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Pulse Oximeters for Medical Purposes - Non-Clinical and Clinical Performance Testing, Labeling, and Premarket Submission Recommendations

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on January 7, 2025.

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For questions about this document, contact OHT1: Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices/DHT1C: Division of Anesthesia, Respiratory, and Sleep Devices at (301) 796-5620.

When final, this guidance will supersede Pulse Oximeters – Premarket Notification Submissions [510(k)s], issued March 4, 2013.



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

GRZAN DRAFT

Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance document provides recommendations regarding non-clinical and clinical performance testing of pulse oximeters for medical purposes, including devices with a pulse oximeter function that estimates the amount of oxygen in arterial blood and pulse rate. Pulse oximeters are widely used by many types of healthcare providers and lay-users to obtain an indirect measure of arterial blood oxygen saturation. Pulse oximetry is a non-invasive and quick alternative to arterial puncture with blood gas analysis (CO-oximetry). These recommendations are being made based in part on concerns that the accuracy of pulse oximeters can be affected by, among other factors, a person's skin pigmentation.[1] The recommendations are being provided to inform the performance evaluation for these devices, to support premarket submissions, regardless of submission type, and to promote consistency and facilitate efficient review of these submissions. Among other topics, the guidance also provides recommendations for labeling, which are intended to promote the safe and effective use of pulse oximeters and help users understand the benefits and risks associated with the use of the device.

[1] See November 1, 2022: Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee Meeting Announcement and materials, https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-1-2022-anesthesiology-and-respiratory-therapy-devices-panel-medical-devices-advisory#event-materials

For the current edition of the FDA-recognized consensus standards referenced in this document, see the FDA Recognized Consensus Standards Database. If submitting a Declaration of Conformity to a recognized standard, we recommend you include the appropriate supporting documentation. For more information regarding use of consensus standards in regulatory submissions, refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Current scientific evidence from laboratory desaturation studies[2, 3] suggests that there are accuracy differences in some pulse oximeters, especially in lower arterial blood oxygen saturations (SaO_2), between lightly and darkly pigmented individuals. Pulse oximeters are widely used to obtain an indirect measure (SpO_2) of arterial blood oxygen saturation (SaO_2). An observed association of a variable with pulse oximeter accuracy does not always imply causation and may be observed for a number of reasons. FDA has engaged in numerous efforts to learn more about sources of variation in pulse oximeter accuracy and to share information regarding pulse oximeters with the public.

As part of these efforts, FDA has engaged interested parties regarding how the Agency can help to ensure patients have access to high-quality, safe, and effective pulse oximeters intended for medical purposes.

- On February 19, 2021, FDA issued a safety communication[4] informing patients and health care providers that although pulse oximetry is useful for estimating blood oxygen levels, pulse oximeters have limitations and a risk of inaccuracy which, under certain circumstances, should be considered. FDA's safety communication stated that multiple factors may affect the performance of a pulse oximeter's readings, such as poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, and use of fingernail polish.

[2] Bickler PE, Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse oximeter accuracy at low saturation. Anesthesiology. 2005;102.4:715-719.
[3] Okunlola OE, Lipnick MS, Batchelder PB, Bernstein M, Feiner JR, Bickler PE. Pulse Oximeter Performance, Racial Inequity, and the Work Ahead. Respir Care. 2022;67(2):252-257.
[4] Available at https://public4.pagefreezer.com/content/FDA/20-02-2024T15:13/https://www.fda.gov/medical-devices/safety-communications/pulse-oximeter-accuracy-and-limitations-fda-safety-communication

- In 2022, as part of the Centers of Excellence in Regulatory Science and Innovation (CERSI) program, FDA partnered with the University of California San Francisco to conduct a prospective clinical study of pulse oximeter errors in adult hospitalized patients with varying skin pigmentation.[5] The study was also designed to assess the extent to which factors such as low perfusion may impact the accuracy of pulse oximeter readings.

- In 2022, as part of the CERSI program, FDA partnered with Stanford University to conduct a prospective clinical study to evaluate the accuracy of pulse oximeters in children.[6] The study was designed to evaluate pulse oximeter performance in hospitalized pediatric patients (21 years old and younger) of different skin pigmentation levels by assessing the level of error in SpO_2 readings. The study was also designed to assess the extent to which factors such as low perfusion may have an impact on the accuracy of pulse oximeter readings.

- On November 1, 2022, FDA convened the Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee ("2022 Panel").[7] The 2022 Panel members indicated that the currently available clinical evidence for prescription pulse oximeters showed performance differences (hereinafter referred to as "disparate performance") in patients with dark skin pigmentation (as compared to patients with light skin pigmentation), which causes increased risk for the patient for their given disease outcome. The 2022 Panel also indicated that factors other than skin pigmentation, including but not limited to low perfusion, explain some of the disparate performance and should be examined. To address these concerns, the 2022 Panel recommended standardization of skin pigmentation assessment. The 2022 Panel recommended that, overall, pulse oximeters for clinical use should be more accurate and proposed reducing the Accuracy Root Mean Square (A_{rms})[8] threshold.

- On November 16, 2023, FDA issued a discussion paper, "*Approach for Improving the Performance Evaluation of Pulse Oximeter Devices Taking Into Consideration Skin Pigmentation, Race and Ethnicity*."[9] In the discussion paper, FDA requested public comment on a series of questions related to an approach to improve the quality of premarket studies and associated methods used to evaluate the performance of pulse oximeters, taking into consideration a participant's skin pigmentation and participant-

[5] For more information, see https://www.fda.gov/science-research/advancing-regulatory-science/prospective-clinical-study-pulse-oximeter-errors-adult-hospitalized-patients-varying-skin

[6] For more information, see https://www.fda.gov/science-research/advancing-regulatory-science/prospective-clinical-study-evaluate-accuracy-pulse-oximeters-children

[7] See November 1, 2022: Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee Meeting Announcement and materials, https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-1-2022-anesthesiology-and-respiratory-therapy-devices-panel-medical-devices-advisory#event-materials

[8] A_{rms} is the root mean square deviation between SpO_2 and SaO_2 across all paired repeated measures and study participants. See ISO 80601-2-61 *Medical electrical equipment – Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment* for formula used for determination of A_{rms}.

[9] Available at https://www.fda.gov/media/173905/download

reported race and ethnicity. The discussion paper continued FDA's efforts to be transparent and informative about how the Agency regulates pulse oximeters intended for medical purposes.[10]

- On February 2, 2024, the Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee ("2024 Panel") was convened and asked to discuss a proposed approach to improve the quality of premarket studies and associated methods used to evaluate the performance of pulse oximeters submitted for premarket review, taking into consideration a participant's skin pigmentation and participant-reported race and ethnicity.[11] The 2024 Panel was also asked to discuss the type and amount of data that should be provided by manufacturers to FDA to evaluate the performance of pulse oximeters submitted for premarket review, including for prescription and nonprescription, over-the-counter (OTC) indications, and to discuss various labeling considerations. After discussing the advantages and challenges, the 2024 Panel was in general agreement with the approach proposed by FDA.

FDA considered comments from the two Panels and discussion paper and incorporated the feedback as appropriate in developing this guidance.

III. Scope

The scope of this document is limited to certain pulse oximeters intended for medical purposes,[12] including devices with a pulse oximeter function to estimate the amount of oxygen in arterial blood and pulse rate. The scope of this guidance includes such pulse oximeters when they are: (1) standalone; or (2) included as part of a multi-parameter device. Pulse oximeters may be regulated under the following classification regulations and the scope of this document includes the existing product codes listed in Table 1 below:

> 21 CFR 870.2700 Oximeter: An oximeter is a device used to transmit radiation at a known wavelength(s) through blood and to measure the blood oxygen saturation based on the amount of reflected or scattered radiation. It may be used alone or in conjunction with a fiberoptic oximeter catheter.

[10] As used in this document, "intended for medical purposes" means that the pulse oximeter is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease and, therefore, meets the definition of "device" set forth in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[11] See February 2, 2024: Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee Meeting Announcement and materials, https://www.fda.gov/advisory-committees/advisory-committee-calendar/february-2-2024-anesthesiology-and-respiratory-therapy-devices-panel-medical-devices-advisory

[12] See footnote 10.

21 CFR 870.2705[13] Infant pulse rate and oxygen saturation monitor for over-the-counter use: An infant pulse rate and oxygen saturation monitor for over-the-counter use is a device that uses photoplethysmography to measure pulse rate and oxygen saturation in infants. The device may contain alarms that alert the caregiver when vital sign(s) go outside preset threshold(s).

21 CFR 870.2710 Ear oximeter: An ear oximeter is an extravascular device used to transmit light at a known wavelength(s) through blood in the ear. The amount of reflected or scattered light as indicated by this device is used to measure the blood oxygen saturation.

Table 1. Device Types within the Scope of this Guidance.

Product Code	Product Code Name	Regulation Number
DQA	Oximeter	21 CFR 870.2700
NLF	Oximeter, Reprocessed	21 CFR 870.2700
OLK	Pulse Oximeter for Over-the-Counter Use	21 CFR 870.2700
QYU	Infant Pulse Rate and Oxygen Saturation Monitor for Over-The-Counter Use	21 CFR 870.2705
DPZ	Oximeter, Ear	21 CFR 870.2710

Although the product codes listed above are current as of the date of issuance of this guidance, new product codes or classification regulations may be created and could fall within the scope of this guidance. We recommend that you reference the product code database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm) or contact OHT1: Office of Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices if you are uncertain whether this guidance applies to your device and the product code for your device is not already identified in this guidance. Some of the recommendations in this guidance may assist in complying with some of the special controls for infant pulse rate and oxygen saturation monitors for OTC use (product code QYU). For information regarding these special controls, see FDA's website.[14]

This guidance does not address oximeters under product codes OCH (oximeter, infrared, sporting, aviation), or PGJ (oximeter, wellness).[15] In addition, this guidance does not address oximeters under product codes MUD (tissue saturation oximeter), NMD (reprocessed tissue saturation oximeter), QEM (cerebral oximeter), or MMA (fetal pulse oximeter).

[13] This classification regulation includes special controls established in the classification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf22/DEN220091.pdf. The publication of this classification in the Federal Register and codification in the Code of Federal Regulations is currently pending.

[14] See classification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf22/DEN220091.pdf

[15] Oximeters in product codes OCH and PGJ are not reviewed or evaluated by the Agency prior to being available to the public at this time because they are intended for general wellness purposes.

The classification regulations 21 CFR 870.2700, 21 CFR 870.2705, and 21 CFR 870.2710 include devices using reflectance, transmittance, and fiber optic technologies, which are collectively referred to as pulse oximeters for the purpose of this guidance. The terms "transmittance" and "reflectance" refer to the sensor geometry and are not related to the principles of pulse oximetry and how the light is absorbed by hemoglobin when placed on intact skin. A pulse oximeter operates as a system typically composed of a sensor for application over intact skin, an extender cable, and a module or a specific pulse oximeter monitor.[16]

This guidance document pertains to non-invasive pulse oximeters to estimate arterial blood oxygen saturation and pulse rate based on the amount of transmitted, reflected and scattered light through various application sites (including, but not limited to finger, ear, foot, hand, forehead, back, and nose). These pulse oximeters could be indicated for OTC or prescription use. These pulse oximeters could be continuous or spot-checking devices and either standalone or a function within a multi-parameter device. A multi-parameter device which includes a pulse oximeter may be classified under different classification regulations.[17] The pulse oximeters described in this guidance are typically labeled with a general indication for non-invasive measurement of blood oxygen saturation. A manufacturer that wishes to seek a specific clinical indication for use of a pulse oximeter, for example to screen for or diagnose a specific disease or condition, should submit clinical data to support the safety and effectiveness of the device for the specific indication.

In addition, pulse oximetry may be an "other function," as that term is used in the FDA guidance "Multiple Function Device Product: Policy and Considerations," which may impact the device "function-under-review" of a multiple function device product. For example, a general wellness[18] pulse oximeter function may provide input data for a device software function that is used to notify the user of a medical condition or event, such as a sleep apnea event. The recommendations described in the aforementioned guidance should also be considered when preparing the documentation for a premarket submission for such a multi-function device product. This guidance may be informative for evaluation and review of pulse oximetry as an "other function" of such a product, which may impact the device "function under review."

This guidance provides recommendations regarding non-clinical and clinical performance testing and other information to support premarket submissions for pulse oximeters, regardless of submission type.[19] Because we anticipate that the majority of pulse oximeter premarket

[16] In this guidance, the Agency is using the terms "pulse oximeter" and "pulse oximeter system(s)" interchangeably.
[17] See, e.g., 21 CFR 870.2300, 21 CFR 870.2340.
[18] For more information on general wellness products, see FDA's guidance "General Wellness: Policy for Low Risk Devices."
[19] We note that some of the information recommended by this guidance could also be a requirement of the submission type appropriate for a specific new device, including a requirement of a class II device's special controls. Alternatively, the recommendations could help manufacturers comply with any applicable premarket submission requirements and/or special controls.

submissions will be premarket notification (510(k)) submissions, the guidance document is tailored to describe the recommended information to be included to support 510(k) submissions.[20] However, the guidance provides recommendations which may also be applicable to pulse oximeters that are reviewed via the De Novo classification[21] or Premarket Approval pathways.[22] This guidance document supplements other FDA documents regarding the specific content requirements and recommendations of premarket submissions.

For both new and currently-marketed pulse oximeters intended for medical purposes within the scope of this guidance, including previously-cleared pulse oximeters that are modified in ways that require a new 510(k), FDA recommends that manufacturers gather clinical data, consistent with the guidance recommendations, to evaluate whether device performance across skin pigmentation levels is non-disparate.[23] For recommendations on clinical performance testing that apply to both new and currently-marketed pulse oximeters, see Section IV.O.

FDA is also updating its recommendations concerning the content and format of certain labeling information for pulse oximeters, as originally described in the 2013 guidance document,[24] based in part on concerns about the disparate performance of pulse oximeters as outlined above. For all new pulse oximeters for medical purposes, see labeling recommendations in Section IV.C(1) - (3), including labeling recommendations for when non-disparate performance has been demonstrated (as recommended in Section IV.O). For further recommendations on labeling and 510(k) submission[25] for pulse oximeters for medical purposes that were previously 510(k)-cleared,[26] see Section IV.C(4). FDA intends to publicly communicate on FDA's website through maintaining a list of pulse oximeters that are labeled as having demonstrated non-disparate performance after clearance of 510(k) submissions.

[20] For more information on premarket notification submissions, refer to 21 CFR 807.87 and FDA's guidance "Electronic Submission Template for Medical Device 510(k) Submissions."

[21] For devices with a pulse oximeter function that are reviewed via the De Novo classification pathway, refer to 21 CFR 860.220 and FDA's guidance "De Novo Classification Process (Evaluation of Automatic Class III Designation)."

[22] For devices with a pulse oximeter function that are reviewed via the Premarket Approval pathway, refer to 21 CFR 814.20 and PMA guidance documents available at https://www.fda.gov/medical-devices/premarket-approval-pma/pma-guidance-documents

[23] See Section IV.O(1)g.ii for the recommended success criteria for non-disparate performance. For purposes of labeling recommendations, which are in Section IV.C, non-disparate performance is described as demonstrating that the pulse oximeter performs comparably across groups of individuals with diverse skin pigmentation.

[24] See FDA guidance "Pulse Oximeters - Premarket Notification Submissions [510(k)s]."

[25] See 21 CFR 807.81. For further guidance on modifications that trigger the requirement that a manufacturer submit a new 510(k) to the FDA, refer to FDA's guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device."

[26] The recommendations also apply to pulse oximeters that were previously authorized through the De Novo classification pathway.

IV. Premarket Submission Recommendations

A. Device Description

We recommend you identify your device by the applicable classification regulation number and product code indicated in Section III above and include the information described below.

We recommend you describe the general purpose or function of the pulse oximeter, including if the device (and accessories) is intended:

- as a stand-alone device or a multi-parameter module;
- for use in spot-checking, continuous real-time monitoring or continuous data archiving;
- for prescription or OTC use;
- for use in specific patient population(s);
- for low perfusion conditions;
- for in-motion conditions (e.g., walking, fidgeting);
- for single use or multi-use;
- for out-of-hospital transport; and/or
- for home use.

We recommend that you identify and describe the device design, including the following:

- scientific principles underlying how the device achieves its intended use (e.g., functional oxygen saturation);
- sensor configuration/geometry (e.g., reflectance vs. transmittance);
- design features (e.g., functions, alarms);
- electro-optical components and their specifications;
- description of the means used to determine SpO_2 and other device outputs from detected optical signals, including processing features intended to evaluate and optimize signal quality, remove noise (e.g., use of numerical/computational methods, machine learning/artificial intelligence routines), and, if applicable, correct for confounding factors including epidermal melanin content;
- description of outputs provided for the user to assess data quality, including range of percent modulation for accurate pulse oximeter performance;
- recommended application sites and relevant anatomical dimension(s);
- all patient interface accessories (e.g., patient cable, extender cables, sensors, bandages);
- whether the device and accessories will be provided sterile;
- whether the device is a reprocessed single-use device; and
- device setup and operation information.

We also recommend you include drawings, diagrams, or photographs of your device that can help explain the function or highlight new features that may affect safety and effectiveness, for example, changes to a sensor.

B. Predicate Comparison (Devices reviewed under 510(k))

For devices reviewed under the 510(k) process, manufacturers must demonstrate that their new device is substantially equivalent to a legally marketed predicate device (sections 513(f)(1) and 513(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 CFR 807.87(f)). This comparison should provide information to demonstrate how your device is similar to and different from the predicate. Side by side comparisons, whenever possible, are desirable. See Table 2 below for an example of how this information might be organized. This table is not intended to represent an exhaustive list of comparative parameters; we recommend you provide all relevant device descriptive characteristics as outlined in the "Device Description" section, above.

Table 2. Sample predicate comparison table to outline differences and similarities between the subject and predicate device.

Description	**Subject Device**	**Predicate Device (Kxxxxxx)**
Intended use (see Section IV.A. above)		
Indications for use, including a description of the patient population for which the device is intended (e.g., neonate, infant, pediatric, adult)		
Intended application site (e.g., finger, ear, foot, hand, forehead, back, nose)		
Electro-optical components and their specifications		
Description of algorithm		
Performance specifications (including use under motion and low perfusion conditions, if applicable, and any indices or signals provided to the user)		
Performance across populations with diverse skin pigmentation[27]		

[27] For information regarding this parameter, refer to Section IV.O(1).

Safety specifications (e.g., electrical, mechanical, environmental)		
Features/design specifications (e.g., alarms, display and indicators, modes)		
Sterility/reprocessing status		
Other relevant characteristics		

C. Labeling[28]

The premarket notification must include proposed labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Proposed labels, labeling, and advertisements sufficient to describe the pulse oximeter, its intended use, and the directions for use must be provided in a premarket submission. FDA is including labeling recommendations for manufacturers of pulse oximeters that were previously 510(k)-cleared and all new pulse oximeters within the scope of this guidance.

For Prescription Use: As a prescription device, a pulse oximeter is exempt from the requirement to have adequate directions for use[29] required under section 502(f)(1) of the FD&C Act if the conditions in 21 CFR 801.109 are met. To be so exempt, labeling that furnishes information for use of the prescription device must, among other things, contain "adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended" (21 CFR 801.109(d)). In addition, the label of the device must bear "[t]he symbol statement 'Rx only' or '*℞* only' or the statement 'Caution: Federal law restricts this device to sale by or on the order of a ___', the blank to be filled with the word 'physician,' 'dentist,' 'veterinarian,' or with the descriptive designation of any other practitioner licensed by the law of the State in which the practitioner practices to use or order the use of the device" (21 CFR 801.109(b)(1)).

For OTC Use: As an OTC device, under section 502(f) of the FD&C Act and 21 CFR 801.5, the device labeling must include adequate directions for use. The labeling (e.g., package insert) must describe the intended use of the device and include a listing of all conditions, purposes, or uses for which it is recommended, suggested, or commonly used (21 CFR 801.5(a)). The labeling recommendations below are not intended to capture all possible limitations or instructions for all pulse oximeters. Therefore, when developing your labeling, it may be necessary for you to include additional limitations (e.g., contraindications, warnings, precautions, adverse reactions), and other instructions that are appropriate for your device, depending on its specific design,

[28] We note that other labeling recommendations are provided in other sections of this guidance as well (e.g., reprocessing).

[29] Adequate directions for use means directions under which the layman can use a device safely and for the purposes for which it is intended (21 CFR 801.5).

features, and performance characteristics, and depending on the results and conclusions drawn from a usability study, if applicable.

Accurate, clear device labeling can help mitigate performance issues associated with pulse oximeters and is important to make users aware of the risks, limitations, and directions for use of pulse oximeters. Moreover, a device shall be deemed misbranded if, among other things: its labeling is false or misleading; its labeling does not contain adequate warnings; or any information required to be in the labeling is not prominently placed with such conspicuousness and in such terms to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use (see sections 201(n), 502(a), 502(c), and 502(f)(2) of the FD&C Act). As always, FDA will make case-by-case decisions regarding the enforcement of legal requirements in response to particular circumstances and questions that arise regarding a specific device. This may include FDA requesting a firm initiate a recall (see 21 CFR 7.45) or taking other actions, including an enforcement action.

This section includes recommended labeling content for pulse oximeters within the scope of this document, as outlined in the following sub-sections: (1) all pulse oximeters (i.e., prescription and OTC); (2) additional labeling specific to prescription pulse oximeters; (3) additional labeling specific to OTC pulse oximeters; and (4) additional labeling specific to pulse oximeters that were previously 510(k)-cleared.

(1) For All Pulse Oximeters

To help manufacturers develop appropriate labeling, FDA recommends that the following labeling content be included for prescription and OTC pulse oximeters within the scope of this guidance. FDA also recommends that you follow the labeling considerations referenced in the currently FDA-recognized version of the consensus standard ISO 80601-2-61 *Medical electrical equipment – Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment*.

a. Package Labeling

Consistent with recommendations shared at the 2024 Panel Meeting,[30] FDA recommends that the package labeling for prescription and OTC pulse oximeters include a prominent statement that the pulse oximeter is intended for medical purposes.[31]

Furthermore, if the manufacturer submits clinical data in a new 510(k) showing non-disparate performance (see Section IV.O), we recommend that you include a prominent statement in the package labeling and package insert, such as “This pulse oximeter has been evaluated to perform

[30] See February 2, 2024: Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee Meeting Announcement and materials, https://www.fda.gov/advisory-committees/advisory-committee-calendar/february-2-2024-anesthesiology-and-respiratory-therapy-devices-panel-medical-devices-advisory

[31] To verify whether a specific device has been cleared/granted/approved for marketing authorization by FDA, please refer to FDA databases, such as https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

comparably across groups of individuals with a wide variety of skin tones based on [details provided consistent with the study conducted]."[32]

b. Package Insert Labeling

FDA recommends that the package insert labeling include the following information, where applicable.

Statement Regarding Non-Disparate Performance

As noted above, if non-disparate performance has been demonstrated in a new 510(k) (see Section IV.O), we recommend that you include a prominent statement in the package insert, such as "This pulse oximeter has been evaluated to perform comparably across groups of individuals with a wide variety of skin tones based on [details provided consistent with the study conducted]."

Indications for Use

- Statement of all conditions, purposes, or uses for which the device is intended, such as;
  - for use as a stand-alone device or a multi-parameter module;
  - for use in spot-checking, continuous real-time monitoring or continuous data archiving;
  - for prescription or OTC use;
  - for use in specific patient population(s);
  - for low perfusion conditions;
  - for in motion conditions (e.g., walking, fidgeting);
  - for single use or multi-use;
  - for out-of-hospital transport; and/or
  - for home use.

Device Description

FDA recommends that you include a description of the pulse oximeter identifying important information, such as:

- Scientific principles underlying how the device achieves its intended use (e.g., functional oxygen saturation);
- Sensor configuration/geometry (e.g., reflectance vs. transmittance);
- Recommended application sites and relevant anatomical dimension(s);

[32] The Agency believes that the labeling recommendations in this guidance should be representative of the clinical data collected (as also recommended in this guidance), and that new clinical data supporting labeling changes can be submitted in a new 510(k) submission.

- Design features (e.g., functions, alarms);
- All patient interface accessories (e.g., patient cable, extender cables, sensors, bandages);
- Whether the device and accessories will be provided sterile;
- Whether the device is a reprocessed single-use device;
- Description of outputs provided for the user to assess data quality, including range of percent modulation (an indicator of signal quality) for accurate pulse oximeter performance; and
- Device setup and operation information.

Warnings

FDA recommends that manufacturers prominently display appropriate warnings in the instructions for use regarding how to avoid known hazards and/or be aware of certain relevant risk or safety information associated with the use of the pulse oximeter. We believe such warnings should inform patients/users of known hazards and other relevant information, such as the following:

- Only a health care provider can diagnose medical conditions;
- Reliance solely on a pulse oximeter to detect health conditions or blood oxygen levels may delay seeking and receiving of appropriate and timely medical attention;
- Pay attention to other signs or symptoms of low oxygen levels;
- Initiating or increasing therapy due to pulse oximeter readings without consulting a health care provider is not intended and may lead to harm;
- Pulse oximeters may not accurately estimate blood oxygenation and there is a range of uncertainty about the displayed SpO_2 value as to the true blood oxygenation level. SpO_2 error may increase with decreasing true blood oxygenation level[33, 34];
- Differences in skin pigmentation may cause differences in pulse oximeter sensor performance and thereby impact SpO_2 readings, especially in very low oxygen levels;
- Trends in measurement may be more meaningful than one single measurement;
- Not all blood oxygenation values have been verified with clinical performance testing; see overview of performance studies for range of SaO_2 values tested for this device;
- Environmental and physiologic conditions may contribute to poor pulse oximeter performance or adverse events;
- Continuous use longer than recommended in the labeling may incur patient injury;
- Continuous sensor wear that restrict movement(s) may interfere with normal activity and age-appropriate development (e.g., turning over, crawling, standing, walking, playing); and
- Alarms or alerts may interfere with sleep stages of user and caregiver(s).

[33] Bickler PE, Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse oximeter accuracy at low saturation. Anesthesiology. 2005;102.4:715-719.

[34] Okunlola OE, Lipnick MS, Batchelder PB, Bernstein M, Feiner JR, Bickler PE. Pulse Oximeter Performance, Racial Inequity, and the Work Ahead. Respir Care. 2022;67(2):252-257.

Examples of the types of warnings that should be included, as listed above, are provided in Appendix A.

Precautions

We recommend that manufacturers prominently display appropriate precautions in the instructions for use regarding use of the device on patients, including patients with the following conditions:

- Hypersensitivity to material intended for patient contact; and
- Poor skin integrity at sensor application site(s).

Directions for Use

FDA recommends manufacturers provide clear and simple directions for use to ensure that users understand how to best apply the pulse oximeter sensor for safe and effective device use. FDA recommends providing a complete set of directions for use, including information to address the following:

- Instructions for optimizing measurements of oxygen saturation should take into account optimal placement (e.g., anatomical site and geometry), conditions, and stable SpO_2 values, when present;
- Instructions on how to evaluate/use indicators of signal quality (e.g., percent modulation) and understand the waveform, when present;
- For accurate SpO_2 and pulse rate values, instructions to consider signal inadequacy (e.g., due to low signal intensity, unstable readings);
- Consideration of percent modulation ranges, when available, and methods to improve percent modulation for accurate pulse oximeter performance;
- Instructions for the frequency of inspection of the application site for skin integrity;
- Instructions for the frequency of sensor relocation to a different measurement site; and
- Device service and maintenance information, including cleaning and disinfection instructions for reusable pulse oximeters and accessories.

Examples of directions for use that could be included are provided in Appendix A.

Magnetic Resonance (MR) Safety Information

We recommend you follow the labeling recommendations in FDA's guidance, "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment." We also recommend using the standardized terminology and icons as described in the currently recognized version of ASTM F2503 *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment*.

(2) For Prescription Pulse Oximeters

FDA recommends that for prescription pulse oximeters within the scope of this guidance, manufacturers provide in the device labeling an overview of clinical performance studies conducted to determine accuracy and non-disparate performance across populations with diverse skin pigmentation. The labeling should identify the specific models of pulse oximeters with which the sensors were clinically validated and are intended to be used.

a. Overview of performance studies for all prescription pulse oximeters

FDA recommends that you include in the labeling relevant performance information from your controlled desaturation laboratory study (as described in Section IV.O(1)) and non-clinical bench testing (as described in Section IV.N), such as the following:

- Demographics of adult study participants – number of participants, sex, age, body mass index (BMI), forehead Monk Skin Tone[35] (MST) and Individual Typology Angle[36] (ITA) (see definition in Section IV.O(1)b), self-reported ethnicity, self-reported race, relevant sensor site description (e.g., index finger, circumference of finger), emitter-sensor site ITA, range of desaturation per MST group (see definition in Section IV.O(1)b), and number of data pairs per participant – for all tested pulse oximeter systems;
- SpO_2 Accuracy (A_{rms}) estimate, standard error, and 95% confidence interval (CI) for all tested conditions (e.g., motion, non-motion, low perfusion) overall and stratified by the SaO_2 deciles, $70\% \leq SaO_2 < 80\%$, $80\% \leq SaO_2 < 90\%$, and $90\% \leq SaO_2 \leq 100\%$;
- Mean and standard deviation of SpO_2 error (SpO_2 - SaO_2) for all tested conditions (e.g., motion, non-motion, low perfusion) overall and stratified by SaO_2 deciles as stated above;
- SpO_2 bias (i.e., mean error) estimate, standard error, and 95% CI for all tested conditions (e.g., motion, non-motion, low perfusion) and stratified into the three MST groups (1-4, 5-7, and 8-10) based on evaluation of the forehead;
- SpO_2 bias (i.e., mean error) by ITA, across an ITA interval that is representative of the surface(s) intended for contact with the sensor emitter;
- Range of percent modulation in study participants undergoing clinical study;
- Summary of test methods for accurate performance in low perfusion conditions, if applicable;

[35] Heldreth CM, Monk EP, Clark AT, Schumann C, Eyee X, Ricco S. Which skin tone measures are the most inclusive? An investigation of skin tone measures for artificial intelligence. ACM Journal on Responsible Computing 1, no. 1 (2024): 1-21. MST is a subjective scale comprising ten values to assess skin tones.

[36] Del Bino S, Bernerd F. Variations in skin colour and the biological consequences of ultraviolet radiation exposure. Br J Dermatol. 2013 Oct;169 Suppl 3:33-40. ITA is an objective, continuous, quantitative measure of skin pigmentation.

- Summary of test methods for accurate performance in motion conditions, if applicable;
- Bench testing pulse rate accuracy specification covering the entire pulse rate display range and summary of test methods;
- Operating and storage temperature and humidity; and
- Device settings used during performance testing.

Bland Altman,[37] modified Bland Altman,[38] Quantile-Quantile (QQ),[39] and inverse prediction plots[40] are also recommended to be included in labeling to characterize device performance (i.e., agreement, bias, and uncertainty).

b. Overview of performance studies for prescription pulse oximeters intended for pediatric populations younger than 12 years of age

Clinical performance testing of a pulse oximeter system in adult populations may not be sufficient to support clinical performance in certain pediatric subgroups such as neonates, infants, and children younger than 12 years of age due to significant differences in form and fit of the pulse oximeter sensor that may lead to differences in overall accuracy of the system. For pulse oximeter systems intended for use in pediatric populations younger than 12 years of age,[41] in addition to the labeling on the controlled desaturation study in adults (see Section IV.C(2)a), we also recommend you include labeling on the convenience arterial sample collection (see Section IV.O(2)). Such labeling should include information regarding each intended pediatric subpopulation – i.e., neonates (birth to 30 days), infants (1 month to less than 2 years), and children (2 years to less than 12 years), as applicable, such as the following:

- Patient population characteristics of the pediatric population tested: sex, age, weight (percentile), diagnosis and/or comorbidities, forehead MST and ITA, emitter sensor site ITA, reported ethnicity, reported race, relevant sensor site description (e.g., mid-foot, circumference of foot), data pairs per participant;
- Number of participants;
- Number of data samples;

[37] Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. J Biopharm Stat. 2007;17(4):571-82.

[38] For two measurements Y and X of the same quantity, the Bland-Altman plot is a plot of the difference $D = Y - X$ vs. average $A = (Y + X)/2$. The modified Bland-Altman plot is a plot of D vs. X.

[39] For paired SpO_2 and SaO_2, a QQ plot of SpO_2 vs. SaO_2 is a scatterplot of the ordered values of SpO_2 vs. the ordered values of SaO_2.

[40] Greenwell BM, Schubert Kabban CM. investr: An R Package for Inverse Estimation. *The R Journal*. 2014 June; 6(1): 90-100.

[41] In the statutory provisions governing the regulation of medical devices, section 520(m)(6)(E)(i) of the FD&C Act defines "pediatric patients" as patients aged 21 or younger at the time of their diagnosis or treatment. FDA generally considers this to be the age from birth through the 21st year of life, up to but not including the 22nd birthday. Pediatric subpopulations are defined in section 520(m)(6)(E)(ii) (and adopted by reference in section 515A(c) of the FD&C Act) to be neonates, infants, children, and adolescents.

- Range of percent modulation in study participants undergoing clinical study;
- SaO_2 range; and
- A_{rms} analyses, including estimate, standard error and 95% CI.

(3) For OTC Pulse Oximeters

For OTC pulse oximeters within the scope of this guidance, the labeling should be written in simple, plain language and instruct the end user on how to use the device safely and for the purposes for which it is intended, and to identify any potential risks. When preparing user labeling for OTC pulse oximeters, we recommend following the FDA guidance "Guidance on Medical Device Patient Labeling," which describes FDA's current thinking on making medical device patient labeling understandable to and usable by patients. FDA recommends that the labeling for OTC pulse oximeters also contain the following additional recommendations for the package insert.

a. Directions for Use

In addition to directions for use discussed in Section IV.C(1)b, FDA recommends that the package insert include clear and simple directions for safe and accurate use by lay users. We recommend that labeling for OTC pulse oximeters include:

- Instructions that reference normal physiologic ranges of SpO_2 for the intended use, intended populations and intended environment of use (e.g., geographic elevation);
- Instructions for lay users to seek timely medical attention for readings outside normal range(s); and
- Instructions for lay users on fluctuating SpO_2 values.

FDA also recommends that manufacturers also consider including drawings or diagrams in the directions for use for lay users, where appropriate.

b. Overview of performance studies for all OTC pulse oximeters

For OTC pulse oximeters, FDA recommends that you include in the labeling a clear and simple overview of the controlled desaturation laboratory study (as described in Section IV.O(1)) and non-clinical bench testing (as described in Section IV.N), such as the following:

- Demographics of adult study participants - number of participants, sex, age, weight range, forehead MST of study participants, self-reported ethnicity, self-reported race, relevant sensor site description (e.g., index finger, circumference of finger);
- Evidence of an accurately printed MST color chart (see Appendix B for details),
- Overall accuracy (A_{rms}) and an explanation of the range of SaO_2 for an SpO_2 value for all tested conditions (i.e., motion, non-motion);
- Accuracy stratified by SaO_2 decile: $70\% \leq SaO_2 < 80\%$, $80\% \leq SaO_2 < 90\%$, and $90\% \leq SaO_2 \leq 100\%$;

- How the clinical study demonstrated accurate performance across participants with diverse skin pigmentation;
- The confidence with which the validation study meets the success criteria[42];
- If percent modulation is provided in device user interface (UI), the range of percent modulation of study participants during the study;
- Summary of test methods for accurate performance in motion conditions, if applicable;
- Bench testing pulse rate accuracy specification covering the entire pulse rate display range and summary of test methods;
- Operating and storage temperature and humidity; and
- Device settings used during performance testing.

An inverse prediction plot is also recommended to be included in labeling to characterize uncertainty of the blood oxygen level given the pulse oximeter estimate of it.

c. Overview of performance studies for OTC pulse oximeters intended for pediatric populations younger than 12 years of age

For pulse oximeter systems intended for use in pediatric populations younger than 12 years of age, in addition to the labeling on the controlled desaturation study in adults (see Section IV.C(3)b), we also recommend you include labeling on the convenience arterial sample collection (see Section IV.O(2)). Such labeling should include information regarding each intended pediatric subpopulation (i.e., neonates (birth to 30 days), infants (1 month to less than 2 years), and children (2 years to less than 12 years)), as applicable, such as the following:

- Patient population characteristics of the pediatric population tested (sex, age, weight (percentile), diagnosis and/or comorbidities, forehead MST value, reported ethnicity, reported race, relevant sensor site description (e.g., mid-foot, circumference of foot)); and
- Overall accuracy (A_{rms})

(4) For Pulse Oximeters That Were Previously 510(k)-cleared

Based on concerns about the disparate performance of pulse oximeters that were previously 510(k)-cleared, the Agency recommends that, if not already done so, manufacturers of such cleared devices should gather clinical data (e.g., controlled desaturation laboratory study or "real-world data" (RWD)) to evaluate their pulse oximeter for non-disparate performance (see success criteria[43] 2 and 3 in Section IV.O(1)g.ii), and submit such data to the Agency in a new

[42] See recommended success criteria for non-disparate performance in Section IV.O(1)g.ii.

[43] For RWD included as support of non-disparate performance, we recommend that manufacturers also include in the package insert labeling an A_{rms} estimate based on RWD.

510(k) submission.[44] Where the manufacturer of a previously 510(k)-cleared pulse oximeter has updated labeling but not otherwise made significant changes or modifications to their device (e.g., hardware, software), FDA generally intends to complete its review of clinical data related to non-disparate performance within 30 days of receipt of the 510(k) submission. If non-disparate performance has been demonstrated in a 510(k), we recommend that package labeling include a prominent statement, such as "This pulse oximeter has been evaluated to perform comparably across groups of individuals with a wide variety of skin tones based on [details provided consistent with the study conducted]." FDA recommends that manufacturers also include such a statement in the 510(k) summary as part of the discussion regarding clinical testing (see 21 CFR 807.92(b)). As part of a new 510(k) submission, manufacturers should also submit the revised device labeling and 510(k) summary to include the clinical data that supports the non-disparate performance. To further promote transparency, FDA intends to publicly communicate on FDA's website through maintaining a list of pulse oximeters that are labeled as having demonstrated non-disparate performance after clearance of 510(k) submissions.

D. Sterility

Significance: Pulse oximeters generally come in contact with intact skin and typically are not provided sterile. However, certain pulse oximeters are provided sterile and these devices should be adequately sterilized to minimize infections and related complications.

Recommendation: For pulse oximeters labeled as sterile, we recommend that you provide information for the final device in accordance with FDA's guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile."

E. Reprocessing

Significance: Many of the patient contacting components of pulse oximeters are reused, and should be adequately cleaned, then disinfected or sterilized between uses to minimize infections while preventing device degradation.

Recommendation: Instructions on how to reprocess a reusable device are critical to ensure that a device is appropriately prepared for its initial and subsequent uses. For recommendations regarding the development and validation of reprocessing instructions in your proposed device labeling, refer to FDA's guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling."

[44] See footnote 32.

(1) For Submissions of Reprocessed Single-Use Sensors, when applicable

If your device includes a reprocessed single-use sensor, we recommend you provide the following additional information:

- electro-optical specifications of the reprocessed sensors;
- means to ensure each reprocessed device meets these specifications; and
- tracking methods used to limit the number of reprocessing cycles.

We recommend you provide complete reprocessing methods and validation data[45] as described in FDA's guidance "Medical Device User Fee and Modernization Act of 2002, Validation Data in Premarket Notification Submissions (510(k)s) for Reprocessed Single-Use Medical Devices." This should include, but not necessarily be limited to the following information.

a. Identification of components and uses

We recommend you provide a detailed diagram of all the components of the sensors, and identification of each component that will be replaced when the device or system is reprocessed and each component that will be retained. In particular, we recommend you indicate whether the reprocessor will replace or save the laminate that encloses the optical components.

b. Performance testing

We recommend you describe the performance testing (e.g., non-clinical bench, clinical performance) conducted to validate the performance of the reprocessed device. We recommend the testing for reprocessed sensors be assessed on worst-case basis (i.e., after the maximum number of times the sensor is intended to be reprocessed). In addition, we recommend you simulate use of the sensor after each reprocessing cycle prior to testing.

F. Shelf Life and Packaging

[45] On October 26, 2002, the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) amended the FD&C Act by adding new section 510(o), which provided new requirements for reprocessed single-use devices (SUDs). According to this provision, to ensure that reprocessed SUDs are substantially equivalent to predicate devices, premarket notification submissions for certain reprocessed SUDs identified by FDA must include validation data. On April 30, 2003, FDA identified a list of those critical reprocessed SUDs that are no longer exempt from 510(k) submission requirements and a list of the non-exempt reprocessed SUDs that are subject to both the 510(k) premarket notification requirement and the validation data submission requirement under MDUFMA (see 68 FR 23139 for original list, 68 FR 38071 for revised list). In the most recent FR notice (see 70 FR 56911), FDA also provided an updated, current listing of all device types subject to these MDUFMA requirements. Reprocessed single-use oximeters are included in *List II: Reprocessed Single-Use Devices Subject to Premarket Notification Requirements That Now Require the Submission of Validation Data*.

Significance: Shelf life testing is conducted to support the proposed expiration date through evaluation of the package integrity for maintaining device sterility and/or evaluation of any changes to device performance or functionality.

Recommendation: With respect to package integrity for maintaining device sterility for devices that are provided sterile, you should provide a description of the packaging, including how it will maintain the device's sterility, and a description of the package integrity test methods, but not the package test data. We recommend that a package validation study include simulated distribution and associated package integrity testing, as well as an aging process (accelerated and/or real-time) and associated seal strength testing, to validate package integrity and the proposed shelf life. We recommend you follow the methods described in the FDA-recognized series of consensus standards ISO 11607-1 *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems* and ISO 11607-2 *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes.*

With respect to evaluating the effects of aging on device performance or functionality, shelf life studies should evaluate the critical device properties to ensure the device will perform adequately and consistently during the entire proposed shelf life. To evaluate device functionality, we recommend that you assess each of the bench tests described in Section IV.N and repeat all tests that evaluate design components or characteristics that are potentially affected by aging using aged devices.

We recommend that you provide a summary of the test methods used for your shelf life testing, results and the conclusions drawn from your results. If you use devices subject to accelerated aging for shelf life testing, we recommend that you specify the way in which the devices were aged and provide a rationale to explain how the results of shelf life testing based on accelerated aging are representative of the results if the devices were aged in real time. We recommend that you age your devices as described in the currently FDA-recognized version of ASTM F1980 *Standard Guide for Accelerated Aging of Sterile Barrier Systems and Medical Devices* and specify the environmental parameters established to attain the expiration date. For devices or components containing polymeric materials or coatings, you should conduct testing on real-time aged samples to confirm the results of the accelerated aging study. This testing can be conducted in parallel with 510(k) review, with results documented to file in the design history file (i.e., FDA generally does not expect the results of the real-time testing to be submitted in the 510(k) submission).

G. Biocompatibility

Significance: Pulse oximeters contain patient-contacting materials, which, when used for their intended purpose (i.e., contact type and duration) may induce a harmful biological response.

Recommendation: You should determine the biocompatibility of all patient-contacting components present in your device. If your device is identical in chemical composition,

manufacturing and processing methods to pulse oximeters with a history of safe use, you might reference previous testing experience or the literature, if appropriate. For some device materials, it may be appropriate to provide a reference to either a recognized consensus standard, or to a Letter of Authorization (LOA) for a device Master File (MAF). You should refer to the following FDA webpage for additional information on using device MAFs: https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/device-master-files.

If you are unable to identify a legally marketed device with the same nature of contact and contact duration that uses the same materials and manufacturing process as is used in your device, we recommend you conduct and provide a biocompatibility evaluation as recommended in FDA's guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'" The evaluation should explain the relationship between the identified biocompatibility risks, the information available to mitigate the identified risks, and any knowledge gaps that remain. You should then identify any biocompatibility testing or other evaluations that were conducted to mitigate any remaining risks. The biocompatibility guidance identifies the types of biocompatibility assessments that should be considered and provides recommendations regarding how to conduct related tests.

As described in ISO 10993-1 *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* and Attachment A of FDA's guidance on ISO-10993-1, pulse oximeters are surface devices in contact with intact skin for a prolonged contact duration. Therefore, the following endpoints should be addressed in your biocompatibility evaluation:

- Cytotoxicity;
- Sensitization; and
- Irritation or intracutaneous reactivity.

Some test methods for the above endpoints are part of the Accreditation Scheme for Conformity Assessment (ASCA) Program, which can be leveraged by manufacturers to streamline the review of these test results. For more information, see the ASCA Program website

This guidance provides recommendations for pulse oximeters that have contact with intact skin. Additional biocompatibility endpoints might be appropriate to address in your biocompatibility evaluation if the pulse oximeters have a different type of tissue contact (e.g., mucosal membrane). Further, additional biocompatibility assessments might be appropriate for pulse oximeters intended for certain patient populations (e.g., neonatal or infants).

When determining the duration of tissue contact, we recommend that you consider the cumulative use (e.g., total exposure period) of the pulse oximeter. For example, as described in ISO 10993-1, the pulse oximeter has prolonged tissue contact if the sum of single, multiple or repeated duration of contact exceeds 24 hours but does not exceed 30 days. Of note, the total

exposure period of the device is the number of elapsed calendar days (not number of hours, minutes or seconds) between first and last use, whether or not the pulse oximeter is used every day and regardless of the duration of exposure on each day. In addition, we recommend that when designing the biocompatibility tests you consider the cumulative exposure of the pulse oximeter (e.g., extraction conditions, duration of cytotoxicity study, single or repeat exposure for dermal irritation). You should refer to ISO 10993-12 *Biological evaluation of medical devices – Part 12: Sample preparation and reference materials* for additional details regarding extraction conditions and methods.

H. Software

Significance: Device software function(s) in pulse oximeters can ensure that the measurement is accurate, reliable, and repeatable. Adequate software testing provides assurance the device functions as intended.

Recommendation: Refer to the FDA guidance "Content of Premarket Submissions for Device Software Functions" for a discussion of the software information that you should provide in your submission. The premarket software guidance outlines the recommended information to be provided in a premarket submission that includes a device software function based on the "Documentation Level" associated with the device. We generally consider the device software function(s) for pulse oximeters to be in the category of a "Basic" Documentation Level. However, certain indications, applications, or technological characteristics could be in the category of an "Enhanced" Documentation Level. For example, an enhanced documentation level is likely appropriate for a pulse oximeter with an alarm to titrate oxygen therapy.

We recommend that you provide a full description of the device software function(s) supporting the operation of the subject device following this premarket software guidance. This recommendation applies to original devices/systems as well as to any software changes made to previously-cleared devices. Changes to software must be revalidated and reverified in accordance with Design Controls, 21 CFR 820.30(i), and documented in the Design History File, 21 CFR 820.30(j).[46] Some software changes may warrant the submission of a new 510(k). For further information on this topic, refer to "Deciding When to Submit a 510(k) for a Software Change to an Existing Device."

[46] On February 2, 2024, FDA issued a final rule amending the device quality system (QS) regulation, 21 CFR part 820, to align more closely with international consensus standards for devices. FDA also made conforming amendments to 21 CFR part 4 (89 FR 7496). This final rule will take effect on February 2, 2026. Once in effect, this rule will amend the majority of the current requirements in part 820 and incorporate by reference the 2016 edition of the *International Organization for Standardization (ISO) 13485, Medical devices – Quality management systems – Requirements for regulatory purposes*, in part 820. As stated in the final rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current part 820, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the FD&C Act. When the final rule takes effect, FDA will also update the references to provisions in 21 CFR part 820 in this guidance to be consistent with that rule.

If the device includes off-the-shelf software, you should provide the additional information as recommended in the FDA guidance documents "Off-the-Shelf Software Use in Medical Devices" and "Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software," which provide additional information regarding medical devices utilizing off-the-shelf software.

If the device is a multiple function device product and includes software function(s) that are considered "other functions," as that term is used in the guidance "Multiple Function Device Product: Policy and Considerations," the recommendations described in the aforementioned guidance should also be considered when preparing the software documentation for a premarket submission.

Overall, the documentation related to the device software function(s) should provide sufficient evidence to describe the role of the software in the context of the device's intended use and testing to demonstrate that the software functions as designed.

I. Cybersecurity

Significance: Pulse oximeters could contain software, firmware, or programmable logic, and have the ability to connect to the internet either directly or indirectly through the connectivity features present in the device design. Failure to maintain cybersecurity can result in risks such as compromised device functionality, loss of device availability, loss of data (medical or personal) availability or integrity, or exposure of other connected devices or networks to security threats. This in turn may have the potential to result in patient injury.

Recommendation: If the device meets the definition of a cyber device under section 524B(c) of the FD&C Act, cybersecurity documentation under section 524B(b) of the FD&C Act is required as a part of the premarket submission. Refer to the FDA cybersecurity guidance "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions" for a discussion of these requirements and cybersecurity documentation that should be provided in submissions that could help satisfy such requirements.

J. Human Factors

Significance: Use-related hazards are hazards resulting from failure modes tied to the use of pulse oximeters. They are a unique form of hazard in that use-related hazards can exist even if the device operates according to specifications. They generally do not involve specific failure modes associated with faulty electrical, mechanical, and software components that are previously known or reasonably anticipated. To understand the use-related hazards associated with the use of a pulse oximeter, you should consider the device use scenarios (e.g., device users, use environments, and user interface), the tasks within these scenarios that could lead to harm (i.e., critical tasks) and how the device supports the user to complete these tasks in a safe manner. For pulse oximeters, use-related hazards may relate to concerns such as the accurate application of a

sensor, user comprehension (e.g., lay-users) of directions for use that influence the accuracy and reliability of measurements and adverse events associated with incorrect sensor placement.

Recommendation: Many pulse oximeters sensors are placed on the fingertip, a standard anatomical location for the measurement of SpO_2. To address use-related hazards for all pulse oximeters that are placed in a non-standard anatomical location (i.e., not fingertip), or have unique technology and/or features, human factors evaluations should start early in the device design process and should occur iteratively. For example, pulse oximeters that are intended to be used on the fingertip but are secured in a novel way (e.g., not clip-on) or use different technological mechanisms (e.g., reflectance technology rather than transmittance technology) could be appropriate for a human factors evaluation. There are various methods for the preliminary human factors analyses and evaluations, which are discussed further in FDA's guidance "Applying Human Factors and Usability Engineering to Medical Devices." The guidance also provides recommendations on human factors information included in a premarket submission.

In addition, for OTC pulse oximeters intended to be placed in a standard or non-standard anatomical location, FDA recommends that usability testing (e.g., labeling comprehension) be conducted to identify potential use error and help mitigate sources of error to determine that the labeling is adequate.[47] Adequate device labeling can support safe and effective use of these devices and are important strategies to address device use hazards.

K. Electrical Safety and Electromagnetic Compatibility (EMC)

Significance: Pulse oximeters are medical electrical equipment and therefore may expose the operator and patient to hazards associated with the use of electrical energy or may fail to operate properly in the presence of electromagnetic disturbance.

Recommendation: Pulse oximeters should be tested to demonstrate that they perform as anticipated in their intended use environment. We recommend that this testing be performed as described in the currently FDA-recognized versions of the following standards for medical electrical equipment safety and electromagnetic compatibility:

- ISO 80601-2-61 *Medical electrical equipment - Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment*.
- IEC 60601-1 *Medical electrical equipment - Part 1: General requirements for basic safety and essential performance (with relevant U.S. national differences applied)*.

[47] 21 CFR 801.5 states that "*Adequate directions for use* means directions under which the layman can use a device safely and for the purposes for which it is intended." As an OTC device, the device labeling must include adequate directions for use.

- IEC 60601-1-2 *Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic disturbances - Requirements and tests.*

If submitting a Declaration of Conformity to the above FDA-recognized consensus standards, we recommend that appropriate supporting documentation[48] be provided. Information regarding test methods chosen and acceptance criteria should be provided because this series of standards includes general methods with multiple options and, in some cases, does not include specific acceptance criteria. For additional information on providing electromagnetic compatibility information in a premarket submission, see FDA's guidance "Electromagnetic Compatibility (EMC) of Medical Devices."

It should also be noted that the above standards are within the scope of the ASCA Program, which can be leveraged by manufacturers to streamline the review of the test results of these standards. For more information, see the ASCA Program website.

L. Wireless Technology

Significance: In the design, testing, and use of wireless medical devices, the correct, timely, and secure transmission of medical data and information is essential for the safe and effective use of medical devices and systems.

Recommendation: If your pulse oximeter incorporates radiofrequency wireless technology such as Bluetooth, IEEE 802.11 (Wi-Fi) or RFID (radio frequency identification) technology, testing beyond what is described in the IEC 60601 standards is recommended to demonstrate that the wireless device functions will perform as intended in environments with other wireless products. For additional recommendations for home use devices with wireless technology, refer to FDA's guidance "Design Considerations for Devices Intended for Home Use."

We recommend that you consult FDA's guidance "Radio Frequency Wireless Technology in Medical Devices" for additional recommendations on this topic. When considering risks associated with wireless coexistence which can arise from multiple wireless systems operating in a shared environment, we recommend testing be performed as described in currently FDA-recognized versions of the following standards for wireless coexistence:

- AAMI TIR69 *Technical Information Report Risk management of radio-frequency wireless coexistence for medical devices and systems*; and
- IEEE ANSI USEMCSC C63.27 *American National Standard for Evaluation of Wireless Coexistence*.

[48] For more information on Declarations of Conformity and on appropriate supporting documentation, refer to FDA's guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."

M. Magnetic Resonance (MR) Compatibility

Significance: Pulse oximeters that are intended to function during an MR procedure or in the MR environment pose the following potential hazards for patients:

- Magnetically induced displacement force and/or torque may cause damage by inducing unwanted movement or dislodgement of the pulse oximeter (e.g., a power supply, a monitor);
- Radiofrequency (RF) of the MR system can induce heating of the tissue adjacent to the pulse oximeter (e.g., a pulse oximeter sensor) and subsequent tissue damage;
- MR interference and the exposure to the MR system's electric and magnetic fields can cause inaccurate oximetry measurement or device malfunction; and/or
- Presence of metallic components can lead to image artifacts in the acquired MR images that can render the images uninterpretable or misleading.

Recommendation: We recommend that you address the issues affecting safety and compatibility of your pulse oximeter in the MR environment as described in the FDA guidance "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment."

If you would like to market pulse oximeters of various sizes and shapes, then we recommend that you follow our recommendations in the FDA guidance "Assessment of Radiofrequency-Induced Heating in the Magnetic Resonance (MR) Environment for Multi-Configuration Passive Medical Devices."

N. Non-Clinical Bench Testing

Non-clinical bench testing supports device safety and device performance. Typical bench testing should demonstrate that the device functions as intended. To assist in determining the appropriate non-clinical bench testing for your device, you can seek input from the Agency via the Q-Submission Program.[49]

For information on the recommended content and format of test reports for the testing described in this section, refer to FDA's guidance "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions."

Non-clinical bench testing involving patient simulators and/or functional testers (see ISO 80601-2-61 describing the definition and appropriate uses of a functional tester) that generate simulated signals for pulse oximeters can potentially be used to verify certain aspects of pulse oximeter performance as discussed below. As discussed in ISO 80601-2-61, functional testers may not be able to represent all physiological and optical factors affecting pulse oximeter performance and are not suitable for evaluating SpO_2 accuracy. When providing test reports for non-clinical

[49] For details on the Q-Submission Program, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

testing using a patient simulator or functional tester, we recommend that manufacturers include a justification for the methods used to perform the test and a rationale of how they provide signals representative of the conditions being evaluated.

(1) SpO_2 accuracy for oximeters labeled for use in low perfusion conditions

Significance: Pulse oximeter performance may degrade under conditions of poor pulsatile signal strength which leads to low percent modulation. This degradation can cause a pulse oximeter to output inaccurate SpO_2 measurements. If the pulse oximeter is labeled for use in low perfusion conditions, testing should demonstrate device performance under such conditions.

Recommendation: We recommend that you conduct testing under conditions of low percent modulation. One recommended method is to verify the SpO_2 accuracy under low percent modulation conditions *in vitro* using a functional tester, set to the signal amplitude defined as low perfusion for the system (e.g., 0.3% modulation). We recommend that a summary of the test methods be provided in the labeling.

(2) Pulse rate accuracy

Significance: Pulse oximeters should demonstrate sufficient accuracy to be suitable for their intended use and to prevent adverse events related to incorrect measurements. If the system provides pulse rate measurements, testing should demonstrate device performance within specification.

Recommendation: We recommend that you conduct testing on the specified pulse rate measurement range. One recommended method is to test your system on the bench (using a functional tester) at the lowest pulse amplitude specified as "normal." We recommend that a summary of the test methods be provided in the labeling.

(3) Pulse rate accuracy for oximeters labeled for use during motion conditions

Significance: Pulse oximeter performance may degrade under conditions of motion. This degradation can cause a pulse oximeter to output inaccurate pulse rate measurements. If the pulse oximeter is labeled for use during motion conditions, testing should demonstrate device performance under motion conditions.

Recommendation: We recommend that all continuous (real-time monitoring and data archiving) pulse oximeters be subject to motion testing. We also recommend non-continuous pulse oximeters labeled for use in motion conditions be subject to motion testing. One recommended approach is to use the same method used to demonstrate sufficient pulse rate accuracy generally, as described in Section IV.N(2), but with motion incorporated. We recommend including a

description of the characteristics of each motion including amplitudes, types, and frequencies selected for testing. We recommend that a summary of the test methods be provided in the labeling.

(4) Pulse rate accuracy for oximeters labeled for use in low perfusion conditions

Significance: Pulse oximeter performance may degrade under conditions of poor pulsatile signal strength. This degradation can cause a pulse oximeter to output inaccurate pulse rate measurements. If the pulse oximeter is labeled for use in low perfusion conditions, testing should demonstrate device performance under low perfusion conditions.

Recommendation: We recommend that you conduct testing under conditions of low percent modulation. A recommended approach is to use the same method used to demonstrate sufficient pulse rate accuracy generally, as described in Section IV.N(2), with a functional tester, set to the signal amplitude defined as low perfusion for the system (e.g., 0.3% modulation). We recommend that a summary of the test methods be provided in the labeling.

(5) Alarms

Significance: Device operators rely on proper operation of alarms to alert them to take appropriate actions in care of a patient or to resolve a device issue. Failure of a pulse oximeter to activate an alarm can cause delayed response to abnormally high or low SpO_2 or pulse rate, if applicable.

Recommendation: We recommend physiological alarms for all continuous real-time monitoring pulse oximeters. We recommend that you address alarm-related clauses of the currently FDA-recognized version of ISO 80601-2-61 or an equivalent method for visual and audible alarms of the monitor and any remote alarm unit.

(6) Display values, outputs and indicators

Significance: Device operators rely on device indicators and outputs to determine if the pulse oximeter is functioning as intended. Degraded performance under conditions resulting in poor signal quality can cause pulse oximeters to output inaccurate or outdated SpO_2 and pulse rate measurements. Testing should demonstrate the device provides an indication of potentially incorrect measurements and when measurements may not be current.

Recommendation: We recommend that the device provide an indicator of signal inadequacy. We also recommend the device provide an indicator that SpO_2 or pulse rate data is not current when the update period is greater than 30 seconds. You can also refer to the currently FDA-recognized version of ISO 80601-2-61 for additional considerations regarding data update period and signal inadequacy.

We recommend that you conduct appropriate testing of all the data outputs, measurement values, and indicators that the device incorporates (e.g., signal inadequacy, perfusion index, pulse amplitude, signal strength).

(7) Saturation pulse information signal, if applicable

Significance: Device operators might rely on changes in auditory pitch to indicate a change in SpO_2. Failure of changes in auditory pitch to follow a change in SpO_2 can result in delayed response by a user to detect clinically meaningful changes in SpO_2.

Recommendation: If your device includes a variable-pitch auditory information signal to indicate the pulse signal, we recommend the pitch change follow the change in SpO_2 reading and be verified through testing (see also currently FDA-recognized version of ISO 80601-2-61).

O. Clinical Performance Testing

Significance: Clinical studies are important to evaluate device safety and effectiveness for all pulse oximeter systems within the scope of this guidance and to assure non-disparate performance across populations with diverse skin pigmentation.

Recommendation: We recommend that you conduct a controlled desaturation laboratory study as described in Annex EE of ISO 80601-2-61 Second edition 2017-12 (Corrected version 2018-02) to determine SpO_2 accuracy. We also recommend that this study be used to demonstrate non-disparate performance for new pulse oximeter systems.[50] In addition, for pulse oximeter systems intended for use in pediatric populations younger than 12 years of age, we recommend that convenience arterial samples (SaO_2, SpO_2) be provided for pediatric populations younger than 12 years of age to assure form and fit of sensor site and clinical performance.

We generally intend to consider alternatives to clinical testing to demonstrate substantial equivalence when the proposed alternatives are supported by an adequate scientific rationale. For example, when changes or modifications made do not affect the optical chain, signal processing path and SpO2 algorithm, then additional clinical studies might not be needed to demonstrate substantial equivalence.

If a clinical investigation is conducted to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, it must comply with the Investigational Device Exemption (IDE) regulation, 21 CFR Part 812. Generally, we believe pulse oximeters addressed by this guidance document would be considered non-significant risk devices; therefore, the study would likely be subject to the abbreviated requirements of 21 CFR 812.2(b). See the FDA guidance titled "Significant Risk and Nonsignificant Risk Medical Device Studies." In addition,

[50] FDA recognizes that a study in a simulated setting (i.e., controlled desaturation laboratory study) is likely to test individuals using a larger range of SaO_2 levels than a study collecting real world evidence from patients.

sponsors of studies of a device intended to demonstrate substantial equivalence that are conducted in the United States (US) are subject to the regulations governing institutional review boards (21 CFR Part 56) and the protection of human subjects (21 CFR Part 50), including requirements for informed consent.

When data from clinical investigations conducted outside the US are submitted to FDA for these devices, the requirements of 21 CFR 812.28 may apply.[51] 21 CFR 812.28(a) outlines the conditions for FDA acceptance of data from clinical investigations conducted outside the US to support an IDE or a premarket submission. For more information, see the FDA guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."

In some cases, "real-world data" (RWD) can be used, for example, to support expansion of an indication or the evaluation of non-disparate performance for a device for which 510(k) clearance has already been obtained. FDA encourages manufacturers to engage with the Agency if they have questions on RWD.[52] Whether the collection of RWD for a legally marketed device requires an IDE depends on the particular facts of the situation. For example, if a cleared device is being used in the normal course of medical practice, an IDE would likely not be required. For additional information regarding this topic, refer to the FDA guidance titled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."

(1) Controlled Desaturation Laboratory Study

a. Purpose/Objective

The purpose of conducting an invasive controlled desaturation laboratory study is to verify the pulse oximeter system's SpO_2 accuracy in comparison with reference measurements of functional SaO_2 by a CO-oximeter and to demonstrate non-disparate performance across diverse skin pigmentation.

b. Study Design

We recommend that you conduct the study as described in Annex EE of ISO 80601-2-61 Second edition 2017-12 (Corrected version 2018-02) in a diversely pigmented group of 150 or more healthy participants.

For study enrollment, we recommend the following:

[51] 21 CFR 812.28 applies to relevant clinical investigations that enroll the first subject on or after February 21, 2019, and that support an IDE or a device marketing application or submission to FDA.

[52] Manufacturers can seek input from the Agency via the Q-Submission Program. See FDA guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

- Evaluate forehead pigmentation of study participants through visual assessment with the Monk Skin Tone (MST) scale[53, 54] – a ten level subjective skin color annotation with a high inter-rater reliability[55] (see Appendix B for printing recommendations) defined in terms of CIELAB[56] color space;
- Evaluate forehead pigmentation of study participants using colorimetry to determine L* and b* values, then calculating the Individual Typology Angle (ITA), which is defined as:[57] $ITA° = \arctan\left(\frac{L^* - 50}{b^*}\right) * \frac{180}{\pi}$;
- Documenting information related to diversity in race and ethnicity during enrollment as described in Section III of FDA's draft guidance "Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products";[58]
- Allocate enrolled participants into three specific MST groups: 1-4, 5-7, 8-10, while ensuring the following:
  - at least 25% of participants fall within each MST group;
  - at least 50% of the participants in MST group 8-10 have an ITA ≤ -50° at the forehead; and
  - in each MST group, at least 40% of participants are male, and at least 40% of participants are female.

We recommend that you submit the protocol(s) used to assign MST and evaluate ITA in your premarket submission. For additional feedback, we recommend early engagement with the Agency through the Pre-Submission process as described in FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" to discuss your proposed plan for MST assignment and ITA assessment in advance of conducting the study.

Additionally, we recommend measuring ITA values at the surface directly in contact with the sensor emitter. For fingertip sensors, to capture the widest variation in skin pigmentation applicable to sensor placement, we recommend evaluating sensor site ITA values (see yellow

[53] Heldreth CM, Monk EP, Clark AT, Schumann C, Eyee X, Ricco S. Which skin tone measures are the most inclusive? An investigation of skin tone measures for artificial intelligence. ACM Journal on Responsible Computing 1, no. 1 (2024): 1-21.

[54] It is important to note that MST, though validated for capturing race and ethnicity diversity in pigmentations within the US (see *ibid* Heldreth *et al*.), is not a proxy for racial and ethnic diversity.

[55] Schumann C, Olanubi GO, Wright A, Monk Jr. E, Heldreth C, Ricco S. 2024. Consensus and Subjectivity of Skin Tone Annotation for ML Fairness. In Proceedings of the 37th International Conference on Neural Information Processing Systems (NIPS '23). Article 1320: 30319-30348. Curran Associates Inc.

[56] For more information on standard colorimetry methods, refer to pp. 7-8 in the FDA's discussion paper "Approach for Improving the Performance Evaluation of Pulse Oximeter Devices Taking Into Consideration Skin Pigmentation, Race and Ethnicity."

[57] Ly BCK, Dyer EB, Feig JL, Chien AL, Del Bino S. Research Techniques Made Simple: Cutaneous Colorimetry: A Reliable Technique for Objective Skin Color Measurement. J Invest Derm. 2020,140(1):3-12.

[58] When final, this guidance will represent the FDA's current thinking on this topic.

circle in Figure 1) at the mid-dorsal pigmented skin surface of the distal phalanx, proximal to the eponychium.

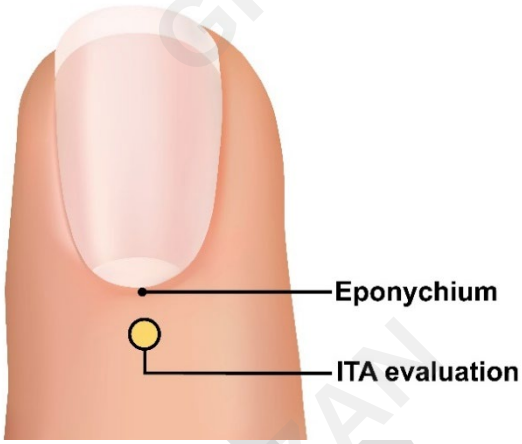


Figure 1: Image of a fingertip

We recommend that you obtain 3,000 or more paired observations of pulse oximeter SpO_2 and CO-oximeter SaO_2. We recommend 20 or more data pairs per participant that span the SaO_2 interval 70-100% and at least 30% of data pairs per MST group (MST 1-4, 5-7, 8-10), and per SaO_2 decile ($70\% \leq SaO_2 < 80\%$, $80\% \leq SaO_2 < 90\%$, and $90\% \leq SaO_2 \leq 100\%$). We recommend that you provide a line listing of the data pairs by participant.

For additional information on principles for the design of premarket clinical studies that are pivotal in establishing the substantial equivalence or safety and effectiveness of a medical device, refer to FDA's guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices."

c. Inclusion/Exclusion Criteria

We recommend that your participants are healthy adults who can tolerate desaturation as described in Annex EE of ISO 80601-2-61 Second edition 2017-12 (Corrected version 2018-02). Additionally, we recommend exclusion of participants with uneven skin tone at the sensor site or at the forehead.

d. Participant Demographics

We recommend that the study population used to determine SpO_2 accuracy consists of diverse participants selected consecutively from an available pool of healthy participants and not contain participants from the calibration curve development study for the same devices(s). We believe that the collection and presentation of race and ethnicity data should generally be submitted in a

premarket submission to the FDA as described in the FDA draft guidance "Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products."[59]

You should describe characteristics of your participant populations that could affect the results of the study, including:

- Age;
- Sex;
- BMI;
- Self/caregiver-reported ethnicity;
- Self/caregiver-reported race;
- Forehead MST and ITA values of each participant;
- ITA value at the emitter sensor site placement;
- Range of applicable dimension(s) of sensor site anatomy;
- Range of percent modulation in study participants when obtaining data pairs (SaO_2, SpO_2); and
- Percent of each MST group that tolerated full desaturation (down to SaO_2 of 70%).

For more information regarding the evaluation and reporting of age, race, ethnicity and sex-specific data in medical device clinical studies, see FDA's guidances "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" and "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies."

e. Protocol

We recommend you provide ranges of percent modulation for study participants while obtaining data pairs (SaO_2, SpO_2) and describe methods used to attain these values in your premarket submission. Additionally, we recommend conducting SpO_2 accuracy testing under conditions of motion for all continuous (real-time monitoring and continuous data archiving) pulse oximeters and non-continuous pulse oximeters intended for use during motion conditions. We recommend including a description of the characteristics of each motion, if any, including amplitudes, types, and frequencies of motion selected for testing in your test report and justification of your method for the device's intended use.

f. Effectiveness Endpoints and Data

We recommend that an A_{rms} specification of less than 3% be shown with statistical significance, e.g., 95% CI. We recognize that accuracy is, among other things, a function of participant characteristics, application site and sensor geometry. Table 3 outlines the recommended A_{rms}

[59] When final, this guidance will represent the FDA's current thinking on this topic.

between measured values (SpO_2) and reference values (SaO_2) under normal conditions ranging from 70% to 100% SpO_2.

Table 3: Typical A_{rms} Specification by Sensor Type

Sensor Type	A_{rms} with 95% CI*
Transmittance, wrap and clip	< 3 %
Ear clip	< 3 %
Reflectance	< 3 %

* 2-sided 95% confidence interval upper limit < 3%

g. Statistical Analysis Considerations

i. Co-Primary Analyses

For pivotal controlled desaturation studies, we recommend co-primary analyses of the following performance metrics:

1. SpO_2 accuracy (A_{rms}) over all study participants.
2. SpO_2 bias (mean error) as a function of SaO_2 and MST at the forehead.
3. SpO_2 bias (mean error) as a function of SaO_2 and ITA measured at the skin surface in contact with the sensor emitter for the device.

ii. Recommended Success Criteria

For the co-primary analyses, we recommend the following success criteria:

1. Overall Accuracy: A_{rms} is less than 3%.
2. Non-Disparate Performance Evaluation 1: Among pairwise comparisons of MST groups 1-4, 5-7, and 8-10, the largest difference in SpO_2 bias is less than 3.5% for the interval $70\% \leq SaO_2 \leq 85\%$ and less than 1.5% for $85\% < SaO_2 \leq 100\%$.
3. Non-Disparate Performance Evaluation 2: For a 100-point change in emitter sensor site ITA, the difference in SpO_2 bias is less than 3.5% for $70\% \leq SaO_2 \leq 85\%$ and less than 1.5% for $85\% < SaO_2 \leq 100\%$.

We recommend all three success criteria be shown with statistical significance, with either a 1-sided hypothesis test at significance level of 2.5% (p-value of the null hypothesis is less than

2.5%) or a 2-sided 95% CI (limits of the 95% CI imply that the success criterion for the parameter is achieved).[60]

To visually characterize device performance (i.e., agreement, bias and uncertainty), FDA recommends that Bland Altman,[61] modified Bland Altman,[62] QQ,[63] and inverse prediction plots[64] should generally be provided in a premarket submission. FDA recommends that these plots be constructed with symbols or colors that code for MST group (1-4, 5-7, and 8-10). FDA also recommends the Bland Altman and modified Bland Altman plots include the 95% limits of agreement.[65]

iii. Sample Size

The sample size of study participants should be the maximum of the sample sizes needed to obtain adequate power (80% or greater power is recommended) to meet each success criterion with statistical significance. For adequate power, FDA recommends a sample size of 150 or more participants who satisfy the enrollment criteria as described in Section IV.O(1)b.

The appropriate number of study participants depends on pulse oximeter accuracy, data variability, and average number of paired repeated measures (SpO_2, SaO_2) per participant. We recommend an average of 20-24 simultaneous paired repeated measures per participant, a minimum of 17 and maximum of 30 pairs per participant, and at least 30% of pairs in each of the SaO_2 deciles, $70\% \leq SaO_2 < 80\%$, $80\% \leq SaO_2 < 90\%$, and $90\% \leq SaO_2 \leq 100\%$. When uncertainty exists concerning data variability or pulse oximeter accuracy, an adaptive study in which sample size is adjusted based on accumulating data is potentially advantageous when feasible.[66]

iv. Analysis Population and Methods

Performance metrics should be analyzed using the intention-to-diagnose (ITD) analysis population, defined as all participants enrolled into the study and all paired repeated measures of (SpO_2, SaO_2) even when one or both were invalid, non-evaluable, or missing. In other words, participants and paired repeated measures should not be excluded from the analysis population, whether the data are complete or not. You should report the number and proportion of incomplete data pairs.

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[60] Ndikintum, N.K., & Rao, M. (2016). A Special Inference Problem in Repeated Measures Design—Test of Statistical Hypothesis on Accuracy Root Mean Square—Application to Pulse Oximetry Studies. *Statistics in Biopharmaceutical Research*, *8*(1), 60-76.

[61] Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. J Biopharm Stat. 2007;17(4):571-82.

[62] For two measurements Y and X of the same quantity, the Bland-Altman plot is a plot of the difference $D = Y - X$ vs. average $A = (Y + X)/2$. The modified Bland-Altman plot is a plot of D vs. X.

[63] For paired SpO_2 and SaO_2, a QQ plot of SpO_2 vs. SaO_2 is a scatterplot of the ordered values of SpO_2 vs. the ordered values of SaO_2.

[64] For a review of statistical methods for calculating inverse prediction intervals, see Greenwell BM, Schubert Kabban CM. investr: An R Package for Inverse Estimation. *The R Journal*. 2014 June; 6(1): 90-100.

[65] For calculation of 95% limits of agreement, see Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. J Biopharm Stat. 2007;17(4):571-82.

[66] Refer to the FDA guidance "Adaptive Designs for Medical Device Clinical Studies" for additional information on adaptive designs for a medical device clinical study.

v. Missing Data

Efforts to reduce missing data

We recommend you describe the efforts that you intend to use during the course of the study to minimize participant dropout and missing data.

Document reasons for missing data

We recommend you identify the reasons for missing data if they occur, for example:

- Participant drop-out;
- Participant has insufficient paired repeated measures (number or SaO_2 span);
- Participant is excluded from analysis; and
- Paired repeated measure is incomplete (SpO_2 or SaO_2 is invalid or missing).

To support a complete and detailed accounting of all study participants, we recommend you collect complete information during the study. Without complete information, data may have been excluded from analysis, potentially introducing analysis bias, which could jeopardize the conclusions that can be drawn about the substantial equivalence or safety and effectiveness of your device.

h. Grouping of sensors for testing

It may be appropriate to group certain sensors for testing if they are of similar design or equivalent performance. We consider sensors to be of similar design if they contain identical materials and electro-optical components and have equivalent sensor characteristics (e.g., location of use). If you choose to group sensors for testing based on their similar design, we recommend that you indicate whether all sensors within each group contain identical materials and electro-optical components and describe the rationale for grouping. Generally, clip and adhesive sensors should not be grouped based on similar design because they differ in form, fit, and functional specifications. If you choose to group sensors for testing based on equivalent performance, we recommend that you provide valid scientific evidence and statistical analysis to demonstrate that the results of testing are poolable.

(2) Additional considerations for pulse oximeters intended for pediatric populations younger than 12 years of age

If a pulse oximeter system is intended for use in pediatric populations younger than 12 years of age, data supporting accuracy of clinical performance for the relevant pediatric subpopulation(s) and associated pathophysiologic state(s) should be considered. As stated earlier in this guidance, clinical performance testing of the pulse oximeter system (see Section IV.O(1)) in adult populations may not be sufficient to support clinical performance in certain pediatric subgroups such as neonates, infants, and children younger than 12 years of age due to significant

differences in form and fit of the pulse oximeter sensor that may lead to differences in overall accuracy of the system.

If the device is intended for use in pediatric populations younger than 12 years of age, FDA recommends that manufacturers consider validating the performance in this population by:

(1) evaluating the performance of the pulse oximeter system using the pediatric sensor in adult participants across diverse skin pigmentation as described in Section IV.O(1)b; and
(2) evaluating the performance in pediatric participants within the age range (and associated clinically relevant pathophysiologic state) specific to the indications for use and sensor placement.

Regarding data in pediatric study participants, specifically for neonates, we recommend you report performance of pediatric sensors on adult participants as described above (Section IV.O(1)). If your device is intended for use with neonates, we recommend you provide testing on additional convenience arterial samples (see Annex EE of ISO 80601-2-61 Second edition 2017-12 (Corrected version 2018-02)) collected on neonates to verify form, fit, and clinical performance. Manufacturers should also consider providing the additional convenience arterial samples collected on other pediatric subgroup(s) as well (e.g., infants, children in stable cyanotic and non-cyanotic states). If the sensor placement site in the pediatric subgroup is expected to have a larger variation of skin pigmentation than in the controlled desaturation adult study, manufacturers should consider including a skin pigmentation assessment, as described in Section IV.O(1)b, to assure diversity in skin pigmentation and non-disparate performance.

Though pediatric (e.g., neonatal) clinical studies are more representative of the intended use than controlled laboratory studies in adults, sampled data pairs may not span the entire SaO2 range verified in controlled adult studies and be drawn under uncontrolled conditions (e.g., temperature, co-morbidities, non-simultaneous data pair). Nonetheless, we recommend you provide data and samples on enough participants equally distributed across the population subgroup and that you justify the sample size, and SaO2 range of data pairs (SaO2, SpO2). Additionally, we recommend that you include range of percent modulation of your study participants when obtaining data pairs. If your study includes enrollment by skin pigmentation (i.e., the sensor placement site in your pediatric subgroup(s) is expected to have a larger variation of skin pigmentation than in the controlled desaturation adult study), we recommend that you include reported race, ethnicity, MST measurement site, and MST values of each participant as well as ITA values at emitter sensor site for each relevant pediatric subgroup in your premarket submission.

For additional feedback regarding validating pulse oximeter performance for patient populations younger than 12 years of age, we strongly recommend early engagement with the Agency through the Pre-Submission process, as described in the FDA guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," to discuss an approach and special considerations for supporting a pediatric indication for each device.

Note that FDA intends to update the recommendations for certain pediatric population(s) as more information becomes available (e.g., CERSI clinical study with Stanford University).[67]

V. Modifications (for previously 510(k)-cleared or authorized devices)

21 CFR 807.81(a)(3) provides that a device change or modification "that could significantly affect the safety or effectiveness of the device" or represents a "major change or modification in the intended use of the device" requires a new 510(k).[68] In addition to the examples already referenced in this guidance (e.g., labeling related to non-disparate performance data), the changes or modifications listed below are examples of changes that are likely to require submission of a new 510(k), but note that this list is not exhaustive. For additional details, see FDA guidances "Deciding When to Submit a 510(k) for a Change to an Existing Device" and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device."

Examples of such changes or modifications include:

- Significant electro-optical sensor modifications (e.g., a new component or new bandage material in or near the light path, extensive re-design where a device is miniaturized). FDA generally considers this to be a significant change or modification in design because this change could significantly affect the safety and effectiveness of the device by affecting the optical chain or signal processing path.
- Significant SpO_2 algorithm modifications. FDA generally considers this to be a significant change or modification in design. This type of change could significantly affect the safety and effectiveness of the device by affecting data processing and calculation of SpO_2.
- Significant changes to the input parameters of an SpO_2 software function. FDA generally considers this to be a significant change or modification in design. This type of change could significantly affect the safety and effectiveness of the device by affecting data processing and calculation of SpO_2.

[67] For more information, see https://www.fda.gov/science-research/advancing-regulatory-science/prospective-clinical-study-evaluate-accuracy-pulse-oximeters-children

[68] Section 3308 of the Food and Drug Omnibus Reform Act of 2022 (FDORA), enacted as part of the Consolidated Appropriations Act, 2023, added section 515C "Predetermined Change Control Plans for Devices" to the FD&C Act (Pub. L. No. 117-328). Section 515C has provisions regarding predetermined change control plans (PCCPs) for devices requiring premarket approval or premarket notification. For example, section 515C states that supplemental applications (section 515C(a)) and new premarket notifications (section 515C(b)) are not required for a change to a device that would otherwise require a premarket approval supplement or new premarket notification if the change is consistent with a PCCP approved or cleared by FDA. Section 515C also states that FDA may require that a PCCP include labeling for safe and effective use of a device as such device changes pursuant to such plan, notification requirements if the device does not function as intended pursuant to such plan, and performance requirements for changes made under the plan. If you are interested in proposing a PCCP in your marketing submission, we encourage you to submit a Pre-Submission to engage in further discussion with CDRH. See FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

- Modifying the patient population, such as indicating the device for pediatric populations younger than 12 years of age (see Section IV.O(2)). FDA generally considers this to be a significant change or modification to the labeling and/or indications for use. This type of change could significantly affect the safety and effectivenessof the device by changing form, fit and clinical performance.

If your device incorporates existing pulse oximetry technology that is legally marketed for the same intended use, and you have determined your device requires submission of a new 510(k), we recommend you provide the following:

- 510(k) numbers for the submissions where each combination of oximeter, sensor, and cable were cleared for use together;
- Report(s) of all relevant clinical studies (see Section IV.O) that support your current premarket submission and labeling (see Section IV.C);
- Testing that demonstrates that SpO_2 and pulse rate values calculated by the Original Equipment Manufacturer (OEM) system are not corrupted during communication to the host device. We recommend that you conduct the testing using a functional tester (see ISO 80601-2-61 for the definition and appropriate uses of a functional tester) to span the range of saturation and pulse rate values to assure communication between the sensor and the host module.

Appendix A. Example of Labeling for Pulse Oximeters

This appendix provides an example of labeling that contains a representative sampling of the important types of warnings and directions for use that FDA recommends in Section IV.C. of this guidance. This appendix is not intended to encompass an exhaustive list of all warnings and directions for use.

Warnings:

- Only your physician or health care provider can diagnose whether you are experiencing hypoxemia (low blood oxygen levels).
- Seek timely attention if you experience signs and symptoms of low oxygen levels, and do not rely solely on a pulse oximeter to assess your health condition or oxygen level.
- If monitoring at home, pay attention to other signs or symptoms of low oxygen levels, such as:
    - Bluish coloring in the face, lips, or nails;
    - Shortness of breath, difficulty breathing, increase in respiratory rate or a cough that gets worse;
    - Restlessness and discomfort;
    - Chest pain or tightness; and
    - Fast or racing pulse rate.
    - Be aware that some patients with low oxygen levels may not show any or all of these symptoms.
- Do not adjust medications or therapy based on your pulse oximeter readings without first consulting your health care provider since doing so may lead to harm.
- Pulse oximeters are not completely accurate and there is a range of uncertainty around the displayed SpO_2 value. Accuracy of SpO_2 generally decreases with decreasing true blood oxygenation. For example, a pulse oximeter saturation value of 90% may be indicative of an arterial blood oxygenation between 87% to 93% while a pulse oximeter saturation of 80% may be indicative of an arterial blood oxygenation of 75% to 85%. Pulse oximeter readings should only be used as an estimate of arterial blood oxygenation.
- Differences in skin tones may affect the accuracy of oxygen level readings, particularly when oxygen levels are very low. Consult your health care provider if you have questions or concerns about your readings.
- Changes or trends in measurements (e.g., decreasing SpO_2 values from 97% to 90%) may be more meaningful than one single measurement (e.g., SpO_2 of 94%). Accuracy of this pulse oximeter is not typically verified below arterial blood oxygen saturation (SaO_2) levels of 70%.
- Some factors that may affect pulse oximetry accuracy include:
    - Lower blood oxygen saturations;
    - Low blood flow or pulsatility (poor circulation);
    - High ambient light levels;
    - Excessive movement (including shivering);
    - (cold) Skin temperature;

    - Nail polish, artificial nails, or tattoo ink;
    - Presence of intravascular dyes used for medical purposes (e.g., methylene blue);
    - Blood disorders like anemia (e.g., sickle cell disease);
    - Smoking;
    - Radio frequency interference;
    - Pulsations in the veins (these may be caused by valvular heart conditions or vascular access used for hemodialysis); and
    - Presence of abnormal hemoglobin (e.g., methemoglobin, carboxyhemoglobin).
- Continuous wear over the maximum specified time may lead to adverse events (e.g., breakdown of the skin, decreased blood flow to sensor site).
- Continuous wear in certain locations (e.g., hand, foot, ankle) in younger populations (e.g., infants, children) may interfere with normal activity and age-appropriate development, such as turning over, crawling, standing, and walking.
- Alarms and alerts may cause sleep interruptions in those caring for and/or wearing the pulse oximeter.

Directions for Use

- Position the sensor (usually on the finger) below the mid-chest. Positioning the sensor above the level of the heart may reduce accuracy.
- Usually, the ring or middle finger work best for fingertip pulse oximeters.
    - Place the sensor so that the path between each side is straight and without any obstruction (e.g., a ring, tattoo).
- For spot-check use, wait for 30 seconds or more of stable SpO_2 reading.
- If percent modulation is displayed on the pulse oximeter, pay attention whether it is within the value(s) provided to consider whether your estimated oxygen level (SpO_2) is accurate.
- Choose a probe location where the skin is intact, healthy, and does not have any cuts, eczema, infections, swelling or other problems such as poor circulation.
- Remove or reposition the sensor every four hours [or manufacturer's maximum specified time] or if it causes discomfort or skin changes at the site of application.
- In between uses, clean your pulse oximeter using the appropriate materials [per manufacturer's instructions].

Appendix B. Considerations for Printing Monk Skin Tone Color Charts

A scale that is well-defined in a standardized color space, such as CIELAB,[69] should be used to support evaluation of non-disparate performance as described in Section IV.O(1)b of this document. One of the options available is the Monk Skin Tone (MST) scale. FDA recommends evaluating skin tone according to the MST approach, where color charts are based on the following L*a*b* values in Table B1.[70] We recommend that color charts be professionally printed with a calibrated printer on appropriate paper. Color chart accuracy should be verified with a calibrated spectrophotometer.

Table B1: MST Scale as Defined in CIELAB Color Space

MST Level	L*	a*	b*
1	94.2	1.5	5.4
2	92.3	2.1	7.3
3	93.1	0.2	14.2
4	87.6	0.5	17.7
5	77.9	3.5	23.1
6	55.1	7.8	26.7
7	42.5	12.3	20.5
8	30.7	11.7	13.3
9	21.1	2.7	6.0
10	14.6	1.5	3.5

[69] See FDA-recognized consensus standard ISO/CIE 11664-4 *Colorimetry – Part 4: CIE 1976 L*a*b* colour space*.
[70] See https://skintone.google for additional information (last accessed on July 12, 2024).