Predetermined Change Control Plan (PCCP)

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Director Regulatory

November 28, 2023

Medical Device Development

ITERATIVE advancements supported by

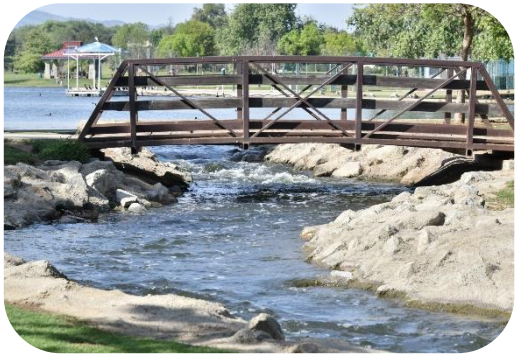
AGILE processes foster

INNOVATION and benefit PATIENTS

November 2023

Prospective Change Management

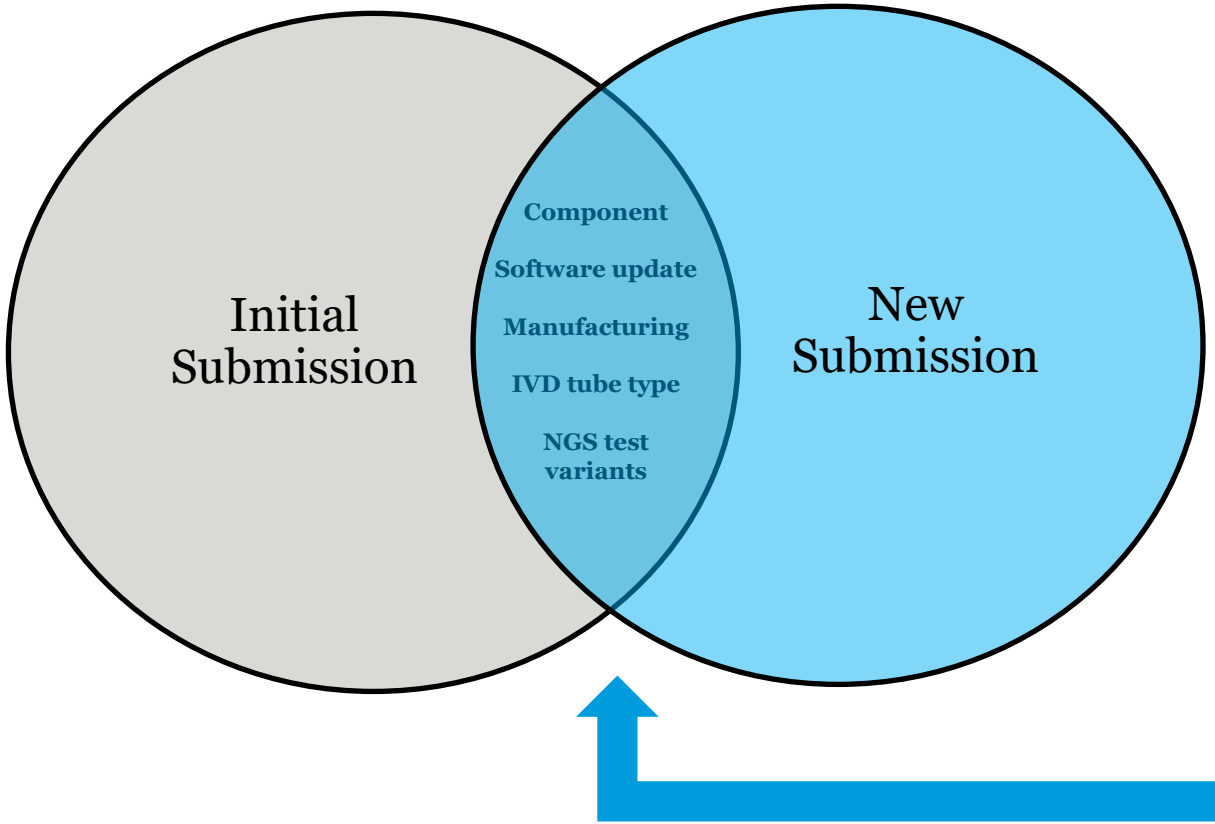
Premarket



Preauthorized Protocol

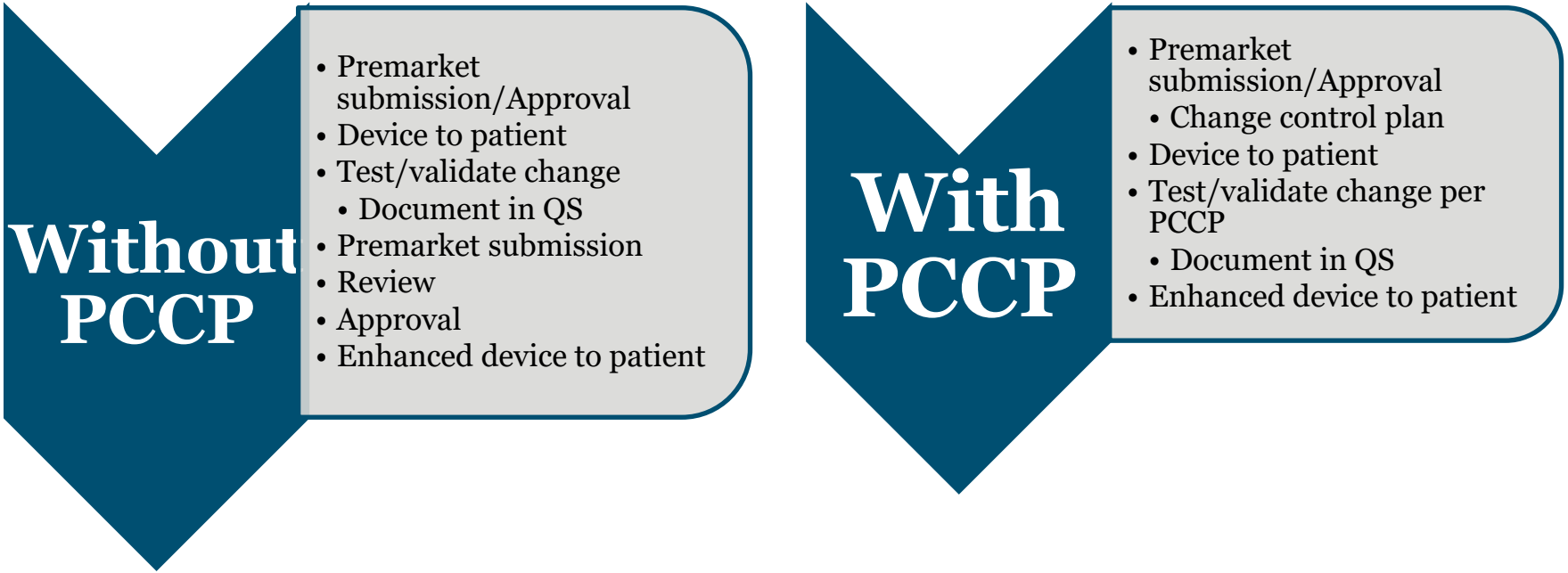
Postmarket

CHANGES ELIGIBLE FOR PREDETERMINED CHANGE CONTROL PLAN (PCCP)

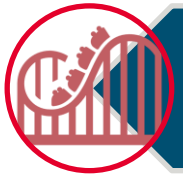


Subset of changes requiring notification and approval before implementation become eligible for PCCP.

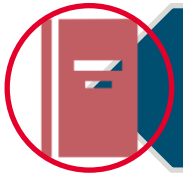
AGILE CHANGE MANAGEMENT



COMPONENTS OF A PCCP



Description of Change

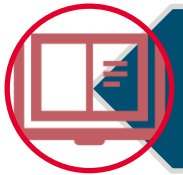


Modifications Protocol

- Validation plan
- Acceptance criteria

Impact Assessment

- Benefit-Risk assessment

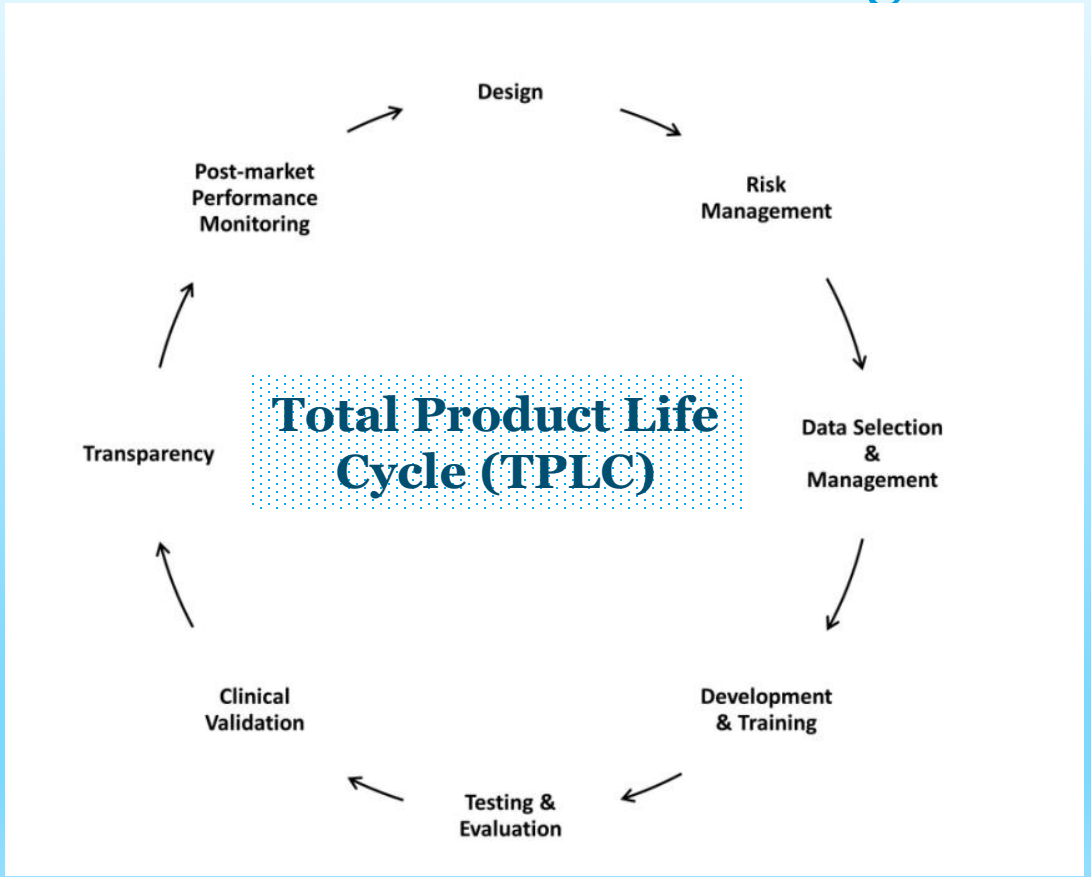


Labeling (if applicable)

Harmonized PCCP for Machine Learning Enabled Devices

Focused and Bounded

Risk-Based



Evidence-Based

Transparent

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

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

Document issued on April 3, 2023.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact digitalhealth@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact ocod@fda.hhs.gov. For questions about this document regarding CDER-regulated products, contact druginfo@fda.hhs.gov. For questions about this document regarding combination pro

U.S. FOOD & DRUG ADMINISTRATION | Health Canada Santé Canada | Medicines & Healthcare products Regulatory Agency

Predetermined Change Control Plans for Machine Learning–Enabled Medical Devices: Guiding Principles

October 2023

In 2021, the U.S. Food and Drug Administration (FDA), Health Canada, and the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) jointly identified 10 guiding principles that can inform the development of Good Machine Learning Practice (GMLP). GMLP supports the development of safe, effective, and high-quality artificial intelligence/machine learning technologies that can learn from real-world use and, in some cases, improve device performance.

In this document, FDA, Health Canada, and MHRA jointly identified 5 guiding principles for predetermined change control plans. These principles draw upon the overarching GMLP guiding principles, in particular principle 10, which states that deployed models are monitored for performance and re-training risks are managed.

Advancements in digital health technologies include artificial intelligence/machine learning-enabled medical devices (MLMD). Regulatory expectations that are aligned with best practices for development and change management, such as those described in the GMLP Guiding Principles, can help to support the quality of such devices. Ultimately, this can lead to patient benefits such as earlier access to innovative technologies or more accurate diagnoses.

The change management process helps to ensure the ongoing safety and effectiveness of devices in the face of change throughout the device's total product lifecycle (TPLC). However, certain changes to MLMDs, such as changes to a model or algorithm, may be substantive or significant. For this reason, they can require regulatory oversight, such as additional premarket review. Such regulatory expectations may not always coincide with the rapid pace of MLMD development.

Internationally, the medical device community is discussing the use of predetermined change control plans (PCCPs) as a way of managing certain device changes where regulatory authorization before marketing is typically required. PCCPs can be used to help:

- align regulatory processes with the rapid and ongoing approach to change management in MLMDs
- manage risks in a timely and ongoing fashion through monitoring, maintenance, and/or improving device performance
- uphold high regulatory standards to ensure device safety and effectiveness.

For this document, the term PCCP describes a plan, proposed by a manufacturer, that specifies:

- certain planned modifications to a device
- the protocol for implementing and controlling those modifications and
- the assessment of impacts from modifications.

PCCPs may be developed and implemented in different ways in different regulatory jurisdictions.

One key objective of the 5 Guiding Principles for PCCPs for MLMD is to provide foundational considerations that highlight the characteristics of robust PCCPs. Another objective of this document is to facilitate and foster ongoing engagement and collaboration among stakeholders on the PCCP concept for MLMD. As with the GMLP Guiding Principles, this document intends to lay a foundation for PCCPs and encourages international harmonization.

International harmonization and stakeholder consensus on the core concepts of PCCPs will help support the advancement of responsible innovations in the digital health space.

We welcome your continued feedback through the FDA public docket (FDA-2019-N-1185) at Regulations.gov, and we look forward to engaging with you on these efforts. This work is being spearheaded by the Digital Health Center of Excellence for the FDA, the Medical Devices Directorate Digital Health Division at Health Canada and the software and AI team at the MHRA. Contact us directly at DigitalHealth@fda.hhs.gov, software@mhra.gov.uk, and mddpolicyconsultquestions@hc-sc.gc.ca.

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FDA FACT SHEET

CDRH'S APPROACH TO TUMOR PROFILING NEXT GENERATION SEQUENCING TESTS

The Food and Drug Administration (FDA) has recently announced the marketing authorization of three tumor profiling next generation sequencing (NGS) tests, Thermo Fisher Scientific's Oncomine Dx Target Test,[1] MSK-IMPACT[2] and Foundation Medicine's FoundationOne CDx[3] which are important advancements in the real-world application of precision oncology. The approach taken to the regulation of these tumor profiling NGS tests includes several key features described below.

Three-Tiered Approach for Reporting Biomarkers in Tumor Profiling NGS Tests

FDA is committed to and works individually with test developers to use the least burdensome approach for its review of tests. Multiplexed tumor profiling tests assess many biomarkers that may have a range of clinical evidence associated with them that is constantly changing as new science emerges. Below, we discuss the three levels of biomarkers addressed collectively in the Oncomine Dx Target Test/MSK-IMPACT, and FoundationOne CDx authorizations, as well as the analytical and clinical evidence used to support claims for those biomarkers.

Level 1: Companion Diagnostics

Companion diagnostics (CDx) are test that provide information that is essential for the safe and effective use of a corresponding therapeutic product, such as a drug. Tumor profiling NGS tests may include CDx claims that are prescriptive for a specific therapeutic product, such as the Table 1 claims listed in the intended use for the Oncomine Dx Target Test and FoundationOne CDx. Such claims are supported by analytical validity of the test for each specific biomarker and a clinical study establishing either the link between the result of that test and patient outcomes or clinical concordance to a previously approved CDx.

Level 2: Cancer Mutations with Evidence of Clinical Significance

Tests for biomarkers described as cancer mutations with evidence of clinical significance enable health care professionals to use information about their patients' tumors in accordance with the clinical evidence, such as clinical evidence presented in professional guidelines, as appropriate. Such claims are supported by a demonstration of analytical validity (either on the mutation itself or via a representative approach, when appropriate) and clinical validity (typically based on publicly available clinical evidence, such as professional guidelines and/or peer-reviewed publications).

Level 3: Cancer Mutations with Potential Clinical Significance

Mutations not considered biomarkers in Level 1 or Level 2 can be described as cancer mutations with potential clinical significance. These mutations may be informational or used to direct patients towards clinical trials for which they may be eligible. Such claims are supported by analytical validation, principally through a representative approach, when appropriate, and clinical or mechanistic rationale for inclusion in the panel. Such rationales would include peer-reviewed publications or in vitro pre-clinical models.

A Fluid Approach to Reporting within Levels 2 and 3

Following FDA review and authorization of a tumor profiling NGS test, the test developers will be able to report additional variants of the same type post-market within the existing analytically validated genes in the panel, for claims consistent with the clinical criteria established in the original submission, without an additional FDA submission. As evidence of clinical significance becomes recognized by the clinical community, and provided that the analytical validity of the test was reviewed and established in the initial or a subsequent submission, mutations can be moved from Level 3 to Level 2 without an additional FDA submission.

[1] Additional information on the premarket approval for the Oncomine Dx Target Test is available at https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180044A.pdf.

[2] Additional information on the marketing authorization of the MSK-IMPACT is available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170058.pdf.

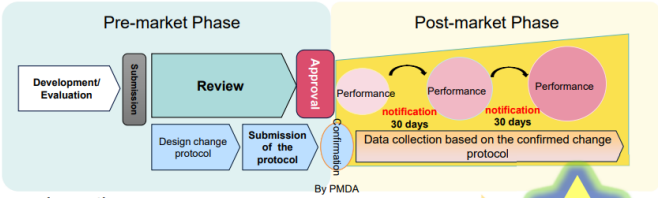
[3] Additional information on the premarket approval for the FoundationOne CDx is available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019A.pdf.

[4] Additional information regarding companion diagnostics is available in FDA's guidance entitled "In Vitro Companion Diagnostic Devices," available at https://www.fda.gov/medical-devices/ivd-regulatory-assistance/in-vitro-companion-diagnostic-devices.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
FDA.GOV

IDATEN (Improvement Design within Approval for Timely Evaluation and Notice)

- Post-Approval Change Management Protocol (PACMP).
- To enable continuous and timely improvements through product lifecycle. (suitable for SaMD. Could be applied to ALL Medical Devices.)



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No review Fee charged, in case the change request is as planned before the approval

Smooth Change Management

Health Canada

Draft guidance document: Pre-market guidance for machine learning-enabled medical devices

Canada

IV. Updating Breakpoints in AST System Device Labeling

A. Establishing and Utilizing a PCCP for Breakpoint Updates in a 510(k) Submission for an AST System Device

Generally, updating the STIC of an AST system device could significantly affect the safety and effectiveness of the device, and therefore, such modifications, if not included in a PCCP or breakpoint change protocol, would likely require submission of a 510(k) prior to updating device labeling.[17] In this guidance, FDA describes an approach that would often be least burdensome

November 2023

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Abbott