Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Preface

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Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

FDA has a longstanding commitment to develop and apply innovative approaches to the regulation of medical device software and other digital health technologies to ensure their safety and effectiveness. [1] As technology continues to advance all facets of healthcare, medical software incorporating artificial intelligence (AI), and specifically the subset of AI known as machine learning (ML) (henceforth referred to as machine learning-enabled device software functions or ML-DSFs), has become an important part of many medical devices. This draft guidance is

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[1] FDA regulates software that meets the definition of a device, which is defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is – recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term 'device' does not include software functions excluded pursuant to section 520(o)" of the FD&C Act.

24 intended to provide a forward-thinking approach to promote the development of safe and
25 effective medical devices that use ML models trained by ML algorithms.
26
27 ML-enabled technologies have the potential to transform healthcare by deriving new and
28 important insights from the vast amount of data generated during the delivery of healthcare every
29 day. Medical device manufacturers[2] are using ML technologies to innovate their products to
30 better assist healthcare providers and improve patient care. Examples of ML applications in
31 medicine include earlier disease detection and diagnosis, development of personalized
32 diagnostics and therapeutics, and development of assistive functions to improve the use of
33 devices with the goal of improving user and patient experience.
34
35 FDA recognizes that the development of ML-DSFs is an iterative process. This draft guidance
36 proposes a least burdensome approach to support iterative improvement through modifications to
37 an ML-DSF while continuing to provide a reasonable assurance of device safety and
38 effectiveness. As such, this draft guidance demonstrates FDA's broader commitment to
39 developing innovative approaches to the regulation of device software functions as a whole.
40 Specifically, this draft guidance provides recommendations on the information to be included in
41 a Predetermined Change Control Plan (PCCP) provided in a marketing submission for an ML-
42 DSF. This draft guidance recommends that a PCCP describe the planned ML-DSF
43 modifications; the associated methodology to develop, implement, and validate[3] those
44 modifications; and an assessment of the impact of those modifications. The PCCP is reviewed as
45 part of a marketing submission to ensure the continued safety and effectiveness of the device
46 without necessitating additional marketing submissions for implementing each modification
47 described in the PCCP.
48
49 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
50 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
51 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
52 the word *should* in Agency guidances means that something is suggested or recommended, but
53 not required.
54

II.   Background

56 In April 2019, FDA published the [Proposed Regulatory Framework for Modifications to](#)
57 [Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)](#)

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[2] For the purposes of this guidance, "manufacturer" is used in accordance with the definitions of manufacturer in 21
CFR Parts 803, 806, 807, and 820 and as described in FDA's guidance "Policy for Device Software Functions and
Mobile Medical Applications" (DSF-MMA) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-device-software-functions-and-mobile-medical-applications.
[3] For the purposes of this guidance, the term "validation" is being used as it is defined in 21 CFR 820.3(z), which
states "[v]alidation means confirmation by examination and provision of objective evidence that the particular
requirements for a specific intended use can be consistently fulfilled." See Section IV. for more information on
definitions used for the purposes of this guidance.

58 - Discussion Paper and Request for Feedback ("2019 discussion paper").[4] The 2019 discussion
59 paper describes FDA's foundation for a potential approach to premarket review for AI/ML-
60 driven software modifications. The ideas delineated in the 2019 discussion paper leveraged
61 practices from our current premarket programs and relied on the International Medical Device
62 Regulators Forum's risk categorization principles,[5] the FDA's benefit-risk framework,[6] risk
63 management principles described in the Software Modifications guidance,[7] and the total product
64 lifecycle approach envisioned in the Digital Health Software Precertification (Pre-Cert) Pilot
65 Program.[8]
66
67 ML can allow software to learn through data, without being explicitly programmed, to perform a
68 task. One of the greatest potential benefits of ML resides in the ability to improve ML model
69 performance through iterative modifications, including by learning from real-world data. To
70 support the iterative development of ML-DSFs, and as part of the proposed framework presented
71 in the 2019 discussion paper, FDA described a "Predetermined Change Control Plan" that could
72 be included in a marketing submission for a device that is or includes an ML-DSF (referred to
73 interchangeably as an "ML-DSF" or a "device").[9] In this draft guidance, we provide
74 recommendations on the marketing submission content for a PCCP, which generally includes: 1)
75 a detailed description of the specific, planned device modifications; 2) the associated
76 methodology to develop, validate, and implement those modifications in a manner that ensures
77 the continued safety and effectiveness of the device across relevant patient populations, referred
78 to as the "Modification Protocol"; and 3) an Impact Assessment to describe the assessment of the
79 benefits and risks of the planned modifications and risk mitigations.
80
81 The 2019 discussion paper received a substantial amount of feedback from a wide array of
82 stakeholders. General comments were received, as well as specific responses to 18 questions

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[4] Available at https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device.

[5] See FDA's website on "Global Approach to Software as a Medical Device" available at https://www.fda.gov/medical-devices/software-medical-device-samd/global-approach-software-medical-device and IMDRF's SaMD Risk Categorization Framework available at http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf.

[6] See FDA's guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de and FDA's guidance "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.

[7] See FDA's guidance "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.

[8] See FDA's website on "Digital Health Software Precertification (Pre-Cert) Program" available at https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-program.

[9] For the purposes of this guidance, the terms "ML-DSF" and "device" are used interchangeably. Additionally, reference to an "ML-DSF" is referring to a software function that meets the definition of device, as defined in section 201(h) of the FD&C Act. See Section IV. for details on definitions.

83 posed in the 2019 discussion paper.[10] Additionally, numerous articles in peer-reviewed journals
84 discuss or reference the framework proposed in the 2019 discussion paper.[11]
85
86 FDA has also held a number of public meetings and workshops on AI/ML topics. On February
87 25-26, 2020, FDA held a Public Workshop on the "Evolving Role of Artificial Intelligence in
88 Radiological Imaging"[12] to discuss emerging applications of AI in radiological imaging,
89 including AI devices intended to automate the diagnostic radiology workflow as well as guide
90 image acquisition. At this workshop, the Agency worked with interested stakeholders, including
91 patients, to identify both benefits and risks associated with the use of AI in radiological imaging,
92 and discussed best practices for the validation of fully automated radiological imaging software
93 and image acquisition devices.
94
95 On October 22, 2020, FDA held a Patient Engagement Advisory Committee meeting on
96 "Artificial Intelligence and Machine Learning in Medical Devices"[13] to further elicit input from a
97 diverse group of patients on AI/ML technologies. The Committee provided recommendations on
98 AI/ML-enabled medical devices and how to foster patient trust in them, considering the diverse
99 populations in which they are and will be used.
100
101 On October 14, 2021, FDA held a Public Workshop on "Transparency of Artificial
102 Intelligence/Machine Learning-enabled Medical Devices"[14] for patients, caregivers, and
103 providers. The purpose of the workshop was to 1) identify unique considerations in achieving
104 transparency for users of AI/ML-enabled medical devices and ways in which transparency might
105 enhance the safety and effectiveness of these devices; and 2) gather input from various
106 stakeholders on the types of information that would be helpful for manufacturers to include in
107 the labeling and public facing information of AI/ML-enabled medical devices, as well as other
108 potential mechanisms for information sharing.
109
110 FDA continues to receive an increasing number of marketing submissions and pre-submissions
111 for devices leveraging ML technologies, and the Agency expects this to increase over time.
112 Moreover, since the 2019 discussion paper's publication, there has been strong interest in
113 utilizing PCCPs for AI/ML-enabled medical devices.
114
115 In light of the public health need to facilitate innovation for ML-DSFs while providing
116 appropriate oversight for them, on January 12, 2021, the CDRH Digital Health Center of

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[10] For more information, see the 2019 discussion paper's public docket available at
https://www.regulations.gov/document/FDA-2019-N-1185-0001.

[11] For example, Gerke S et al., "The need for a system view to regulate artificial intelligence/machine learning-based software as medical device," NPJ Digit Med 3, 53 (2020); Harvey et al., "How the FDA Regulates AI," Academic Radiology 27, 58-61 (2020); and Subbaswamy et al., "From development to deployment: dataset shift, causality, and shift-stable models in health AI," Biostatistics 21, 345-352 (2020).

[12] Available at https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/public-workshop-evolving-role-artificial-intelligence-radiological-imaging-02252020-02262020.

[13] Available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-22-2020-patient-engagement-advisory-committee-meeting-announcement-10222020-10222020.

[14] Available at https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/virtual-public-workshop-transparency-artificial-intelligencemachine-learning-enabled-medical-devices.

117 Excellence issued FDA's [Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a](#)
118 [Medical Device Action Plan](#) ("the Action Plan").[15] The Action Plan describes FDA's strategy for
119 addressing AI/ML-enabled medical devices in a holistic, collaborative, and multidisciplinary
120 manner. An important pillar of the Action Plan is the further advancement of the tailored
121 regulatory framework for ML-enabled medical devices that was proposed in the 2019 discussion
122 paper.
123
124 Further, on October 4, 2022, the White House released a [Blueprint for an AI Bill of Rights](#),[16]
125 which outlined five principles that should guide the design, use, and deployment of automated
126 systems. These five principles discuss: safe and effective systems; algorithmic discrimination
127 protections; data privacy; notice and explanation; and human alternatives, consideration, and
128 fallback. This draft guidance is consistent with and promotes the principles described in the
129 Blueprint for an AI Bill of Rights.
130
131 Additionally, section 3308 of the Food and Drug Omnibus Reform Act of 2022, Title III of
132 Division FF of the Consolidated Appropriations Act, 2023, Pub. L. No. 117-328 ("FDORA"),
133 enacted on December 29, 2022, added section 515C "Predetermined Change Control Plans for
134 Devices" to the FD&C Act. Section 515C provides FDA with express authority to approve or
135 clear PCCPs for devices requiring premarket approval or premarket notification. For example,
136 section 515C provides that supplemental applications (section 515C(a)) and new premarket
137 notifications (section 515C(b)) are not required for a change to a device that would otherwise
138 require a premarket approval supplement or new premarket notification if the change is
139 consistent with a PCCP previously approved or cleared by FDA. Section 515C also provides that
140 FDA may require that a PCCP include labeling for safe and effective use of a device as such
141 device changes pursuant to such plan, notification requirements if the device does not function as
142 intended pursuant to such plan, and performance requirements for changes made under the
143 plan.[17] In this draft guidance, we provide recommendations on the marketing submission content
144 for PCCPs, which are based on the statute and feedback obtained through our various
145 interactions with stakeholders.
146

147 # III. Scope

148 This draft guidance is applicable to ML-DSFs that the manufacturer intends to modify over time.
149 This includes ML-DSFs for which modifications to the ML model are implemented
150 automatically (i.e., for which the modifications are implemented automatically by software), as
151 well as for ML-DSFs for which modifications to the ML model are implemented manually (i.e.,
152 involving steps that require human input, action, review, and/or decision-making, and therefore
153 are not implemented automatically).
154

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[15] Available at https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device.
[16] Available at https://www.whitehouse.gov/ostp/ai-bill-of-rights/.
[17] Sections 515C(a)(3) and (b)(3) of the FD&C Act.

155 This draft guidance describes an approach that would often be least burdensome and would
156 support the ability to modify an ML-DSF while continuing to provide a reasonable assurance of
157 safety and effectiveness across relevant patient populations. Specifically, this draft guidance
158 proposes recommendations on the information to be included in the PCCP in a marketing
159 submission[18] for a device that is or includes an ML-DSF. For the purposes of this guidance, the
160 term "PCCP" refers to a plan that includes device modifications that would otherwise require a
161 premarket approval supplement, De Novo submission, or a new premarket notification. A plan
162 that contains only minor modifications that would not require a new submission is outside the
163 scope of this guidance. For more information on whether a modification would require a new
164 submission, see [Deciding When to Submit a 510(k) for a Software Change to an Existing
165 Device](https://www.fda.gov)[19] and [Deciding When to Submit a 510(k) for a Change to an Existing Device](https://www.fda.gov)[20] or
166 [Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement
167 Decision-Making Process](https://www.fda.gov)[21] guidances. Throughout this guidance, a PCCP that has been
168 reviewed and established through a device marketing authorization is also referred to as an
169 "authorized PCCP." See Section IV. for more information on definitions used for the purposes of
170 this guidance.
171
172 By including a PCCP in a marketing submission, manufacturers can proactively pre-specify and
173 seek premarket authorization[22] for intended modifications (and their method of implementation)
174 to an ML-DSF without necessitating additional marketing submissions for each modification
175 delineated and implemented in accordance with the PCCP. In other words, a PCCP, as part of a
176 marketing submission, is intended to provide a means to implement modifications to an ML-DSF
177 that generally would otherwise require additional marketing submissions prior to
178 implementation.[23]
179
180 Modifications to an ML-DSF that could significantly affect,[24] or that could affect,[25] the safety or
181 effectiveness of the device, unless those modifications are covered by a PCCP, require premarket
182 authorization.[26] Premarket authorization for an ML-DSF with a PCCP may be established

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[18] For purposes of this guidance, unless otherwise stated, the term "marketing submission" includes premarket
notification (510(k)) submission, De Novo Classification request, and Premarket Approval (PMA) application.
[19] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.
[20] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.
[21] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process.
[22] For the purposes of this guidance, the term "authorization" includes clearance of a 510(k) submission, grant of a
De Novo Classification request, or approval of a PMA application.
[23] 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).
[24] 21 CFR 807.81(a)(3).
[25] 21 CFR 814.39(a).
[26] In accordance with 21 CFR 807.81(a)(3), a 510(k) is required for significant changes or modifications to a device
and include 1) those that "could significantly affect the safety or effectiveness of the device, e.g., a significant
change or modification in design, material, chemical composition, energy source, or manufacturing process" or
include 2) "a major change or modification in the intended use of the device." In accordance with 21 CFR 814.39(a),
a PMA supplement is required for "change[s] affecting the safety or effectiveness of the device" unless an exception

183 through the 510(k) pathway (see section 515C(b) of the FD&C Act), PMA pathway (see section
184 515C(a) of the FD&C Act), or the De Novo pathway (see section 513(f)(2) of the FD&C Act).[27]
185 FDA considers the PCCP to be part of the technological characteristics of the device. For devices
186 subject to 510(k) requirements, the determination of substantial equivalence includes, among
187 other requirements, a comparison of the technological characteristics of the predicate device to
188 the technological characteristics of the subject device.[28] In making a determination of substantial
189 equivalence where the predicate device was authorized with a PCCP, the subject device must be
190 compared to the version of the predicate device cleared or approved prior to changes made under
191 the PCCP.[29]
192
193 Generally, the recommendations in this guidance apply to the device constituent part of a
194 combination product[30] (such as drug-device and biologic-device combination products) when the
195 device constituent part[31] is or includes an ML-DSF. Early engagement with the appropriate
196 CBER or CDER Divisions is recommended for drug-device and biologic-device combination
197 products that include an ML-DSF.[32] For more information, contact the FDA review division that
198 will have the lead review for the combination product.
199
200 FDA encourages early engagement regarding a proposed PCCP with the FDA review division
201 that will review the ML-DSF; in particular, early engagement could be especially helpful for
202 certain ML-DSFs, including combination products and high-risk, life-sustaining, life-supporting,
203 or implantable devices. FDA encourages manufacturers to leverage the Q-Submission process
204 for obtaining FDA feedback on a proposed PCCP for an ML-DSF.[33]
205
206 This draft guidance is not intended to provide a complete description of what may be necessary
207 to include in a marketing submission for an ML-DSF. It is also not intended to delineate the
208 types of modifications the Agency would consider acceptable in a PCCP. However, some
209 considerations on modification types are described, including examples of questions for

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applies (see 21 CFR 814.39). For simplicity, in this guidance, we state "significantly" affect the safety or
effectiveness of the device" for when a marketing submission may be required, "significant" modifications, and
similar phrasings, aligning with 21 CFR 807.81(a)(3). However, for devices subject to PMA requirements, the
broader requirement pursuant to 21 CFR 814.39(a) of a "change affecting the safety or effectiveness" applies.

[27] The De Novo classification process allows FDA to classify a device into class I or II when general controls or
general controls and special controls provide a reasonable assurance of safety and effectiveness, but for which there
is no legally marketed predicate. The De Novo pathway, therefore, allows FDA to develop special controls that
provide a reasonable assurance of the safety and effectiveness. At this time, FDA expects that if it authorizes an ML-
DSF with a PCCP via the De Novo pathway, the Agency would develop appropriate special controls, which may
include specific requirements for a PCCP.

[28] See section 513(i) of the FD&C Act.

[29] See section 515C(c) of the FD&C Act.

[30] 21 CFR 3.2(e).

[31] 21 CFR 4.2.

[32] See FDA's guidance "Requesting FDA Feedback on Combination Products" available at
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requesting-fda-feedback-combination-products.

[33] See FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission
Program" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

210 consideration that manufacturers should address in a Modification Protocol (see Appendix A)
211 and illustrations of different ML-DSF scenarios where a PCCP could be employed (see
212 Appendix B). The FDA review division with purview over the device under review will
213 determine the acceptability of a proposed PCCP. That is, the FDA review division will determine
214 whether the scope of the modifications is appropriate for inclusion in a PCCP and what evidence
215 and information are required to support proposed modifications in a marketing submission.[34]
216

IV. Definitions

218 This section defines certain terms as they are used for the purposes of this guidance.

A.   Software Functions

220 **Device Software Function (DSF):** A software function that meets the device definition in
221 section 201(h) of the FD&C Act.[35,36] As discussed in other FDA guidances, the term "function"
222 is a distinct purpose of the product, which could be the intended use or a subset of the intended
223 use of the product.[37]
224

225 **Machine Learning-Enabled Device Software Function (ML-DSF):** A device software
226 function (as defined above) that implements an ML model trained with ML techniques.
227

B.   Data Sets

229 **Training Data:** These data are used by the ML-DSF manufacturer in procedures and ML
230 training algorithms to build an ML model, including to define model weights, connections, and
231 components. Training the ML model happens after the exploratory phase of ML-DSF
232 development. These data typically should be representative of the proposed intended use
233 populations (e.g., with respect to race, ethnicity, disease severity, gender, age, etc.). The result is
234 an operational ML-DSF.
235

236 **Tuning Data:** These data are typically used by the ML-DSF manufacturer to evaluate a small
237 number of trained ML-DSFs in order to explore, for example different architectures or
238 hyperparameters. The tuning phase is the last phase before ML-DSF testing and is often
239 considered part of the training process. The ML community sometimes refers to the tuning data
240 and phase with the word "validation." However, we recommend that the word "validation" not

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[34] 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).
[35] See footnote 1.
[36] Device software functions may include Software as a Medical Device (SaMD) and Software in a Medical Device (SiMD). See FDA's website on "Software as a Medical Device (SaMD)," available at https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd.
[37] See FDA's guidance "Multiple Function Device Products: Policy and Considerations" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-function-device-products-policy-and-considerations.

241 be used when referring to data or operations related to training or tuning ML models intended for
242 medical applications.[38]
243
244 **Testing Data:** These data are used to characterize the performance of the ML-DSF. The testing
245 phase is expected to provide data to establish a reasonable assurance of safety and effectiveness
246 before an ML-DSF is marketed. Testing data should be independent of data used for training and
247 tuning and should be from multiple sites different from those that were used to generate training
248 and tuning data.
249

250 ## C.   Predetermined Change Control Plan

251 **Predetermined Change Control Plan (PCCP):** The documentation describing what
252 modifications will be made to the ML-DSF and how the modifications will be assessed. The
253 modifications described in the PCCP include device changes that would otherwise require a
254 PMA supplement, De Novo submission, or new 510(k) notification. The PCCP includes a
255 Description of Modifications, Modification Protocol, and Impact Assessment.

256 **Authorized Predetermined Change Control Plan (Authorized PCCP):** A PCCP that has been
257 reviewed and established through a device marketing authorization. An authorized PCCP is a
258 technological characteristic of the authorized device with which it was established.

259 **Modification Protocol:** The documentation describing the methods that will be followed when
260 developing, validating, and implementing modifications delineated in the Description of
261 Modifications section of the PCCP. The Modification Protocol includes the verification and
262 validation activities (including pre-defined acceptance criteria) for those modifications and is
263 intended to provide a step-by-step delineation of how the modifications proposed in the PCCP
264 will be implemented while ensuring the device remains safe and effective.

265 **Impact Assessment:** The documentation of the assessment of the benefits and risks of
266 implementing a proposed PCCP, as well as the plan for risk mitigation. It could be a separate
267 section of a PCCP or incorporated into the Modification Protocol, whichever is least burdensome
268 for a particular marketing submission.

269

270 # V.   Policy for Predetermined Change Control Plans

271 Software development is an iterative process, and FDA appreciates that manufacturers of device
272 software functions strive to continually improve and update their devices. Manufacturers should
273 evaluate the impact of modifications to their devices and must submit a marketing submission
274 when device modifications affect the intended use of the device or could significantly affect the
275 safety or effectiveness of the device.[39]

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[38] The way the term "validation" is used in the ML community to refer to training or tuning data sets is not
consistent with the broad understanding of the word "validation," defined in 21 CFR 820.3(z) as "confirmation by
examination and provision of objective evidence that the particular requirements for a specific intended use can be
consistently fulfilled."
[39] 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).

276　An authorized PCCP specifies planned modifications that, if not included in a PCCP, could
277　otherwise require a new marketing submission pursuant to 21 CFR 807.81(a)(3) and 21 CFR
278　814.39(a), and in accordance with [Deciding When to Submit a 510(k) for a Software Change to
279　an Existing Device](#)[40] and [Deciding When to Submit a 510(k) for a Change to an Existing
280　Device](#)[41] or [Modifications to Devices Subject to Premarket Approval (PMA) - The PMA
281　Supplement Decision-Making Process](#)[42] guidances (hereafter referred to as the "device
282　modifications guidances"). An authorized PCCP includes the "range of FDA-authorized
283　specifications" for the characteristics and performance of the planned modifications to the device
284　(as part of the detailed Description of Modifications section included in the PCCP), along with
285　the associated verification and validation testing and acceptance criteria to assure the device
286　remains safe and effective across relevant patient populations (as part of the Modification
287　Protocol section included in the PCCP), and documentation of the assessment of the benefits and
288　risks of implementing a proposed PCCP (which could be a separate Impact Assessment section
289　of a PCCP or incorporated into the Modification Protocol). Because modifications made to an
290　ML-DSF in accordance with an authorized PCCP were reviewed and authorized through the
291　marketing submission containing the PCCP, the modifications can be implemented to the ML-
292　DSF without triggering the need for a new marketing submission under 21 CFR 807.81(a)(3) and
293　21 CFR 814.39(a), and in accordance with the device modifications guidances.
294
295　Deviations from the authorized PCCP reviewed in the marketing submission could significantly
296　affect the safety or effectiveness of the device. For example, when implementing a modification
297　that is a deviation from the PCCP, the device's clinical functionality or performance
298　specifications could be compromised. Deviations from the PCCP include instances where the
299　PCCP is not followed or cannot be followed (e.g., issues related to the Modification Protocol,
300　such as data management, re-training, or performance failure). Accordingly, modifications made
301　to an ML-DSF that are not specified in, or implemented in accordance with, the authorized
302　PCCP (i.e., the manufacturer deviates from the authorized PCCP when implementing the
303　modification) likely require a new marketing submission.[43, 44] In such a circumstance, continued
304　distribution of the ML-DSF without submitting a new marketing submission would constitute
305　adulteration and misbranding under sections 501(f)(1)(B) and 502(o) of the FD&C Act,
306　respectively. Adulteration and misbranding are prohibited acts under section 301 of the FD&C
307　Act, and where appropriate, FDA may take legal or regulatory action against violations of
308　prohibited acts, including, without limitation, seizure or injunction.
309

310　## A.　Components of a PCCP

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[40] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.

[41] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

[42] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process.

[43] 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).

[44] See Section V.D. below for further details on implementing device modifications that may or may not require a new marketing submission in accordance with 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).

311 A PCCP should consist of a detailed Description of Modifications, a Modification Protocol, and
312 an Impact Assessment (see Sections VI. – VIII.) because these components are intended to
313 provide FDA with the information needed for our review of the proposed modifications. The
314 detailed Description of Modifications should outline the modifications that will be made to the
315 ML-DSF, and the Modification Protocol should describe the verification and validation activities
316 (including pre-defined acceptance criteria) that will support those modifications. The Impact
317 Assessment helps to tie the Description of Modifications to the Modification Protocol in that the
318 Impact Assessment identifies the benefits and risks introduced by the specified, planned
319 modifications and how the verification and validation activities of the Modification Protocol will
320 continue to assure the safety and effectiveness of the device. The detailed Description of
321 Modifications, Modification Protocol, and Impact Assessment are all components of a PCCP and
322 should exist in tandem.
323

324 ## B.   Establishing a PCCP

325 Premarket authorization for an ML-DSF with a PCCP must be established through the 510(k)
326 pathway, De Novo pathway, or PMA pathway, as appropriate, as a PCCP must be reviewed and
327 established as part of a marketing authorization for a device prior to a manufacturer
328 implementing any modifications under that PCCP.[45] For 510(k) submissions, in making a
329 determination of substantial equivalence where the predicate device was authorized with a
330 PCCP, the subject device must be compared to the version of the predicate device cleared or
331 approved prior to changes made under the PCCP.[46]
332

333 For a manufacturer who would like to establish a new PCCP for a previously authorized device
334 with a PCCP, the marketing submission must include the appropriate marketing submission
335 requirements[47] and the proposed PCCP for the device (see Section V.E.).[48] FDA intends to focus
336 its review on the aspects of the device that are most significantly modified.[49] For example, if the
337 device has been relatively unchanged since FDA's prior authorization and a new PCCP is
338 proposed, FDA would focus its review on the proposed PCCP.
339

340 An authorized PCCP is a technological characteristic of the authorized device with which it was
341 established. If the authorized device is significantly modified other than as specified in the
342 authorized PCCP, a new marketing submission is required for the significantly modified
343 device.[50] In that case, for the original authorized PCCP to apply to the significantly modified
344 device, the PCCP will need to be reviewed and established as part of such marketing submission.
345

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[45] See sections 513(f)(2) and 515C of the FD&C Act.
[46] See section 515C(c) of the FD&C Act.
[47] See, e.g., 21 CFR 807.87, 21 CFR 860.220, or 21 CFR 814.20.
[48] E.g., through a Traditional 510(k) for a device that has already been authorized, or a PMA supplement, such as a panel-track supplement or 180-day supplement.
[49] Note that "focus of the review" is not intended to imply a review of the PCCP *only*; rather, the focus on the PCCP is as a significant change to the device that could affect the safety or effectiveness of the device.
[50] 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).

346 FDA encourages manufacturers to leverage the Q-Submission process for obtaining FDA
347 feedback on a proposed PCCP prior to submitting a marketing submission. For more information
348 on the Q-Submission process, refer to the Requests for Feedback and Meetings for Medical
349 Device Submissions: The Q-Submission Program guidance.[51] While manufacturers are
350 encouraged to discuss their plans through a Pre-Submission, PCCPs are not authorized in Pre-
351 Submissions.
352

353 ## C.   Identifying a PCCP in a Marketing Submission

354 The PCCP should be included as a standalone section within the marketing submission.
355 Additionally, it should be prominently included and discussed in the cover letter and included in
356 the marketing submission's table of contents as "Predetermined Change Control Plan." The
357 PCCP should be discussed in the marketing submission as part of the device description,
358 labeling, and relevant sections used for determining substantial equivalence or reasonable
359 assurance of safety and effectiveness. Any information pertaining to the PCCP content included
360 outside of the PCCP section should be referenced within the PCCP section.
361

362 Device labeling must comply with applicable statutes and regulations,[52] which includes adequate
363 directions for use.[53] FDA may require that a change control plan include labeling required for
364 safe and effective use of the device as such device changes pursuant to such plan.[54] For ML-
365 DSFs with an authorized PCCP, the labeling should explain that the device incorporates machine
366 learning and has a PCCP so that users are aware that the device may require the user to perform
367 software updates, and that such software updates may modify the device's performance, inputs,
368 or use. Information on the ML-DSF and its PCCP in the labeling is important in order for a user
369 to use the device safely and for the purposes for which it is intended. In particular, this
370 information may be necessary for a user to understand changes in the device and to continue to
371 use the device safely and effectively across relevant populations as the device changes pursuant
372 to the PCCP.
373

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[51] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[52] 21 CFR 801 (Labeling) and 21 CFR 809 (In Vitro Diagnostic Products for Human Use). See, e.g., 21 CFR 801.5 (requiring that labeling include adequate directions for use); 21 CFR 801.109(c) (for prescription devices, requiring that labeling include any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended); and 21 CFR 809.10(b)(6) (for in vitro diagnostic products, requiring labeling accompanying any instruments use or function, installation procedures, performance characteristics and specifications, service and maintenance information, etc.).

[53] 21 CFR 801.5 (requiring that labeling include adequate directions for use).

[54] See sections 515C(a)(3), 515C(b)(3), and 513(f)(2) of the FD&C Act.

374 The PCCP should be described in the 510(k) summary,[55,56] De Novo decision summary,[57] or
375 PMA summary of safety and effectiveness document (SSED) and approval order.[58] Details of the
376 PCCP should be included in sufficient detail in the public-facing documents to support
377 transparency to users of FDA's determination of substantial equivalence or reasonable assurance
378 of safety and effectiveness for the device and its range of FDA-authorized specifications.
379

380 ## D.   Utilizing an Authorized PCCP to Implement Device
381 ## Modifications

382 Once a PCCP has been reviewed and established through a marketing submission, the PCCP is
383 considered part of the marketing authorization. In general, a PCCP should be evaluated within
384 the existing risk management framework of the device and implemented in accordance with the
385 manufacturer's quality system.
386

387 Figure 1 depicts the process for implementing a modification to a device with an authorized
388 PCCP. Manufacturers should first consider whether the modification is or is not consistent with
389 the authorized PCCP; a modification is considered consistent with the authorized PCCP when
390 the modification has been specified in the Description of Modifications included in the PCCP
391 *and* has been implemented in accordance with the Modification Protocol. If the modification is
392 consistent with the authorized PCCP, a new marketing submission is not necessary, the
393 modification can be implemented in accordance with the Modification Protocol, and the
394 manufacturer should document that modification and the analysis in accordance with the
395 manufacturer's quality system.[59]
396

397 As described previously, an authorized PCCP specifies planned modifications that, if not
398 included in a PCCP, would otherwise require a new marketing submission pursuant to 21 CFR
399 807.81(a)(3) and 21 CFR 814.39(a), and in accordance with the device modifications guidances.
400 Therefore, if the modification is not consistent with the authorized PCCP – including if the
401 specific modification is not included in the authorized PCCP or if the modification is included in

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[55] In accordance with 21 CFR 807.92, "a 510(k) summary shall be in sufficient detail to provide an understanding of the basis for a determination of substantial equivalence." This includes, but is not limited to, a description of the device, and for those 510(k) submissions in which a determination of substantial equivalence is also based on an assessment of performance data, non-clinical tests, and clinical tests.

[56] If a sponsor chooses to submit a 510(k) Statement rather than 510(k) Summary, the sponsor should provide to requestors all PCCP information in the 510(k) that supports transparency to users of FDA's determination of substantial equivalence for the device and its range of FDA-authorized specifications, as such information constitutes safety and effectiveness information. See 21 CFR 807.93 for requirements on the content and format of a 510(k) Statement.

[57] The De Novo decision summary is intended to present an objective and balanced summary of the scientific evidence that served as the basis for the FDA's decision to grant a De Novo request; see
https://www.fda.gov/medical-devices/premarket-submissions/de-novo-classification-request.

[58] In accordance with 21 CFR 814.9(e), "FDA will make available to the public … a detailed summary of information submitted to FDA respecting the safety and effectiveness of the device that is the subject of the PMA and that is the basis for the order."

[59] Manufacturers are required to comply with the quality system regulation (21 CFR 820). The device and PCCP must be implemented consistent with 21 CFR 820, including, but not limited to: 21 CFR 820.30 Design controls; 21 CFR 820.90 Nonconforming products; and 21 CFR 820.100 Corrective and preventive action.

402 the authorized PCCP but is not implemented in accordance with the methods and specifications
403 described in the Modification Protocol – the manufacturer should then proceed to evaluate the
404 modification in accordance with applicable laws and regulations and the device modifications
405 guidances, if applicable, and proceed accordingly. If, after review of applicable laws and
406 regulations, a new marketing submission is required,[60] then the manufacturer must submit the
407 appropriate marketing submission before the modified device is marketed. The appropriate
408 marketing submission could request authorization for 1) a device modification effected through a
409 change to the authorized PCCP[61] (see Section V.E.); or 2) a device modification not
410 implemented through a PCCP; or 3) both. In each of these cases, a marketing submission for the
411 device modification must include the appropriate marketing submission requirements[62] for the
412 device. As noted in Section V.B., an authorized PCCP is a technological characteristic of its
413 authorized device with which it was established. Therefore, for the original authorized PCCP to
414 apply to the modified device, the manufacturer must include the proposed PCCP in the
415 marketing submission for the device modification;[63] the PCCP is reviewed and established as
416 part of the review of the modified device.
417
418 See Appendix B for example scenarios for implementing modifications to a device with an
419 authorized PCCP. Manufacturers may contact the appropriate FDA review division (e.g., through
420 a Pre-Submission)[64] for a discussion about the proposed modification and whether it may be
421 considered consistent with the current, authorized PCCP.
422

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[60] See, e.g., 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).
[61] A change to the authorized PCCP could include a change in Description of Modifications, the Modification Protocol, and/or the Impact Assessment, as appropriate.
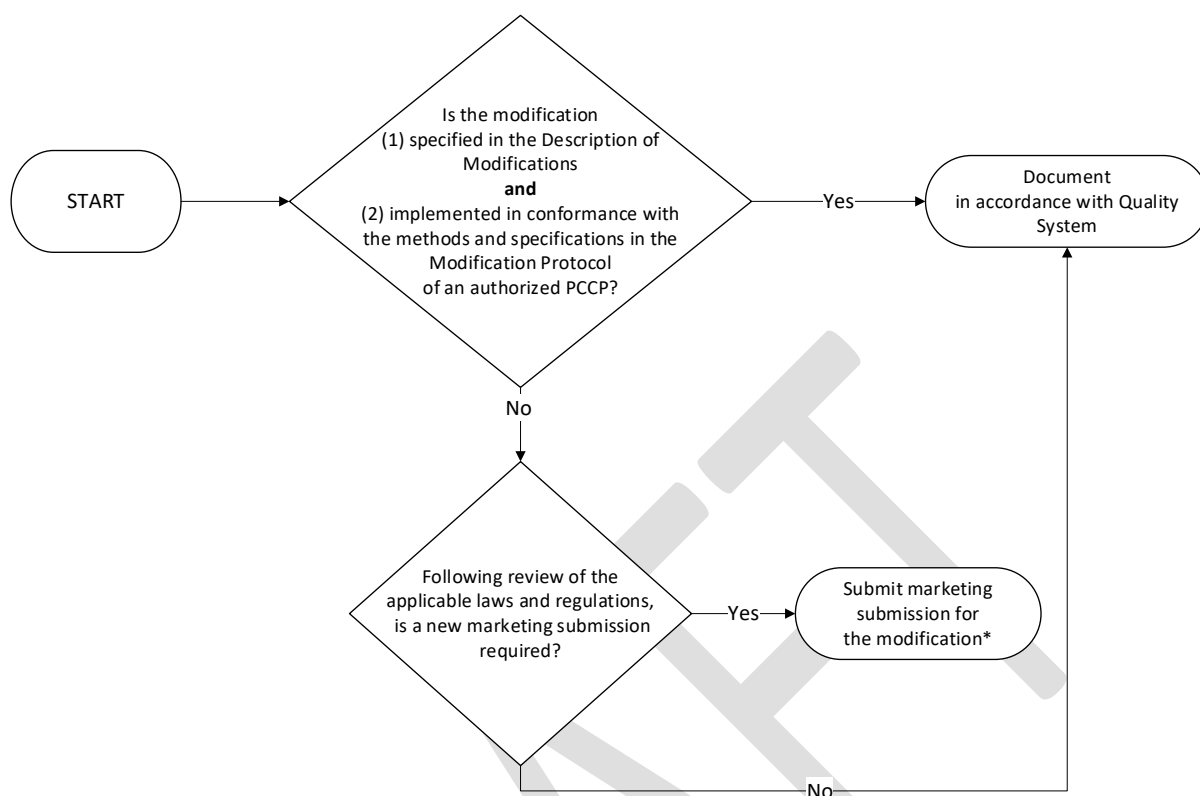[62] See, e.g., 21 CFR 807.87, 21 CFR 860.220, or 21 CFR 814.20.
[63] See sections 513(f)(2) and 515C of the FD&C Act.
[64] See FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program."

*For the modified device to have a PCCP, a PCCP should be submitted with the marketing submission so that the device and PCCP can be authorized together.

Figure 1: Implementing a Modification to a Device with an Authorized PCCP

E. Modifying a PCCP for an Authorized Device

Because the modifications described in the PCCP include device changes that would otherwise require a PMA supplement, De Novo submission, or new 510(k) premarket notification, at this time, FDA believes that modifications to an authorized PCCP will generally constitute changes to the ML-DSF that require a new marketing submission for the device, which will include the modified PCCP.[65] In other words, FDA expects that the modified PCCP will need to be reviewed and established as part of the premarket review of the modified device because a modification to the PCCP will generally significantly affect the safety or effectiveness of the device.[66] In those cases where modifications to the PCCP are the only significant modifications introduced since FDA's prior authorization for the device and its PCCP, FDA intends to focus its review on the proposed PCCP. For a manufacturer who would like to modify a PCCP for a previously authorized device with a PCCP, the marketing submission must include the appropriate marketing submission requirements for the device and the proposed PCCP.[67]

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[65] Section 510(*l*)(1) and section 515(d)(5)(A)(i) of the FD&C Act.
[66] See, e.g., 21 CFR 807.87, 21 CFR 860.220, or 21 CFR 814.20.
[67] See sections 513(f)(2) and 515C of the FD&C Act.

VI. Description of Modifications

As introduced above, a description of each planned modification to an ML-DSF should be included in the Description of Modifications section of a PCCP. The detailed description should describe changes to the device characteristics and performance resulting from implementation of the modifications. To ensure an efficient review, FDA recommends that a PCCP include only a limited number of modifications that are specific, and that can be verified and validated.

A. Goals of the Description of Modifications Section

A dedicated Description of Modifications section in a PCCP identifies the specific, planned modifications to the ML-DSF that the manufacturer intends to implement. The Description of Modifications draws a "range of FDA-authorized specifications" around the initial characteristics and performance of the device that, following the agreed upon verification and validation described in the Modification Protocol, can be implemented without a new marketing submission. Upon FDA review of a PCCP, it is possible that FDA may determine that a Modification Protocol supports some but not all modifications identified in a PCCP; in such cases, only those modifications that are appropriate in the FDA's findings of substantial equivalence or reasonable assurance of safety and effectiveness would be included in the authorized PCCP.

B. Content of the Description of Modifications Section

The Description of Modifications should enumerate the list of individual proposed device modifications discussed in the PCCP, as well as the specific rationale for the change to each part of the ML-DSF that is planned to be modified. In some situations, a Description of Modifications will consist of multiple modifications. It may be helpful to reference the labeling changes that are associated with each modification in the Description of Modifications section (such labeling changes should be included in a Modification Protocol, as described in Section VII.B.).

FDA recommends that a PCCP include modifications that are specific, and that can be verified and validated. Modifications should also be presented at a level of detail that permits understanding of the specific modifications that will be made to the ML-DSF. Each modification should be linked to a specific performance evaluation activity within the Modification Protocol (for an example, see Table 1 in Section VII.C.).

The Description of Modifications should clearly state if the planned modifications are proposed to be implemented automatically (i.e., whether the modifications are implemented automatically by software) or whether modifications are implemented manually (i.e., involving steps that require human input, action, review, and/or decision-making, and therefore are not implemented automatically). Understanding that this is an evolving area, FDA is proposing to consider PCCPs for ML-DSFs where modifications are implemented automatically to the extent the Agency can properly review them for substantial equivalence to the predicate or a reasonable assurance of safety and effectiveness. The Agency recognizes that this subset of ML-DSFs has an additional degree of complexity; as with all ML-DSFs, FDA will consider the benefit-risk assessment, and

483 the Agency's current experience applying this policy when reviewing PCCPs containing
484 automatically implemented modifications.
485
486 The Description of Modifications should also clearly specify if the proposed modifications will
487 be implemented in a uniform manner across all devices on the market (sometimes referred to as
488 homogenous or global changes, or global adaptations) or implemented differently on different
489 devices on the market based on, for example, the unique characteristics of a specific clinical site
490 or individual patients (sometimes referred to as heterogenous or local changes, or local
491 adaptations). For local adaptations, the Description of Modifications should include describing
492 what local factors or conditions warrant a local change.
493

494 ## C.   Types of Modifications

495 Modifications that are appropriate for a PCCP include those that are intended to maintain or
496 improve the safety or effectiveness of the device. Modifications proposed within the Description
497 of Modifications should be able to be verified and validated within the existing quality system of
498 the device. As such, not all modifications may be appropriate for inclusion within a PCCP. Types
499 of modifications that may be acceptable within a PCCP include:
500
501   (i) modifications related to quantitative measures of ML-DSF performance specifications;
502   (ii) modifications related to device inputs to the ML-DSF; and
503   (iii) limited modifications related to the device's use and performance (e.g., for use
504   within a specific subpopulation).
505
506 Examples of modifications related to quantitative measures of ML-DSF performance
507 specifications include improvements to analytical and clinical performance resulting from re-
508 training the ML model based on new data within the intended use population from the same type
509 and range of input signal.
510
511 Modifications related to device inputs to the ML-DSF may involve expanding the algorithm to
512 include new sources of the same signal type (e.g., different makes, models, or versions of a data
513 acquisition system) or limited modifications related to new types of inputs.
514
515 Modifications related to the device's use and performance could include authorization of a
516 device for a specific subset of a population within the originally indicated population based on
517 re-training on a larger data set for that subpopulation that was not previously available.
518
519 All modifications included in a PCCP must maintain the device within the device's intended
520 use.[68] At this time, FDA expects that modifications included in a PCCP should also maintain the
521 device within the device's indications for use.[69] As with modifications to the intended use, FDA

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[68] Section 515C(a)(2) and section 515C(b)(2) FD&C Act.
[69] FDA has a long-standing policy of applying the definition of indications for use in the PMA regulation at 21 CFR
814.20(b)(3)(i) in the same way in the 510(k) context. See the FDA guidance "The 510(k) Program: Evaluating
Substantial Equivalence in Premarket Notifications [510(k)]," available at https://www.fda.gov/regulatory-

522 believes modifications to the indications for use would not allow the device to remain safe and
523 effective.[70]
524
525 Recognizing there is a spectrum of risk for devices, for the purposes of reviewing a PCCP, FDA
526 intends to, among other considerations, take into account the benefit-risk profile of the specific
527 device that is the subject of the PCCP, the specific modifications being proposed, and its
528 experience applying this policy across different device types. See Appendix B for examples of
529 modifications.
530

VII. Modification Protocol

532 The Modification Protocol includes the documentation describing the methods that will be
533 followed when developing, validating, and implementing modifications delineated in the
534 Description of Modifications section of the PCCP. The Modification Protocol includes the
535 verification and validation activities (including pre-defined acceptance criteria) for those
536 modifications and is intended to provide a step-by-step delineation of how the modifications
537 proposed in the PCCP will be implemented while assuring the device remains safe and effective.
538 Documentation of modifications verified and validated per the Modification Protocol must be
539 compliant with the quality system (QS) regulation.[71] The QS regulation requires manufacturers
540 of finished medical devices to review and approve modifications to device design and production
541 (21 CFR 820.30 and 820.70) and document changes and approvals in the device master record
542 (21 CFR 820.181).
543

A.   Goals of the Modification Protocol Section

545 Whereas the Description of Modifications outlines the planned modifications to an ML-DSF, the
546 Modification Protocol describes the methods that will be followed when developing, validating,
547 and implementing those modifications, to ensure the device remains safe and effective. The
548 methods described in the Modification Protocol should be consistent with and support the
549 modifications outlined in the Description of Modifications.
550
551 The goals of the Modification Protocol are to:
552

- 553 • Identify the methods and data used to develop, validate, and implement all proposed
554 modifications;
- 555 • Identify the test methods, data, statistical analyses, and specified acceptance criteria
556 for all proposed modifications;
- 557 • Ensure that the information that would otherwise be generated and submitted to the
558 Agency (i.e., if the modifications were implemented on a device that did not have an
559 authorized PCCP) will be generated by the manufacturer for each modification and

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information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-
notifications-510k.
[70] Section 515C(a)(2)(A) and section 515C(b)(2) FD&C Act.
[71] 21 CFR Part 820.

560   maintained consistent with recordkeeping requirements[72] and in accordance with the
561   manufacturer's QS;
562   • Ensure that the risks that have been identified in the Impact Assessment as related to
563   modifications detailed in the Description of Modifications (including the update
564   process and communication to users) will be mitigated; and
565   • Be least burdensome for the manufacturer to develop and for FDA to review. This
566   includes being traceable and specific to the modifications detailed in the Description
567   of Modifications section and sufficiently comprehensive to support specific
568   modifications.
569

570 This draft guidance identifies four primary components of a Modification Protocol, described
571 below, that outline a manufacturer's 1) data management practices, 2) re-training practices, 3)
572 performance evaluation protocols, and 4) update procedures, including communication and
573 transparency to users and real-world monitoring plans, for each modification in a PCCP. In
574 FDA's experience, these four components generally provide FDA with the information needed to
575 evaluate the PCCP. For a particular marketing submission, additional components of a
576 Modification Protocol may be important to provide a reasonable assurance of safety and
577 effectiveness.
578

579 In some cases, the same methods in each component of the Modification Protocol may support
580 all modifications in a PCCP for a device. In other cases, the same methods in each component
581 may not be adequate for every modification in a PCCP. It is important to note, however, that for
582 each planned modification provided in the Description of Modifications, FDA recommends that
583 each of the four primary components of a Modification Protocol be addressed. Additionally, the
584 Modification Protocol should include a description of how its proposed methods are similar to or
585 different from methods used elsewhere in the marketing submission. For example, if the
586 validation methods in the Modification Protocol represent a subset of the original testing for the
587 device, or if the acceptance criteria for the validation are different, manufacturers should
588 describe these differences and provide a justification. The justification for a different
589 methodology may include references to other marketing submissions where the methodology
590 was used for similar modifications.
591

592 As noted above in Section V.E., manufacturers should follow their risk management processes to
593 develop a Modification Protocol that considers each modification. Upon FDA review of a PCCP,
594 FDA may determine that the Modification Protocol supports some but not all proposed
595 modifications identified in the PCCP. In such cases, only those modifications that were
596 supportable by the proposed Modification Protocol would be appropriate for inclusion in the
597 PCCP and would become part of the authorized PCCP. Those modifications that were not
598 supportable by the proposed Modification Protocol, or that FDA considered inappropriate for
599 other reasons (e.g., the modification changes the device's indications for use), would be removed
600 from the PCCP.
601

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[72] 21 CFR 820 Subpart M – Records.

602 # B.   Content of the Modification Protocol Section

603 As part of their Modification Protocol, manufacturers should outline the methods for each
604 component described below. Example elements of each of the four Modification Protocol
605 components are provided in Appendix A.
606

607 ## (1)   Data management practices

608 *What they are:* ML-DSF training and testing typically utilize data that include the inputs (e.g.,
609 medical images) that will be used by the device and often utilize a label or 'reference standard'
610 that is determined through a reference standard determination and/or an annotation process.
611 Training data and testing data are sequestered to prevent overfitting and misquotes of test
612 performance. The training and testing methods aim to identify and eliminate bias in the data
613 (which may be inherent from historical datasets) and to improve the robustness and resilience of
614 these algorithms to withstand changing clinical inputs and conditions. To support modifications
615 to an ML-DSF that may need training and/or testing, it is anticipated that new data (i.e., data that
616 were not used to develop the initial ML-DSF) will be collected. The data management practices
617 in a Modification Protocol should outline how those new data will be collected, annotated,
618 curated, stored, retained,[73] controlled, and used by the manufacturer for each modification. The
619 data management practices in a Modification Protocol should also clarify the relationship
620 between the Modification Protocol data and the data used to train and test the initial and
621 subsequent versions of the ML-DSF. It should also describe the control methods employed to
622 curb the potential for data or performance information leaking into the development process
623 during modification development or assessment.
624

625 *Why they are recommended:* This information allows FDA to understand the manufacturer's data
626 management practices that will be used to support each modification to an ML-DSF, including 1)
627 how the manufacturer plans to obtain and use training and testing data that are complete and
628 representative of the proposed intended use populations (e.g., with respect to race, ethnicity,
629 disease severity, gender, age, etc.[74]); 2) whether identifiable subpopulations will be adequately
630 represented, including intersectional groups, and separated into training and testing sets to
631 minimize ML model bias; 3) how training and testing data will be sequestered to prevent
632 overfitting and misquotes of test performance; 4) how older data will be complemented or
633 replaced by newer data so that the performance is representative of the current patient population
634 and standard of care; 5) whether the reference standard represents the best available process for
635 determining the ground truth; and 6) how the data management practices may reduce the
636 potential to produce discriminatory outcomes. A clear explanation of data management practices
637 also provides assurance to FDA that modifications to the ML-DSF are based on data that are

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[73] The QS regulation requires manufacturers to retain all records for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer (21 CFR 820.180(b)).

[74] We recommend that manufacturers consider additional characteristics, such as those described in the Blueprint for an AI Bill of Rights (https://www.whitehouse.gov/ostp/ai-bill-of-rights/): race, color, ethnicity, sex (including pregnancy, childbirth, and related medical conditions, gender identity, intersex status, and sexual orientation), religion, age, national origin, disability, veteran status, and genetic information.

638 representative of the device indications for use. This includes information regarding products
639 that will be used to generate data as inputs for the ML-DSF, patient populations in which the
640 device will be used, and clinical scenarios where the device will be used.
641
642 *What manufacturers should include in a submission:* Examples of the types of information
643 manufacturers should provide in a Modification Protocol describing their data management
644 practices are provided in Appendix A. In general, this information should describe: how data will
645 be collected, including clinical study protocols with inclusion/exclusion criteria; information on
646 how data will be processed, stored, and retained;[75] the process that will be followed to determine
647 the reference standard; the quality assurance process related to the data; the data sequestration
648 strategies that will be followed during data collection to separate the data into training and
649 testing sets; and the protocols in place to prevent access during the training and tuning process to
650 data intended for performance testing.
651

(2)   Re-training practices

653 *What they are:* ML software generally involves multiple processing steps from the point the ML-
654 DSF receives the input data to the point it provides an output. The re-training practices
655 component of a Modification Protocol should identify the processing steps that are subject to
656 change for each modification and the methods that will be used by the manufacturer to
657 implement modifications to the ML-DSF. In addition, if re-training involves ML architecture
658 modifications (e.g., in a neural network, modifications to training hyperparameters or the number
659 of nodes, layers, etc.), the re-training practices component of a Modification Protocol should also
660 describe the rationale or the justification for each specific architecture modification.
661
662 *Why they are recommended:* Information on the manufacturer's re-training practices allows FDA
663 to understand how the proposed modifications will be achieved through re-training, to determine
664 if modifications are implemented following appropriate, well-defined practices,[76] and to
665 determine if the performance evaluation and update procedures (discussed below) support the
666 modifications. Information on the manufacturer's re-training practices is typically provided in
667 the "device description" of a marketing submission for the majority of ML-DSFs that FDA
668 reviews. The specifics of what should be included in this component of the Modification
669 Protocol will depend on the type of modification and specific device.
670
671 *What manufacturers should include in a submission:* Examples of the types of information
672 manufacturers should provide in a Modification Protocol describing their re-training practices
673 are provided in Appendix A. In general, this information should identify the objective of the re-
674 training process, provide a description of the ML model, identify the device components that
675 may be modified, outline the practices that will be followed (e.g., data sequestration strategies
676 during re-training), and identify any triggers for re-training (e.g., when new data reaches a
677 certain size or when a drift in data is observed over time).

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[75] See 21 CFR 820.180(b).

[76] For example, FDA has published a document on "Good Machine Learning Practice for Medical Device Development: Guiding Principles," available at https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles.

678

(3)   Performance evaluation

680   *What they are:* The FDA may require that performance requirements for changes made under the
681   plan be provided in a PCCP.[77] Performance evaluation methods should describe the processes
682   that will be followed to validate that the modified ML-DSF will meet the specifications
683   identified as part of a specific modification, in addition to maintaining the specifications that are
684   not part of the modification but may be impacted by the modification. Performance evaluation
685   should include the plans for verification and validation of the entire device following ML-DSF
686   modifications for each individual modification and in aggregate for all implemented
687   modifications. This includes, but is not limited to, ML model testing protocols comparing the
688   newly modified device to both the original device (the version of the device without any
689   modifications implemented) and the last modified version of the device. For example, for device
690   software functions that drive hardware functionality, performance evaluation should include not
691   only the device software functions, but also the effect of the modifications on hardware
692   functionality. The content of this section in a Modification Protocol should provide details on the
693   study design, performance metrics, pre-defined acceptance criteria, and statistical tests for each
694   planned modification. More comprehensive testing can potentially support a broader set of
695   proposed modifications.

696

697   *Why they are recommended:* Information regarding the manufacturer's performance evaluation
698   methods allow FDA to confirm that appropriate study designs, including performance metrics
699   and statistical tests, will be used to evaluate the effect of modifications on overall device
700   performance. Performance evaluation of the device is essential to ensure that specified
701   acceptance criteria for all proposed modifications will continue to be met over the range of FDA-
702   authorized specifications.

703

704   *What manufacturers should include in a submission:* Examples of the types of information
705   manufacturers should provide in a Modification Protocol describing their performance evaluation
706   are provided in Appendix A. In general, this information should describe how performance
707   evaluation will be triggered; how sequestered test data representative of the clinical population
708   and intended use will be applied for testing; what performance metrics will be computed; and
709   what statistical analysis plans will be employed to test hypotheses relevant to performance
710   objectives for each modification. In addition, the Modification Protocol should affirmatively
711   state that if there is a failure in performance evaluation for a specific modification, the failure(s)
712   will be recorded, and the modification will not be implemented.

713

(4)   Update procedures

715   *What they are:* Data management practices, re-training practices, and performance evaluation
716   described above largely relate to making and testing modifications to the ML-DSF. Once these
717   meet the performance objectives, manufacturers will need to update the ML-DSF to implement
718   the modifications and communicate information to users about the modifications that is needed

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[77] Section 515C(a)(3) and (b)(3) of the FD&C Act.

719   to safely use the device. The update procedures in a Modification Protocol should describe how
720   manufacturers will update their devices to implement the modifications, provide appropriate
721   transparency to users, and, if appropriate, updated user training about the modifications and
722   perform real-world monitoring, including notification requirements if the device does not
723   function as intended pursuant to the authorized PCCP.[78] The PCCP should include a description
724   of any labeling changes that will result from the implementation of the modifications. The
725   available labeling must include adequate directions for use and reflect information about the
726   current version(s) of the ML-DSF available to the user, including information regarding site-
727   specific modifications.[79] The labeling should not reflect information on modifications to the ML-
728   DSF that have not been implemented in the available version, because it could cause confusion
729   and would be misleading. If such information is included in the labeling, the ML-DSF could be
730   deemed misbranded.[80]
731
732   *Why they are recommended:* Information on the manufacturer's update procedures allows FDA
733   to understand 1) how risks from implementing modifications may be mitigated by the update
734   process; 2) how communication regarding the device updates will be provided to users (e.g., so
735   that updates in device output results will be correctly interpreted by users); 3) how the device
736   operation will remain reliable after the update; and 4) how all stakeholders will be kept up-to-
737   date about device functionality and performance. In addition, it is important for FDA to
738   understand how potential risks associated with the update process, itself, may be mitigated.
739
740   *What manufacturers should include in a submission:* Examples of the types of information
741   manufacturers should provide in a Modification Protocol describing their update procedures are
742   provided in Appendix A. In general, this information should include 1) confirmation that the
743   verification and validation plans for the modified version of the device are the same as those that
744   have been performed for the version of the device prior to the implementation of the
745   modifications, or identification of any differences between the two plans; 2) a description of how
746   software updates will be implemented; 3) a description of how legacy users will be affected by
747   the software update (if applicable); and 4) a description of how modifications will be
748   communicated to the users, including transparency on any differences in performance,
749   differences in performance testing methods, and/or known issues that were addressed in the
750   update (e.g., whether there is an improvement in performance in a subpopulation of patients).
751   Communication of performance changes should be consistent with performance evaluation
752   described in the Modification Protocol.
753

C.   Traceability Between the Description of Modifications Section and the Modification Protocol Section

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[78] Section 515C(a)(3) and (b)(3) of the FD&C Act.
[79] See 21 CFR 801.5, requiring that labeling include adequate directions for use including statements of all conditions, purposes, or uses for which the device is intended.
[80] See section 502(a)(1) of the FD&C Act, stating that a medical device is deemed misbranded if its labeling is false or misleading in any particular.

756　The PCCP should clearly delineate which parts of the Modification Protocol are applicable to
757　each modification within the Description of Modifications. For a PCCP with multiple
758　modifications, this may be accomplished through a traceability table; a sample traceability table
759　is provided below in Table 1. This sample traceability table provides an example of how a
760　manufacturer can depict the traceability between the Description of Modifications and
761　Modification Protocol, as well as how to provide clear references to where within the PCCP this
762　information is located in a marketing submission.
763
764　**Table 1. Example of Description of Modifications to Modification Protocol Traceability**
765　**Table**
766
767　Table 1: A traceability table can help to identify where each method supporting each modification may be found in the marketing
768　submission.

Modification	Modification Protocol Component			
	Data management practices	Re-training practices	Performance evaluation	Update procedures
Modification #1	*Method A (see Section X.A)*	*Method D (see Section X.D)*	*Method G (see Section X.G)*	*Method J (see Section X.J)*
Modification #2	*Method A (see Section X.A)*	*Method E (see Section X.E)*	*Method H (see Section X.H)*	*Method J (see Section X.J)*
Modification #3	*Method B (see Section X.B)*	*Method F (see Section X.F)*	*Method I (see Section X.I)*	*Method J (see Section X.J)*

769

VIII.　　Impact Assessment

771　An Impact Assessment, in the context of a PCCP, is the documentation of the assessment of the
772　benefits and risks of implementing a PCCP for an ML-DSF, as well as the mitigations of those
773　risks. The manufacturer's existing quality system should be used as the framework in which to
774　conduct an Impact Assessment for the modifications set forth in the PCCP.
775
776　Documentation for an Impact Assessment provided to the Agency in a marketing submission
777　containing a PCCP should 1) compare the version of the device with each modification
778　implemented to the version of the device without any modifications implemented, 2) discuss the
779　benefits and risks, including risks of social harm, of each individual modification, and 3) discuss
780　how the activities proposed within the Modification Protocol continue to reasonably ensure the
781　safety and effectiveness of the device. The Impact Assessment documentation in a marketing
782　submission should also discuss 4) how the implementation of one modification impacts the
783　implementation of another, and 5) the collective impact of implementing all modifications. FDA

784   believes it is important to address these elements in an Impact Assessment in order to
785   demonstrate that the combination of the proposed modifications is unlikely to introduce
786   additional, unmitigated risks, and that the safety and effectiveness of the device under review is
787   maintained as modifications are implemented.
788
789   Impact Assessment documentation in a marketing submission should discuss how the individual
790   modifications included in the PCCP impact not only the ML-DSF, but also how they impact the
791   overall functionality of the device, including how they impact other device software functions, as
792   well as device hardware. Additionally, if the ML-DSF is a device function of a multiple function
793   device product, we recommend considering FDA's guidance Multiple Function Device Products:
794   Policy and Considerations[81] to determine if any information should be included in the Impact
795   Assessment documentation in a marketing submission (and the marketing submission overall) so
796   that FDA may assess the impact of the "other function(s)" on the safety or effectiveness of the
797   ML-DSF and modifications to the ML-DSF.
798
799   The Agency acknowledges that for some devices, it may be least burdensome to include the
800   content of the Impact Assessment within the Modification Protocol rather than as a separate
801   section within the PCCP.

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[81] See FDA's guidance "Multiple Function Device Products: Policy and Considerations" available at
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-function-device-products-policy-and-considerations.

Appendix A: Example Elements of Modification Protocol Components for ML-DSFs

In general, a Modification Protocol that is included as part of a PCCP in a marketing submission should include four components that outline a manufacturer's 1) data management practices, 2) re-training practices, 3) performance evaluation protocols, and 4) update procedures, for each modification in the Description of Modifications for the ML-DSF. However, manufacturers may include other or additional components if they believe that their proposed protocols do not fit into any of these four components. Examples of questions for consideration and the types of information manufacturers should provide in these components of a Modification Protocol are provided below.

Note that this is a developing area, and as FDA gains experience, these example questions may change. *The items below are also not an exhaustive list of topics that a manufacturer is expected to cover, and all questions may not apply to all marketing submissions*. Likewise, the Agency may request additional Modification Protocol components or information to be included in a PCCP for some device types so that the Agency can review the PCCP as part of the marketing submission.[82] Some sections of a Modification Protocol may be more or less detailed depending on the complexity and risks of each modification in the PCCP.

(1) Data Management

Different data can be collected and used for training and testing ML model updates. For collection of new training and testing data, the Modification Protocol should include how the data will be used (e.g., for ML model development or testing), and how the data management supports these uses.

a. Collection protocols

1.a.1. For each modification, what are the inclusion/exclusion criteria for data collection, and how are they linked to the intended use population?

1.a.2. What is the intended distribution of your data set along covariates describing the patient population (e.g., sex, age, race, height, weight, disease conditions) and data acquisition conditions (e.g., sites, data acquisition devices/methods, imaging and reconstruction protocols)? Is this distribution representative of the intended use population, including intersectional groups?

1.a.3. Will the data be collected prospectively or retrospectively? Will the data set include consecutive cases within a given date range? Otherwise, if random sampling is planned, what method or technique will be used and how will it account for bias and randomness?

1.a.4. Are there any plans for enrichment or stratified sampling to include specific patient subgroups (e.g., sex, age, race)?

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[82] Such information would be required in the marketing submission pursuant to 21 CFR 807.81(a)(3) and 21 CFR 814.39(a).

840   1.a.5. What is the number and geographical distribution of data collection sites?

841   1.a.6. What are the measures to mitigate potential unwanted bias in learning or
842   performance estimation, for example, due to issues related to new training or
843   testing data, respectively?

844   1.a.7. What are the strategies and measures to understand and mitigate potential biases
845   in the data, such as those due to historical inequalities to medical treatment access
846   by different populations?

847   1.a.8. What are the strategies to ensure data sets remain relevant over time with respect
848   to changes in, for example, data acquisition technologies or protocols, clinical
849   practice, patient populations, and disease conditions?

850   1.a.9. Are data collection, storage, retention, and use protocols in compliance with
851   regulations for human subject protections and requirements for clinical
852   investigations (e.g., pursuant to 21 CFR Part 812, 45 CFR Part 46, 21 CFR Part
853   50, and 21 CFR Part 506, as applicable)?

854   1.a.10. For ML-DSFs that use input data from dedicated acquisition systems (e.g.,
855   software device functions in a patient monitor that uses connected sensors), is the
856   data acquired with the systems and settings with which the ML-DSF will be used?
857   For device software functions that use input data from different acquisition
858   systems (e.g., interoperable medical devices), does the data acquired meet the
859   input specifications of the ML-DSF?

860   **b. Assurance of Data Quality**

861   1.b.1. What techniques will be employed to fortify data consistency and completeness?

862   1.b.2. What are the strategies used to promote data authenticity, transparency, and
863   integrity?

864   1.b.3. How will potentially missing data elements within a case/record be handled?

865   1.b.4. Are there criteria for including/excluding cases/records based on data quality (in
866   addition to inclusion/exclusion criteria listed in 1.a.1. above), and if so, what are
867   the criteria and rationale?

868   1.b.5. If data might be excluded as a result of the quality assurance process, what
869   methods are planned to minimize the impact on the generalizability of training
870   and accuracy of testing?

871   1.b.6. Are there strategies to trace a data issue to an individual record? What are the
872   strategies to identify and investigate data issues?

873   1.b.7. Will data that are obsolete or no longer needed be removed?

874   1.b.8. What controls are in place to prevent and identify unauthorized access or
875   manipulation of the training and testing data sets? For example, what controls are
876   in place to prevent malicious addition or deletion of data for the purpose of
877   adversarial machine learning?

878   1.b.9. Is there an automated process to ensure data quality?

879   **c. Reference standard determination**

880   For the purposes of this guidance, the reference standard is the best available truth standard to
881   define the true condition for each patient/case/record. The reference standard may be used in
882   device training, device testing, or both.

883
884   1.c.1. What is the justification for the method for the determination of the reference
885   standard?
886   1.c.2. If the reference standard is based on evaluations from clinicians, what was the
887   grading protocol used (e.g., what are the total number of clinicians who
888   participated and their qualifications; what data are these clinicians provided with;
889   and how are the clinicians' evaluations collected/adjudicated for determining the
890   reference standard)?
891   1.c.3. What is the strategy for addressing cases where results obtained using a reference
892   standard may be equivocal or missing?
893   1.c.4. What is the uncertainty inherent in your reference standard?
894   1.c.5. Will any of the methods for determining the reference standard be automated?
895   Are there differences between the reference standards used for training versus
896   testing?
897   1.c.6. Are there differences between the reference standard used to support the initial
898   ML-DSF marketing authorization and the reference standard being applied to
899   update the ML model?

900   **d. Sequestration of test data sets**
901 For the purposes of this guidance, sequestration of test data sets means that manufacturers do not
902 have access to the test data set for the purpose of ML-DSF development.
903
904   1.d.1. What strategies will be employed at the outset of data collection to shield the test
905   data set from the ML-DSF development?
906   1.d.2. What are the specific procedures to be followed so that the test data set remains
907   sequestered during re-training?
908   1.d.3. If test data are planned to be used multiple times for performance evaluation, what
909   measures are in place to prevent unwanted bias from being introduced through
910   ML model manufacturers learning substantial information about the test data set
911   and results?
912

913   **(2) Re-Training**

914   **a. Re-training objectives and focus**
915   2.a.1. How are the modifications presented in the Description of Modifications in the
916   PCCP related to the planned re-training methods?
917   2.a.2. Which parts of the ML-DSF are planned to be modified (e.g., transfer learning,
918   data pre-processing, data augmentation, only a certain set of coefficients, ML
919   architecture and hyper-parameters, loss functions, optimization methods and
920   criteria, types of ML model inputs and outputs), and what are the details of the
921   planned modifications to the ML-DSF design? What is the specific rationale for
922   the change to each part that is planned to be modified?
923   2.a.3. For each part of the ML-DSF that will be modified, is ML model re-training
924   needed to achieve the modifications specified in the PCCP?

925 926	2.a.4.	If re-training applies to only certain parts of the ML-DSF, what are the plans to ensure that other functions or software components are not affected?

b. Re-training implementation:

928 929	2.b.1.	What are the triggers for re-training (e.g., when new data reaches a certain size, when a drift is observed, periodically in time)?
930	2.b.2.	What strategies will be employed to identify and limit overfitting?
931 932	2.b.3.	Are there risks related to ML model bias introduced by re-training a modified ML model, and if so, what are planned mitigations?

(3) Performance Evaluation

a. Triggers to initiate performance evaluation

936 937 938 939	3.a.1.	What are the triggers for initiating performance evaluation of a re-trained ML model or modified ML-DSF (e.g., re-training shows a certain performance level on the training or validation data, test data reaches a certain size, periodically in time)?
940	3.a.2.	How frequently is this expected to occur?

b. Assessment metrics and elements

942 943 944	3.b.1.	How is the Data Management Plan in (1) above applied to produce the testing data for performance evaluation that are different from any training or tuning data?
945	3.b.2.	What metrics will be computed to understand device performance?
946	3.b.3.	How do these metrics demonstrate that the modified device can be safely used?
947 948	3.b.4.	How will the metrics provide a comprehensive assessment of device performance and patient safety?
949 950	3.b.5.	What corner cases (i.e., cases outside the norm) or known challenging scenarios will be evaluated?

c. Statistical analysis plans

952 953	3.c.1.	What is the plan for evaluating equivalent or improved performance with respect to previously validated versions, including the original version, of the ML-DSF?
954 955	3.c.2.	What are the high-risk subpopulations and subgroups (e.g., sex, gender differences, acquisition protocols) that need to be evaluated?
956	3.c.3.	How will this evaluation be used to support labeling specifications?
957 958	3.c.4.	How will you test that performance in one area (e.g., sensitivity) does not result in degrading performance in another (e.g., specificity)?
959	3.c.5.	How will the sample size be determined?
960 961 962	3.c.6.	Is the primary analysis based on the intention-to-diagnose population (no study subjects will be excluded) or the per-protocol population (subjects with protocol violations will be excluded)?
963 964	3.c.7.	How is variability in the reference standard accounted for (e.g., in the case of reader variability when clinical interpretation is used)? When the reference

965   standard may be imperfect (e.g., sometimes includes a diagnostic error), are errors
966   made by the imperfect reference standard conditionally independent of errors
967   made by the ML-DSF, or are they positively correlated?
968   3.c.8.   How will missing data be addressed in analysis?

d. Performance targets

970   3.d.1.   What are the acceptance criteria?
971   3.d.2.   What clinical considerations were used to develop the acceptance criteria?
972   3.d.3.   How will the acceptance criteria support that the modification will be successfully
973   implemented?

e. Additional testing needs

975   3.e.1.   Is database testing sufficient to address the risks associated with the proposed
976   modification (e.g., does the user need to interact with the device to evaluate the
977   performance or address a clinical risk or, for software that is part of a hardware
978   device,[83] how is the effect of the modification on hardware functionality
979   evaluated)?
980   3.e.2.   How may clinical usability need to be addressed for a modification?
981

(4) Update Procedures

a. Software verification and validation

984   4.a.1.   Does the proposed modification necessitate a different software verification and
985   validation plan from that used for the version of the device without any
986   modifications implemented?
987   4.a.2.   What type of testing will be performed? Will the modified device be validated to
988   function in an integrated environment?
989   4.a.3.   If the device includes other device functions in addition to the ML-DSF, how will
990   the impact of modifications to the ML-DSF on the other device functions be
991   evaluated?
992   4.a.4.   If the device includes "other functions" in addition to the ML-DSF, how will the
993   "other functions'" impact on the safety or effectiveness of the modified ML-DSF
994   be evaluated?

b. When and how updates will be implemented

996   4.b.1.   How will the decision be made on when to perform an update? What is the
997   expected timeline for implementing the modifications? Is there a set frequency of
998   updates?
999   4.b.2.   When and how will an update be implemented (e.g., automatically when the
1000   device is not being used, manually by users or hospital technicians, or both

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[83] For the purposes of this guidance, "part of a hardware device" means the software is used to control a device, or the software is necessary for a hardware device to achieve its intended use.

1001	manually and automatically)? What is the basis on which the mechanism of
1002	implementation is dependent?
1003	4.b.3. For ML-DSF updates to reusable medical equipment, how will the device
1004	operation, including function of critical safety features (e.g., medical device
1005	alarms), be verified following the update?
1006	4.b.4. Will updates be made globally (i.e., the same update applied to all devices in the
1007	field) or locally (e.g., the devices may be modified for a patient/provider/care
1008	unit/hospital)?
1009	4.b.5. What cybersecurity protocols[84] will be applied during updates?

c. Communication and transparency to users

1011	4.c.1. How will the PCCP be described in the public summary document and/or
1012	labeling?
1013	4.c.2. How will updates be communicated to users, including, but not limited to, in
1014	updated labeling (e.g., release notes)?
1015	4.c.3. What information about modifications to the device (e.g., performance) will be
1016	communicated to the user?
1017	4.c.4. How will version information be presented to the user when reviewing device
1018	outputs?
1019	4.c.5. Will users have the option to review labeling before implementing an update?
1020	4.c.6. How will any known biases or other performance issues with the potential to
1021	result in individual or social harms be disclosed, including, but not limited to, in
1022	labeling?
1023	4.c.7. How will any changes in performance related to known issues or sources of bias
1024	be communicated to the user, including, but not limited to, in labeling?
1025	4.c.8. What information about the population and methods for validation will be
1026	provided?
1027	4.c.9. If patient data from previous device use is available and can be rerun on an
1028	updated ML model, will this activity be performed for the available data and will
1029	those updated results be available to patients and users? Is there a plan to
1030	communicate if patient results before and after an update would provide clinically
1031	meaningful differences?

d. Device monitoring plan

1033	4.d.1. How will adverse events be tracked for different updates?
1034	4.d.2. Is there a plan to monitor real-world device performance (beyond general
1035	controls) and, if not, why is it not necessary?
1036	4.d.3. How will changes in performance in patient subpopulations be identified?

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[84] For recommendations related to cybersecurity, please consult FDA guidance documents on this topic, including "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices) and "Postmarket Management of Cybersecurity in Medical Devices" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-management-cybersecurity-medical-devices).

1037	4.d.4.	What will be the response to the identification of previously unknown risks or
1038		previously unrecognized high-risk patient subpopulations?
1039	4.d.5.	What is the strategy to respond to unexpected performance deficiencies or other
1040		hazards, or to higher levels of adverse events, as compared with previous
1041		iterations of the device?
1042	4.d.6.	How will errors in diagnosis (i.e., misdiagnosis), attributable or partially
1043		attributable to the device that do not meet the criteria for an adverse event, be
1044		tracked?

1045

Appendix B: Example ML-DSF Scenarios Employing PCCPs

The examples in this appendix illustrate different ML-DSF scenarios where a PCCP could be employed. Due to the complexity of ML-DSFs, all examples are hypothetical and do not reflect any specific authorized device.

Each example begins with a brief description of an authorized device, its intended use, and one summary of a modification from the Description of Modifications in its authorized PCCP (in the examples, denoted as "Brief Overview of Pre-Specified Modification"). Please note that the provided summaries of the devices and modifications in this appendix are *not* intended to reflect the complete content or detail expected in a Description of Modifications section in a PCCP. Rather, proposed modifications should be described in much greater detail in a PCCP, consistent with the recommendations provided throughout this guidance. The post-authorization modification scenarios are described to illustrate how the PCCP would be implemented. A distinction is drawn between post-authorization modifications that 1) would be acceptable for the authorized device with a PCCP and could be implemented without a new marketing submission or 2) would not be acceptable for the authorized device with a PCCP and likely requires a new marketing submission[85] before the device could be introduced into interstate commerce.

Due to the complexity of ML-DSFs, it is not practical to describe all relevant considerations, or a complete PCCP, for the limited examples presented below. Therefore, while these examples highlight important concepts that could inform the development and utility of a PCCP, the PCCP will be specific to the circumstances of a particular ML-DSF, based on factors including a scientifically valid assessment of benefits and risks.

FDA recommends that the PCCP strategy be discussed with the appropriate FDA review division through the Q-Submission program[86] prior to submitting a marketing submission containing a PCCP. As part of a marketing submission, the manufacturer should provide a PCCP, consisting of a Description of Modifications (Section VI), a Modification Protocol (Section VII), and an Impact Assessment (Section VIII).

(1)   Patient Monitor Software

Background:

The device is an ML-DSF intended for use in high-acuity healthcare environments (e.g., an intensive care unit). The software obtains physiological signals (e.g., electrocardiogram, blood pressure, pulse oximetry) from a primary patient monitor. The physiological signals are

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[85] 21 CFR 807.81(a)(3) or 21 CFR 814.39(a).
[86] See FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

1084 processed and analyzed by an ML model to detect patterns that occur at the onset of physiologic
1085 instability. When physiologic instability is detected, an audible alarm signal is generated to
1086 indicate that prompt clinical action is needed to prevent potential harm to the patient. The ML-
1087 enabled medical device was authorized with a PCCP.
1088
1089 **Brief Overview of Pre-Specified Modification:**
1090
1091 The manufacturer would like to re-train the ML model with more data to reduce the false alarm
1092 rate while maintaining or increasing sensitivity to the onset of physiologic instability. The
1093 baseline sensitivity is y%. The manufacturer would like to demonstrate a significant
1094 improvement in the false-alarm rate while the sensitivity remains within a pre-specified
1095 non-inferiority margin of z% when compared with the original device, i.e., the version of the
1096 device without any modifications.[87]
1097
1098
1099 **Post-Authorization Modification Scenarios:**
1100
1101 *Modification Scenario 1: Modification related to quantitative measures of device performance,*
1102 *as specified in the PCCP, and implemented in accordance with the PCCP*
1103
1104   In accordance with the Modification Protocol, data were collected and used to re-train the
1105   ML model. The modified ML model was tested per the methods specified in the
1106   Modification Protocol. The results demonstrated that the false alarm rate was
1107   significantly reduced while the mean sensitivity estimate was statistically within the
1108   proposed non-inferiority margin of the baseline sensitivity y%. Labeling was updated in
1109   accordance with the modified ML-DSF performance, and communication was provided
1110   to the device users. Because the device modification was specified in the PCCP, and it
1111   was implemented in conformance with the PCCP, the device modification would not
1112   require a new marketing submission. The manufacturer should document the
1113   modification that was specified in the PCCP in accordance with their quality system.
1114
1115 *Modification Scenario 2: Modification beyond quantitative measures of device performance,*
1116 *which was not specified in the PCCP*
1117
1118   In accordance with the Modification Protocol, the manufacturer re-trained their ML
1119   model using additional data to improve the sensitivity. Analytical validation
1120   demonstrated that the revised ML model has the same false alarm rate and sensitivity as
1121   the previous version. However, the manufacturer also noticed that the modified ML
1122   model maintained the same sensitivity and can now also predict physiologic instability in
1123   advance of its onset, which the previous version of the ML model could not do. The
1124   manufacturer would like to update the device's indications for use to reflect this
1125   additional performance claim to predict physiologic instability in advance of its onset,

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[87] The values in this example are shown as variable terms. A completed PCCP should include specific criteria
whenever possible.

1126 which was not previously included in the PCCP. The methods used for analysis,
1127 performance, and statistics were not specified in the PCCP for predicting a future state.
1128 Because this modification that was not included in the PCCP could significantly affect
1129 the safety or effectiveness of the device, a new marketing submission would be required.
1130

1131   ## (2)   Skin Lesion Software

1132
1133 **Background:**
1134
1135 The device is an ML-DSF that analyzes images of skin lesions by identifying and characterizing
1136 its features (e.g., color, quantification of area change over time) to aid in diagnosis. It was
1137 validated with a specific camera and is intended to be used by a primary healthcare provider. The
1138 device was authorized with a PCCP.
1139
1140 **Brief Overview of Pre-Specified Modification:**
1141
1142 The manufacturer would like to extend the ML-DSF for use on additional general-purpose
1143 computing platforms, including smartphones and tablets. The general-purpose computing
1144 platform must include a two-dimensional camera that meets the minimum specifications defined
1145 in the PCCP. The updated device must achieve a minimum performance defined in the
1146 Modification Protocol using a specified methodology.
1147
1148 **Post-Authorization Modification Scenarios:**
1149
1150 *Modification Scenario 1: Modification in input, as specified in the PCCP and implemented in*
1151 *accordance with the PCCP*
1152
1153   The manufacturer's analytical validation demonstrated the ML-DSF can be deployed on
1154   two additional smartphones that have image acquisition specifications that meet the
1155   minimum specifications provided in the PCCP. The analytical performance using the new
1156   image acquisition systems was found to be statistically equivalent to the baseline
1157   performance, as specified in the Modification Protocol. Labeling was updated to reflect
1158   the new ML-DSF compatibility with the additional smartphones, which may increase
1159   access of the ML-DSF in the healthcare community. Communication updates on device
1160   compatibility were also provided. Because the device modification was specified in the
1161   PCCP, and it was implemented in conformance with the PCCP, the device modification
1162   would not require a new marketing submission. The manufacturer should document the
1163   modification that was specified in the PCCP in accordance with their quality system.
1164
1165 *Modification Scenario 2: Modification in input that was not specified in the PCCP*
1166
1167   The manufacturer would like to deploy a modified ML model that uses images captured
1168   by a thermographic camera; however, the new camera technology was not specified in
1169   the PCCP. Because this modification that was not included in the PCCP could

1170   significantly affect the safety or effectiveness of the device, a new marketing submission
1171   would be required.
1172
1173 *Modification Scenario 3: Modification related to the device's use and performance, which was*
1174 *not specified in the PCCP*
1175
1176   The manufacturer would like to distribute a new version of the ML-DSF that is patient-
1177   facing. The ML-DSF would provide an analysis of the physiological characteristics of
1178   skin lesions, as it does currently, and direct patients to follow-up with a dermatologist
1179   based on the preliminary analysis of the malignancy of the skin lesion. The modification
1180   introduces many new, unconsidered risks that were not yet mitigated in the current
1181   PCCP, given that the modified ML-DSF will be patient-facing. Because this modification
1182   that was not included in the PCCP could significantly affect the safety or effectiveness of
1183   the device, a new marketing submission would be required.
1184

1185   (3)   Ventilator Settings Software

1186
1187 **Background:**
1188
1189 The device is an ML-DSF intended for use in the healthcare or home-use setting. The ML-DSF
1190 recommends the ideal ventilation parameters based on input data interpretation, which can then
1191 be programmed into the ventilator by a healthcare provider. The manufacturer proposes
1192 modifications to the ML-DSF to improve performance within the original indications. The
1193 device was authorized with a PCCP.
1194
1195 **Brief Overview of Pre-Specified Modification:**
1196
1197 The manufacturer would like to re-train the ML model to optimize site-specific performance for
1198 a specific subset of patients with a particular condition, for whom sufficient data were not
1199 previously available. Specifically, the manufacturer would like to modify the ML model to
1200 improve its ability to optimize ventilator settings for minute volume and tidal volume to reduce
1201 the variability to ±x% within the specified range to improve treatment outcomes for that subset
1202 of patients at different sites.
1203
1204 **Post-Authorization Modification Scenarios:**
1205
1206 *Modification Scenario 1: Modification related to the device's use and performance in a subset of*
1207 *the patient population, which was specified in the PCCP and implemented in accordance with*
1208 *the PCCP*
1209
1210   The manufacturer re-trained and re-validated the ML model on newly acquired data in a
1211   subpopulation of patients with a particular disorder. As evidenced by additional clinical
1212   performance data collected and analyzed per the Modification Protocol, the re-training on
1213   new data improved the reliability and precision of ventilator setting recommendations,

1214   showing improvements and specializations to improve site-specific ventilator operation.
1215   The updated recommendations were validated against patient outcomes and adverse
1216   events that may occur due to ventilator setting inaccuracies following the methods in the
1217   Modification Protocol. The adverse event rates and outcomes acceptance criteria were
1218   established in the Modification Protocol, and as such, were used to validate the updated
1219   ML model. The ML-DSF was updated to implement the re-trained ML model and the
1220   labeling was updated for clarity to inform users how the updated ML model accounts for
1221   local experience and prevalence. The implementation of this modification was done only
1222   at applicable sites. Because this device modification was specified in the PCCP, and it
1223   was implemented in conformance with the PCCP, the device modification would not
1224   require a new marketing submission. The manufacturer should document the
1225   modification that was specified in the PCCP in accordance with their quality system.
1226
1227   *Modification Scenario 2: Modification related to device's use and performance in a subset of the*
1228   *patient population, which was specified in the PCCP, but was not implemented in conformance*
1229   *with the PCCP*
1230
1231   The manufacturer re-trained and re-validated the ML model on newly acquired data, but
1232   was unable to fulfill the protocol because the manufacturer had to implement a reference
1233   standard that was different from the one described in the Modification Protocol. Even
1234   though the modification was specified in the PCCP, it was not implemented in
1235   conformance with the PCCP. Because this modification that was not implemented in
1236   conformance with the PCCP could significantly affect the safety or effectiveness of the
1237   device, a new marketing submission would be required.
1238

1239   # (4) Image Acquisition Assistance Device

1240   **Background:**

1241   The ML-DSF is integrated into an imaging system and is intended to assist healthcare providers
1242   during acquisition of ultrasound images of the shoulder region in adult and pediatric populations
1243   by highlighting portions of the image where it detects a potential abnormality in real time. The
1244   ML-DSF interfaces with the device acquisition system, analyzes its output using an ML model,
1245   provides real-time alerts to the operator if an abnormality is detected, and automatically adjusts
1246   parameters in the device acquisition system during image acquisition to optimize the imaging.
1247   The device does not provide a diagnosis. The ML-enabled medical device was authorized with a
1248   PCCP.

1249   **Brief Overview of Pre-Specified Modification:**

1250   The manufacturer would like to re-train their ML model to further optimize the accuracy of the
1251   abnormality detection. The PCCP pre-specifies that both the sensitivity and specificity will be
1252   shown to be significantly superior for abnormality identification during the shoulder exam.

1253 **Post-Authorization Modification Scenario:**

1254 *Modification Scenario 1: Modification related to quantitative measures of device performance,*
1255 *as specified in the PCCP, and implemented in accordance with the PCCP*

1256   In accordance with the Modification Protocol, imaging data were collected and used to
1257   re-train the ML model. The modified ML model was tested according to a specified test
1258   protocol in the Modification Protocol. The results demonstrated that the sensitivity and
1259   specificity for abnormality identification met statistical superiority pre-specifications.
1260   Labeling was updated in accordance with the modified device performance, and
1261   communication was provided to the device users. Because the device modification was
1262   specified in the PCCP, and because it was implemented in conformance with the PCCP,
1263   the device modification would not require a new marketing submission. The
1264   manufacturer should document the modification that was specified in the PCCP in
1265   accordance with their quality system.

1266 *Modification Scenario 2: Modification related to the device's use and performance that was not*
1267 *specified in the PCCP*

1268   The manufacturer used new images to re-train the ML model and would like to update
1269   their labeling to reflect improved performance in the same shoulder region in a subset of
1270   the pediatric patient population identified in the device's indications for use. However,
1271   the modification was not specified in the PCCP. Because this modification that was not
1272   included in the PCCP could significantly affect the safety or effectiveness of the device, a
1273   new marketing submission would be required.
1274

1275   **(5)   Feeding Tube Placement Radiograph Analysis Software**

1276
1277 **Background:**
1278
1279 The device is an ML-DSF that analyzes chest radiographs from hospitalized patients to evaluate
1280 feeding tube placement. The ML-DSF reorders the radiologist's review queue so that
1281 radiographs identified as having a higher likelihood of feeding tube misplacement are placed
1282 higher in the queue. The device was authorized with a PCCP.
1283
1284 **Brief Overview of Pre-Specified Modification:**
1285
1286 The manufacturer would like to improve ML model performance by increasing sensitivity to
1287 misplaced feeding tubes by re-training on new data. The baseline sensitivity is x%.
1288
1289 Additionally, the manufacturer would like to modify the device so that it would notify nursing
1290 staff to check on the patient, in parallel with prioritization in the review queue. This modification
1291 requires achieving a sensitivity of z%.
1292

Post-Authorization Modification Scenarios:

Modification Scenario 1: Modification related to quantitative measures of device performance, and modification related to device's use and performance, which were both specified in the PCCP and implemented in accordance with the PCCP

The manufacturer re-trained and re-validated the ML model on newly acquired data as described in the Modification Protocol, which significantly improved the ML-DSF sensitivity from x% to z% to detect incorrect feeding tube placements. The improved sensitivity achieved the required sensitivity (z%) statistically to enable the nursing staff notification function, and that notification function was enabled. Labeling of the device was changed in accordance with the PCCP. Because the device modification was specified in the PCCP, and it was implemented in conformance with the PCCP, the device modification would not require a new marketing submission. The manufacturer should document the modification that was specified in the PCCP in accordance with their quality system.

Modification Scenario 2: Modification related to device's use and performance that was not specified in the PCCP

The manufacturer used the same database of images to re-train the ML model to identify pneumonia on chest radiographs. The pneumonia identification function was found to have the same sensitivity and specificity as the feeding tube ML model. The manufacturer would like to employ the new pneumonia identification function feature alongside the feeding tube placement ML model in radiograph triage. The modification was not specified in the PCCP. Because this modification that was not included in the PCCP could significantly affect the safety or effectiveness of the device, a new marketing submission would be required.