Race and ethnicity data should be able to be broken into subpopulations and have numerous options to ensure proper representation of different populations.
- Data collection methods should include data on sex and gender.
- Data collection methods should include data on age.
    - This is particularly important if a product designed for children is also being tested on adults.

3.1.1.5. Software Development Plan (SDP)

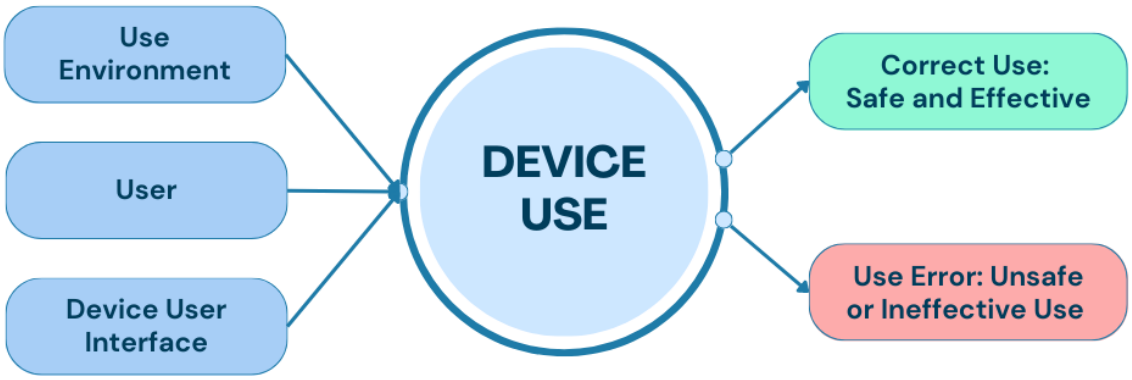
IEC 62304, "Medical Device Software – Software life cycle processes" is an excellent standard that provides guidance on how to develop medical device software, requiring initiation of a Software Development Plan (SDP). The SDP should address all activities of the software development lifecycle process such as software classification, the type of software development process(es) used, establishment and traceability of requirements, tools that will be used, risk measures, configuration management, change management and much more.

However, since this standard does not directly address equity and inclusion, the following should also be added to the Software Development Plan:

- Datasets used for AI/ML are developed and trained from historical datasets, leaving them open to bias. This generates algorithmic bias. Methods and/or tools should be put in place to prevent, identify and eliminate bias in datasets (FDA, January 2021).
    - This entails careful collection of training with initial data (especially for devices with AI/ML components) and testing data after development is complete to ensure maximum accuracy and equity.
- Establish software requirements that include consideration of demographics (e.g. skin color, gender, accessibility, etc.).
- Consider product development risk levels and assignment of overall software level of concern associated with people of color and the disadvantaged.

- For example, people of darker skin tones are more likely to receive over estimated oxygen saturation levels which can lead to hypoxia (low O_2 levels) not being detected (Australian Government). If not addressed in a timely manner, this could lead to serious injury or death.

3.1.1.6. Human Factors/Usability (HF/UFE) Plan



The FDA released a guideline Applying Human Factors and Usability Engineering to Medical Devices, which intends to support manufacturers in improving the design of devices to minimize potential use errors and resulting harm. The Human Factors Engineering and Usability Engineering (HFE/UE) planning document should outline the process of how to analyze, identify, and eliminate hazards associated with the use of medical devices. HFE/UE considers three major components in the development of medical devices: device users, device use environments and device user interfaces. The HFE/UE Plan and its results should feed into the overall Risk Management process.

Equity can be operationalized in this phase of Design and Development Planning as follows:

- Like the Clinical Planning Document, the Human Factors protocols should ensure that the sample size of participants represents the demographics (for example, age, gender, sex, race, and ethnicity) of the intended patient population.
- The plan should also consider usage hazards and harms that can be caused by skin color, socioeconomic status, gender identity and status, first language, nationality, ability status, age, etc.

- The HFE/UE Plan should also consider how different cultures or backgrounds might make a particular group more susceptible to misuse of a device. For example:
    - Language: is the user able to adequately read the directions, engage with the device, etc.?
    - While the ability of a user to operate a medical device is said to depend on their personal characteristics, the HFE/UE analyses should relate these characteristics to experiences of social identities.
    - What quantifies "ability to learn and adapt to a new device," and who might we be more accommodating of by maintaining the plan without inclusivity?
- The HFE/UE Plan should also take into consideration subpopulation-specific willingness to use and try a given device and how to balance this with populations' differing needs for certain products/services (FDA, 2016).

3.1.1.7. Risk Management Plan

The Risk Management Plan's purpose is to create a system to identify and mitigate risks associated with the medical device. Risk Management is realized not only during the design development process but is managed throughout the lifecycle of the product.

Equity can be operationalized in this phase of Design and Development Planning as follows:

- Identification of errors associated with the interface of the device and user:
    - For example, User Failure Mode and Effect Analysis (UFMEA) is an analysis to identify risks associated with the intended use and foreseeable misuse of the device. The identified risks from the HFE/UE, clinical studies and design validation activities are assessed and mitigated.
    - Additionally, the differing susceptibilities of people from different cultures /backgrounds /subpopulations to misuse a given device should also be considered as a risk factor, which ties into the HFE/UE plan.
- Identification of errors associated with the design of the device:
    - For example, Design Failure Mode and Effect Analysis (DFMEA) is an analysis to identify risk associated with the product design, including component, sub-assembly, and finished product failure modes.

- Manufacturers should determine risks and mitigation associated with people from different cultures/backgrounds/subpopulations when it comes to the design of the product and record this in their Risk Management Plan.
- Manufacturers should consider risks associated with limited availability of resources in low-income areas, for example: limited power, higher humidity levels, different levels of altitude, etc.
- For AI/ML SaMD models, consideration should be given to mathematical approaches for de-biasing models during development and establish a means for identification of bias during model evaluation (Vokinger, 2021) during design verification.

- Post-market Risk Management Monitoring (for example: Complaint Handling, Corrections and Removals, Adverse Events, Nonconformances, Post Market Surveillance, Cybersecurity, etc.):
  - A feedback system to collect data and evaluate risks that occur after the product is released into the market is critical to allow continuous improvement of the device design.
  - Data collection methods should be designed based upon demographic data.
  - Residual risks, including those that are related to demographics, should be monitored, and re-evaluated for scoring during the lifecycle of the product.
  - Feedback should be obtained from users and clinicians on the quality of care the product provides.

3.1.1.8. Cybersecurity Plan

The rise of the age of Artificial Intelligence (AI) and Software as a Medical Device (SaMD) increases the rise of threats to the end user. Cybersecurity is imperative for medical devices that contain software. FDA regulation 21 CFR 820.30(g) specifies the requirement for software validation and risk analysis. According to the (FDA, September 2023), cybersecurity mitigation must be built into medical device design controls along with post market monitoring controls for the lifecycle of the product to ensure patient safety. Therefore, medical device manufacturers should include cybersecurity planning during the Design Development Planning process.

Equity can be operationalized in this phase of Design and Development Planning as follows:

- According to (Seals,2021), "Lower-income and vulnerable populations are disproportionately affected by cybercrime, according to a new survey, which uncovered that demographics play a big role in how often individuals are targeted". Cybersecurity Planning should account for these disparities and

implement design input requirements and risk mitigations to ensure that devices with software elements are designed equitably and safe for all users.

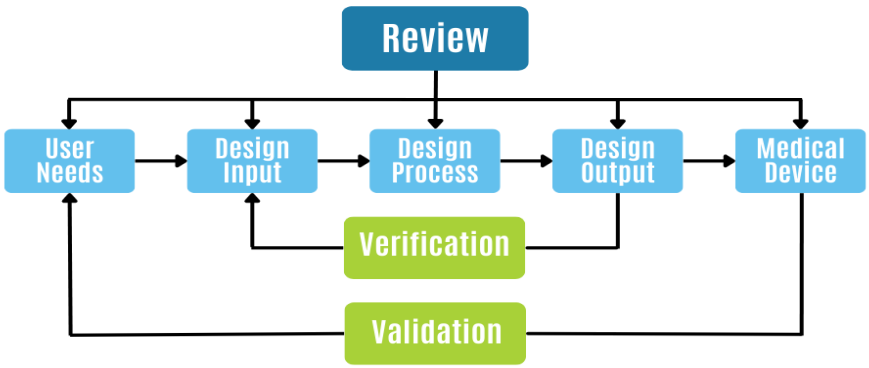
- Cybersecurity Planning should be designed to provide feedback mechanisms into the overall Risk Management Plan.

3.2. DESIGN AND DEVELOPMENT INPUTS

Regulatory References: 21 CFR 820.30 (c); ISO 13485:2016 7.3.3

Design and Development Inputs is the critical stage where the design work begins. Design Inputs establishes the various types of requirements for the device under development. These requirements establish the foundation of how the device will be designed, built, and tested. If adverse events occur post-product launch, it is most likely because the developers did not account for important requirements during this phase of the development process. Hence, this is a critical stage where equity can be operationalized and implemented in medical device design. The FDA states, "Effective development of Design Input requirements encompasses input from both the product developer as well as those representing the needs of the user, such as marketing." The FDA further states how incorrect assumptions of user needs "can have serious consequences that may not be detected until late in the development process." (FDA, March 1997)

Design Inputs define the success criteria for verification and validation. Referring to the FDA "waterfall" diagram, the top level of Design Inputs starts with identifying and defining the user needs and the intended use of the medical device under development. Then, the design input requirements can be created.



Reviewing these important examples below, it is clear that equity must be first and foremost when designing products to benefit a large-scale population. As in the case of pulse oximeters, there are several significant faults in the devices that were overlooked due to lack of generating requirements with a diverse population in mind.

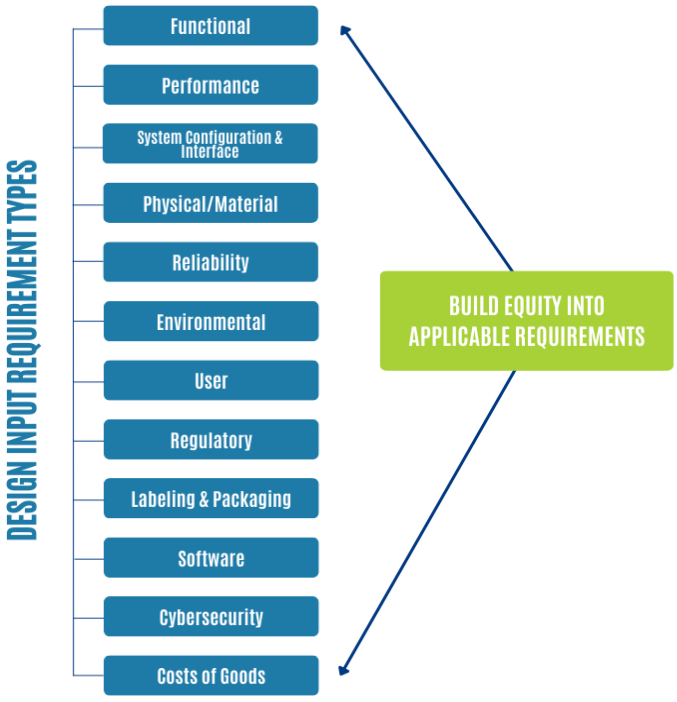
TABLE 2: Design Input Scenarios

Study	Issues Identified	Key Takeaways
Rathod M, Ross H, Franklin D, et al. Improving the Accuracy and Equity of Pulse Oximeters. JACC Adv. 2022 Oct, 1 (4). https://doi.org/10.1016/j.jacadv.2022.100118	*"Objective quantification of skin tone would allow for more robust models when studying biophotonic interactions and would not be susceptible to varied ambient lighting conditions and differences in individual visual perception."*	An important **performance characteristic** for a pulse oximeter is to accurately measure SpO_2 levels regardless of skin tone, which should be clearly defined as a design input and translated into the design outputs that match this dire need.
Feiner, John R. MD; Severinghaus, John W. MD; Bickler, Philip E. MD, PhD. Dark Skin Decreases the Accuracy of Pulse Oximeters at Low Oxygen Saturation: The Effects of Oximeter Probe Type and Gender. Anesthesia & Analgesia 105(6):p S18-S23, December 2007. | DOI: 10.1213/01.ane.0000285988.35174.d9	*"A significant issue for pulse oximeter accuracy is finger size and geometry. In 20 yrs of testing pulse oximeters, it is our impression that women, especially those with smaller fingers, tend to exhibit greater bias and variability in oximeter performance, especially at low SaO_2…"*	The **user interface and physical characteristics** are essential considerations for the design input sector. Without careful consideration of the target population, (for oximeters, the adult population) we create harmful biases in the device measurements.
Pu, L.J., Shen, Y., Lu, L. et al. Increased blood glycohemoglobin A1c levels lead to overestimation of arterial oxygen saturation by pulse oximetry in patients with type 2 diabetes. Cardiovasc Diabetol 11, 110 (2012). https://doi.org/10.1186/1475-2840-11-110	*"Given that chronic hyperglycemia accelerates the accumulation of advanced glycation end products (AGE) in the skin collagen… which poses specific autofluorescence feature, may emit light by absorbing specific wavelengths light[15], and interfere with the accuracy of pulse oximetry, it is pertinent to examine if elevated blood HbAlc concentrations could result in an overestimation of SaO_2 by SpO_2 with finger probes particularly for type 2 diabetic patients with poor glycemic control."*	Defining **performance characteristics** to keep the overestimation of oxygen saturation from occurring in the event that a patient has a pre-existing condition is critical to ensure that a product can be used in a variety of diagnostic situations.

Equity can be operationalized in this phase of Design and Development Inputs as follows:

- Before brainstorming Design Input requirements, this phase should begin with manufacturers providing DEI (diversity, equity and inclusion) training along with training on incorporating equity in designing new products for the design team members. This can help prevent potential initial biases at the start of the design control process.
- As the design inputs feed into the rest of the process, it is important to ensure that design team members are trained to confirm if the manufacturer's requirements are addressing the intended use of the device in a statistically valid, equitable manner (e.g., include design input requirements based upon demographics and inclusion).
- Additionally, including a qualified Health Equity expert on the team during this phase will also aid in the process of developing equitable design input requirements (Refer to Table 1 of the Quality and regulatory Planning section).

The following are some examples of the type of design input requirements of a medical device under design control development. Equity principles can be operationalized into many of these categories:



3.2.1. Case Study: MelanOxi, A Novel Solution to Patient-Specific Pulse Oximetry

To further demonstrate the significance of implementing equitable processes in the medical device design process, we present a case study on MelanOxi, a pulse oximeter designed to give accurate blood oxygen saturation readings regardless of the user's skin tone, created by the Cornell University Biomedical Device Team (CUBMD).

Design inputs should include requirements that reflect the demographics of the intended end-user. The following is an excerpt of the MelanOxi development file and traceability matrix initiated at the design inputs stage, which aims to address the aforementioned concerns while incorporating the traditional aspects of pulse oximetry.

3.2.1.1. Example of MelanOxi Intended Use Statement

The MelanOxi Pulse Oximeter is indicated for repeated spot-checking and non-invasive measuring of functional oxygen saturation of arterial hemoglobin (SpO_2) and pulse rate at the index fingertip for use with the adult population at home.

3.2.1.2. Traceability Matrix Example Initiation

Top-level User Need UN-1 requires accurate detection of SpO2 in the user. Several design inputs can be created from this requirement. For example, DI-1 is related to the measurement accuracy, and DI-2 is a health equity-related design input that considers the skin tone ranges of the users.

TABLE 3: Traceability Matrix of User Needs to Design Inputs

UN ID#	User Needs	DI ID#	Design Input
UN-1	Adult user requires that blood oxygen levels, SpO_2, are measured accurately.	DI-1	SpO_2 measurements shall be within 2% of actual SaO_2 via Arterial Blood Gas test comparison.
		DI-2	Difference in measurement for the MelanOxi pulse oximeter shall be less than 0.5% between skin tone ranges.
		DI-X	XXX…etc.

If manufacturers of oximeters approved by the FDA used requirement DI-2 in their design and verified and validated the requirement successfully, it could have eliminated erroneous results that commonly occurred with people of color during the COVID-19 pandemic. Let's continue to trace Requirement DI-2 at the next stage of development: Design and Development Outputs.

3.3. DESIGN AND DEVELOPMENT OUTPUTS

Regulatory References: 21 CFR 820.30 (d); ISO 13485:2016 7.3.4

Design Outputs are based on Design Input requirements which provide characterization of these requirements and are used to test product builds for conformance. They include (but are not limited to) assembly drawings, components and material specifications, product and process specifications, software machine code, work instructions, quality assurance specifications and procedures, installation and servicing procedures, and packaging and labeling specifications. Having specific Design Outputs corresponding to the Design Inputs that focus on reducing bias, can aid in device performance and functionality in an equitable way.

The following are examples of Design and Development Output scenarios that fail to address bias in the case of pulse oximeters:

TABLE 4: Design Output Scenarios

Study	Issues Identified	Key Takeaways
Rathod M, Ross H, Franklin D, et al. Improving the Accuracy and Equity of Pulse Oximeters. JACC Adv. 2022 Oct, 1 (4) . https://doi.org/10.1016/j.jacadv.2022.100118	*"Current 510(k) Guidance only requires "2 darkly pigmented participants or 15% of the participant pool, whichever is larger.""*	There are not enough **specifications** for equitable device testing processes that involve a diverse validation data set.
Rathod M, Ross H, Franklin D, et al. Improving the Accuracy and Equity of Pulse Oximeters. JACC Adv. 2022 Oct, 1 (4) . https://doi.org/10.1016/j.jacadv.2022.100118	*"The FDA also clarified that devices should be considered an estimate of oxygen saturation and explicitly states a ±4% standard deviation such that "if an FDA-cleared pulse oximeter reads 90%, then the true oxygen saturation in the blood is generally between 86% and 94%" for prescription oximeters. Over-the-counter devices, which do not pass through even these low regulatory standards, may be even less accurate, but there is a lack of consolidated data."*	Lack of design output criteria such as a **minimum standard deviation** between the device and actual values of the desired measurement (in this case blood oxygen saturation levels) are not required for over-the-counter products.

Study	Issues Identified	Key Takeaways
Feiner, John R. MD; Severinghaus, John W. MD; Bickler, Philip E. MD, PhD. Dark Skin Decreases the Accuracy of Pulse Oximeters at Low Oxygen Saturation: The Effects of Oximeter Probe Type and Gender. Anesthesia & Analgesia 105(6):p S18-S23, December 2007. | DOI: 10.1213/01.ane.0000285988.35174.d9	*"Gender is a statistically significant determinant of pulse oximeter bias, with the magnitude of the gender bias differences varying with oximeter/probe type and Sao2 range. With five of the six oximeter/probe combinations, females had greater bias in saturation estimates over the saturation range from 60% to 100%."*	Design outputs should consider biases in gender and detail validation tests that account for these important **measurement differences between males and females**.

3.3.1. TRACEABILITY MATRIX

Below is a continuation to trace DI-2 (Design Input) from UN-1 (User Need). DI-2 generates several design outputs, but this paper will focus on DO-1 through DO-3. A design output test method is needed for the laboratory bench testing of SpO_2 levels of the device builds. A design output test method is also required for verification testing to compare the oximeter test to the user blood gas test. A design output specification will also be needed to formalize the Monk Skin Tone Scale test.

TABLE 5 : Traceability Matrix Through Design Outputs

UN ID#	User Needs	DI ID#	Design Input	DO ID#	Design Output
UN-1	Adult user requires that blood oxygen levels, SpO_2, are measured	DI-2	Difference in measurement for the MelanOxi pulse oximeter shall be less than 0.5% between	DO-1	Approved Bench Test Method to determine SpO_2 levels in the Laboratory.
				DO-2	Approved Verification Test Method to determine SaO_2 levels using the Arterial Blood Gas test.

	accurately		skin tone ranges.	DO-3	Specification for Monk Skin Tone Scale.
				DO-X	XXX…etc.

Design Inputs and Design Outputs are reviewed during the design review process typically at the end of each stage of design control. From there, the traceability matrix is updated with the verification and validation results. The next section will discuss the Design Review process and then we will return to complete the Traceability Matrix of DO-1 through DO-3 under the Design Verification and Design Validation sections.

3.4. DESIGN REVIEW

Regulatory References: 21 CFR 820.30 (e); ISO 13485:2016 7.3.5

The Design Review process works to continuously evaluate the manufacturer's development progression at different development stages. The Design Review process also evaluates the device's adequacy in meeting the overall intended use. Determination of when the Design Reviews occur are determined and documented in the DDP. The goal is to ensure that the objectives and deliverables of each design stage were met according to the DDP, and to confirm that the team is ready to move on to the next stage.

According to the (FDA, March 1997), *"It is a well-accepted fact that the cost to correct design errors increases as the design nears completion, and the flexibility to implement an optimal solution decreases. When an error is discovered at the end of the development cycle, difficult decisions have to be made regarding an acceptable corrective action. When that corrective action is implemented in haste, the result is often an unintended consequence leading to a new problem. Thus, formal design reviews should be planned to detect problems early."*

This supports the overall concerns presented in the introduction of this paper: **there is not enough emphasis to meet the user needs of all the different cultures / backgrounds / subpopulations and eliminate bias to achieve equity throughout the development process which is why FDA cleared or approved devices can have inherent bias and may not be reliable for all demographics.**

Equity can be operationalized in the Design Review process as follows:

Subject matter expert(s) (SME) on health equity should be part of the Design Review Team, whose purpose is to ensure that devices are designed equitably. This ties into the overall Design Health Equity Plan and Table 1 of the Quality and Regulatory Planning sections proposed earlier in this paper. Design Review activities should include verification that the Health Equity Assessments were performed during each stage of the development process (e.g., add this task as a Design Review checklist item). Having the health equity SME (or health equity certified product developer) attend all design reviews should be a requirement, along with

the project engineer, quality engineer and any other subject matter experts and specialists that performed activities during the specific phase under review.

3.5. DESIGN VERIFICATION

Regulatory References: 21 CFR 820.30 (f); ISO 13485:2016 7.3.6

When the Design and Development Outputs phase is completed, the designers are ready to generate manufacturing product device builds based on all of the Design Output specifications, drawings, and overall requirements. Upon completion, the product device builds are required to undergo verification and validation testing to verify that they meet all of the design input requirements.

There are several types of verification. The method used depends on the design output requirements where manufacturers apply guidelines traditionally used for the technologies found in the device. Examples of practices include performance testing, package integrity tests, biocompatibility testing, stability testing, and comparing the product design to an FDA cleared device with a successful use history.

Documenting verification activities requires generation of verification protocol(s) outlining device build test requirements and a final verification report of the test results. The results should include traceability that all applicable design input requirements have been verified.

Equity can be operationalized in the Design Verification process as follows:

- For AI/ML devices, it is imperative that the data used to train the software is free of bias along with the verification tools used to confirm this.
- Per the Design Verification Planning section, it is important to include ranges for testing to consider the range of demographic differences when considering specifications and scenarios for testing.
    - The ranges for testing are determined by the design outputs for the corresponding design input. The outputs design review should confirm that the outputs specification ranges cover the demographic differences.
- The executed Verification Plan can confirm the Design Output specifications meet the Design Input requirements by testing across a range of demographic differences.

For MelanOxi, the Verification Test Report includes results which confirm that the oximeter's difference in measurement is less than 0.5% between skin tone ranges. Below is a continuation of the Traceability Matrix

example. Verification testing in the laboratory for SpO_2 will be done on device builds, along with a quantifiable laboratory test to verify detection of Monk Scale skin tones.

TABLE 6: Traceability Matrix Through Design Verification

UN ID#	User Needs	DI ID#	Design Input	DO ID#	Design Output	Design Verification
UN-1	Adult user requires that blood oxygen levels, SpO_2, are measured accurately.	DI-2	Difference in measurement for the MelanOxi pulse oximeter shall be less than 0.5% between skin tone ranges.	DO-1	Approved Bench Test Method to determine SpO_2 levels in the Laboratory.	Approved Verification Protocol and Report with evidence of product builds passing SpO_2 levels <0.5%.
				DO-2	Approved Verification Test Method to determine SaO_2 levels using the Arterial Blood Gas test.	Approved Verification Protocol and Report to determine SaO2 levels using the Arterial Blood Gas test.
				DO-3	Specification for Monk Skin Tone Scale.	Approved Verification Protocol and Report with evidence of the product builds passing quantified monk scale test results in the lab with <0.5% between skin tone ranges.

3.6 DESIGN VALIDATION

Regulatory References: 21 CFR 820.30 (g); ISO 13485:2016 7.3.7

Design Validation is the stage where device developers put their product to the test on users to confirm the device meets the user's needs and intended use. This is done in the intended use environment, or an equivalent environment. Production device builds (or equivalent builds, for example, off a pilot line that will be scaled) are created based on the Design Outputs, then undergo verification testing to ensure they are working according to the established specifications. After this, the product is tested on the user. This is the stage where Human Factors Summative testing and clinical evaluation are performed. The Design Validation Planning section summarizes recommendations on how to implement equity in this phase of development. Candidates

selected for HF/UFE and clinical evaluation should be carefully selected with statistical significance, based upon the demographics of the target population.

Below is the final traceability matrix example from the design input, output, verification, and validation example using the MelanOxi Case Study. Testing SaO_2 (oxygen saturation) levels require blood drawn from the user via the arterial blood gas test. These SaO_2 measurement readings will be compared to the user's pulse oximeter SpO_2 measurements. The oximeter will also be calibrated to skin tone using a select number of patients matching the Monk Skin Tone Scale specification range.

TABLE 7: Traceability Matrix Through Design Validation

UN ID#	User Needs	DI ID#	Design Input	DO ID#	Design Output	Design Verification	Design Validation
UN-1	Adult user requires that blood oxygen levels, SpO_2, are measured accurately.	DI-2	Difference in measurement for the MelanOxi pulse oximeter shall be less than 0.5% between skin tone ranges.	DO-1	Approved Bench Test Method to determine SpO_2 levels in the Laboratory.	Approved Verification Protocol and Report with evidence of product builds passing SpO_2 levels <0.5%.	N/A
				DO-2	Approved Verification Test Method to determine SpO_2 levels compared to the SaO_2 Arterial Blood Gas test.	Approved Verification Protocol and Report to determine SaO_2 levels using the Arterial Blood Gas test.	N/A
				DO-3	Specification for Monk Skin Tone Scale.	Approved Verification Protocol and Report with evidence of the product builds passing quantified monk scale test results in the lab <0.5% between skin tone ranges.	Approved Validation Protocol and Report(s) (HFE/UE and/or Clinical) with evidence of the product builds passing monk scale test results with <0.5% between skin tone ranges. Users are selected based upon intended use demographics and monk scale model skin tone

UN ID#	User Needs	DI ID#	Design Input	DO ID#	Design Output	Design Verification	Design Validation
							range requirements.

3.6. DESIGN CHANGES

Regulatory References: 21 CFR 820.30 (i); ISO 13485:2016 7.3.9

Design Changes is a process that must be established at the beginning of design controls and is ongoing throughout the product's lifecycle process. Changes to the device design must be controlled. Design Changes should be classified based on risk levels and are evaluated, verified and/or validated before their implementation. Every company's change control system has checks and balances to determine the impact of the change on the product and the user.

Equity can be operationalized in Design Changes as follows:

Risk Evaluations for design changes should consider the population demographics of the user. The FDA issued draft guidance on predetermined change control plans for AI/ML enabled devices, stating:

"*digital health technologies should be designed and targeted to meet the needs of diverse populations. Predetermined Change Control Plans can take this further by facilitating more rapid and continuous improvement of AI/ML-enabled device performance across diverse populations.*"

- Although this is for AI/ML, it is a concept that can be used for all hardware and software medical device change control processes.
- Population demographic considerations should be considered for all change evaluations during device design development and for continuous changes that occur throughout the product's lifecycle.
- Design changes that are related to use of the device should refer to the UFMEA (or equivalent risk tool) which should have included use-related risks of people from different cultures, backgrounds, and subpopulations.

3.7. DESIGN TRANSFER AND DESIGN HISTORY FILE

Regulatory References: 21 CFR 820.30 (h)(j); ISO 13485:2016 7.3.8 & 7.3.10

Design Transfer is the stage where the design is successfully translated into production specifications and requirements. The manufacturing process is scaled up and all manufacturing production activities have proven that the product can be repeatedly and reliably produced. This is where the manufacturing process is validated and a Manufacturing Plan with a device master record (i.e., the product "recipe"), containing all the specifications and requirements, is generated.

The Design History File (DHF) and the Risk Management File (RMF) are living documents that are referenced when complaints happen with the end users, post-launch. Feedback allows for changes and improvements to the design. It is a good practice to prepare a strategic record such as a Post Market Monitoring Plan. A Post Market Monitoring Plan would include how the product will be maintained and monitored through its lifecycle and will provide an overview of the product owner's quality management system. The plan should outline the post-market feedback system of adverse events, complaints, and inquiries that are fed into the RMF and DHF for evaluation and continuous product improvement. A strategy for post market cybersecurity monitoring should also be included in the plan. Manufacturers who are distributing their products in Europe are required to have a Post Market Surveillance Plan (PMS) where most of these principles are already required per the European Medical Device Regulation.

Equity can be operationalized during the design transfer phase as follows:

- The Post Market Monitoring Plan (or PMS Plan) should also include a strategy or point to a document where product equity will continually be monitored by the health equity subject matter experts.
- The PMS plan should include requirements for annual assessments on equity throughout the lifecycle of the product as part of the continuous improvement and change control activities.
    - One example is for AI/ML medical device models that continue to be trained post-deployment. Controls need to be in place to detect risks related to unintended bias. (FDA, October 2021).
- The Quality unit should ensure equity is operationalized into the Quality Management System (QMS) not only during the development process (such as the Quality and Regulatory Plan), but also after design transfer into manufacturing and post market maintenance of the product.
    - Establishment of the Fairness Statement or equivalent into the Quality Policy will drive company policies and procedures to incorporate principles of equity in the QMS.
    - Establish QMS related metrics and key performance indicators (KPIs) related to equity and review them during the Management Review process.

4. CONCLUSION

Evidence reveals that bias is a prominent issue in the systematic design of biomedical devices. Biased devices result in unjust health disparities for individuals of marginalized communities. The flaws of pulse oximetry accuracy for the disadvantaged have been well-known within the medical community for over four decades. The COVID-19 pandemic set forth a wave of urgency and widespread attention with advocacy centered around the need for equitable clinical testing during the Design Validation process. Unfortunately, this intervention causes a change in only one of the nine stages of the development process for biomedical devices. At this stage, the product under test will already be subject to built-in bias. Therefore, a clear, purposeful change must be made in the way that developers design medical devices.

This paper presented a systematic way for equity to be realized throughout the medical device development process. Using FDA 21 CFR 820 and ISO 13485:2016 regulatory references, we proposed how equity can be operationalized at the initial phases of development, starting at the design planning, and creating a thread through to design inputs, design outputs, and subsequent phases of the medical device development process.

Planning for bias prevention, establishing quality system fairness statements into the company quality policy, adding health equity subject matter experts on the design team, implementing independent health equity assessments as part of the design review process, creating design input requirements to ensure demographic qualities can be tested, verified and validated, and building in risk mitigations for issues that specifically affect disadvantaged people are among some of the concepts that were proposed in this paper.

It is predicted that in the next 30 years, the American population will experience a shift to more than a 50% non-white population (Konkel, 2015). While the case study of the MelanOxi Oximeter developed by CUBMD has been presented, the guidelines laid out in this paper can be applied to any future biomedical device to ensure medical devices are designed to diagnose and meet the needs of people in our diverse nation, not just a select few.

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Cornell University Biomedical Device (CUBMD) is a team of multidisciplinary undergraduate students that aims to identify and solve contemporary issues in the healthcare industry by designing innovative and novel biomedical devices. The collaborative nature of our approach enables us to conduct extensive gap-driven research and communicate with experts across a variety of fields. CUBMD engages in nationwide engineering competitions and develops its ideas with the vision of patenting and ultimately, bringing our devices to market to set a precedent for the future of biotechnology. If you are interested in sponsoring us, collaborating, or hearing more about our work, visit cubmd.org.

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7.3. REVISION HISTORY

Version	Summary of Changes	Release Date
1	New Document	September 14, 2023
2	1. Updated Expired FDA Links due to updates to referenced regulatory guidance in the following sections: a. p. 5 section 2.12. added "1997" to FDA reference. b. p. 8 footnote corrected link to References Section 7.2. c. p. 11 section 3.1.1.5 updated "FDA (January 2021) link. d. p. 14 section 3.1.1.8 updated "FDA" to "FDA September 2023". e. p.22 section 3.5 and p. 23 section 3.6, updated the link to Design Verification section. f. p.31 section 7.2 updated "2005May11" to "June2023" for Content of Premarket Submission for Software Contained in Medical Devices. g. p. 31 section 7.2 Added "October" to "2016" for Collection of Race & Ethnicity Data in Clinical Trials. h. p. 32 section 7.2 updated "April 2022" to "September 2023" for Cybersecurity in Medical Devices. i. p. 32 section 7.2 Corrected link for Artificial Intelligence/Machine Learning (AI/ML) – Based Software as a Medical Device (SaMD) Action Plan 2. Removed duplicate references.	May 10th, 2024