Executive Summary

On 22 August 2024 FDA issued a draft guidance document for comment. The subject is Predetermined Change Control Plans (PCCPs) for Medical Devices (FDA-2024-D-2338). This proposal is a great example how to balance the public interest and the interest of the medical device industry in a practical way. In Europe with the Medical Device Regulation (MDR, (EU) 2017/745) this balance has gone lost, and therefore FDA should serve as an example on how to create a win-win for all stakeholders.

The guidance document proposes to allow manufacturers to self-certify modifications of approved medical devices based on an FDA approved Modification Protocol. This allows manufacturers to spread out the implementation of changes over time without undue delay. The PCCP approach creates flexibility and efficiency without compromising the level of oversight by regulators.

The PCCP concept could easily be adopted by the European MDR, if the political will would be present. Bringing back a form of self-certification is highly needed to relieve the pressure on manufacturers and Notified Bodies.

This article provides in 10 minutes reading time an overview of the PCCP concept as proposed by FDA. In addition, the author provides his opinion how the PCCP concept could be embedded in the MDR regulations.

Background

In 2019, FDA issued a discussion paper that introduced the term PCCP and its description in the context of managing modifications to Artificial Intelligence/Machine Learning based software. Via the Food and Drug Omnibus Reform Act (FDORA, 2022) this concept was formalized in section 515c of the Federal Food, Drug and Cosmetic Act (FDC act). Since then, FDA issued several (draft) guidance documents related to PCCP, the first in 2023 on Artificial Intelligence/Machine Learning (AI/ML)-enabled device software functions. Also, in other guidance documents the PCCP concept was introduced on specific topics. The latest guidance document was published for comment on 24 August 2024 and is subject of this article. It broadens the PCCP concept to all device types that are brought to market via either the PMA, 510(k) or De Novo pathway.

The PCCP concept explained

The general idea behind the PCCP concept is to allow manufacturers to obtain upfront FDA approval for implementing significant modifications to an approved device. The timing of implementation is up to the manufacturer and can be spread over time. To obtain approval FDA reviews a Modification Protocol that relates to the changes, and if after approval the manufacturer sticks to the approved protocol the implementation can be self-certified within the manufacturer's Quality Management System. This will give the manufacturer flexibility to pick the best moment to introduce the change without having to wait for FDA review and approval.

Criteria to allow approval via PCCP

Changes that can be implemented by documenting the rationale in a note-to-file or periodic report as indicated in the current FDA guidance documents are not eligible for inclusion in an PCCP.

From the changes that require an FDA review before implementation per current FDA guidance documents only a subset is eligible for inclusion into a PCCP. Changes that are eligible need to meet all the following criteria:

1) Intended use of the device remains the same.
2) Patient population of the device remains the same.
3) No change in contraindications.
4) No new clinical data is needed to confirm safety or effectiveness.

5) Change does not introduce new hazards or hazardous situations.
6) Existing risks that increase due to the change can be mitigated by additional risk mitigation measures within the existing risk management framework.
7) Approval route dependent rule:
    a. PMA approved: change must qualify for 30 day notice or real-time review per current FDA guidance documents
    b. 510(k) or De Novo cleared: the device must remain substantially equivalent with the predicate device.

Content of a PCCP

A PCCP exists out of three components:

1) Description of Modifications
2) Modification Protocol
3) Impact Assessment

The Description of Modifications includes a detailed description of the changes planned, and the rationale for the changes. It also defines in detail the specifications for the characteristics and performance for the modified device. So, it includes all information needed to allow the reviewer to understand the change in the context of the approved device.

The second component is the Modification Protocol. This describes the verification and validation plans, including the pre-defined acceptance criteria. The verification and validations plans will be executed to confirm that the device remains safe and meets the specified performance characteristics. In addition, the Modification Protocol addresses changes to be made in the Quality Management System documentation, changes in device labeling, as well as how the intended change will be communicated to the relevant stakeholders.

The third and final component of a PCCP is the Impact Assessment. To me this is the most critical part of the submission as it ties the Description of Modifications and the Modification Protocol together. The Impact Assessment must describe the benefits and risks related to the proposed changes and needs to justify how the planned verification and validation activities will assure continued safety and effectiveness. Also the cumulative effect of changes need to be assessed as part of this Impact Assessment. In

essence the Impact Assessment is the outcome of a thorough risk management review per ISO14971. For this reason, the risk management process of the manufacturer plays a central role in driving the PCCP process.

If you have a mature ISO13485 Quality Management System, the components of a PCCP will match the planning phase of your design control process and/or change control process, and the Modification Plan will leverage the deliverables of the risk management process.

Review, approval and implementation of a PCCP

It is mentioned multiple times in the draft guidance that manufacturers are highly encouraged to involve FDA early in the process. This early engagement allows FDA to provide advice on the feasibility and the content of a PCCP, so that after formal submission the review can go as smooth as possible. This shows the intent of FDA to collaborate with the manufacturers to create a win-win, which is a big contrast to Europe, where regulators explicitly forbid Notified Bodies to advice manufacturers.

The PCCP cannot be stand-alone and must be part of a formal FDA submission (e.g. abbreviated 510(k), or PMA supplement). Therefore, the actual review and approval process is following the regular proven review process and timelines of FDA for the specific type of submission. As part of the PCCP review FDA must be able to conclude that reasonable assurance of safety and effectiveness is confirmed. For 510(k) or De Novo cleared devices it also requires confirmation that the device after change is still substantially equivalent with the predicate device referenced in the latest cleared device.

Once a PCCP is approved, FDA expects manufacturers to follow their Quality Management System to execute the PCCP per approved Modification Protocol. Objective evidence of adequate execution much be archived is quality records. The timing of implementation of the changes is up to the manufacturer.

Deviations from the approved PCCP would generally cause the device to be adulterated and misbranded, which means that this likely would lead to a recall of products in the market, and even further legal action. If a PCCP cannot be executed as approved, the Quality Management System must ensure that the deviation from the approved PCCP is evaluated for regulatory impact. Only when the deviation is considered not significant from

a regulatory perspective manufacturers may continue to implement the change, however, again here FDA recommends consulting them before implementing a change based on incorrect assumptions. If the deviation is incorrectly assessed this could lead to having adulterated product in the market.

In most cases a deviation from an approved PCCP will result in a regular FDA-submission as if this was a stand-alone change. As the submission preparation and FDA review time would cause a delay in implementation, the benefit of spending sufficient time to develop a robust PCCP is worthwhile the effort.

Although not specifically mentioned, my assumption is that during FDA inspections (or MDSAP equivalents) the correct implementation of a PCCP will be verified by reviewing the objective evidence present in the Quality Management System records.

The small print

There is one section in the draft guidance document that manufacturers may not like: The PCCP should be described in sufficient detail in public-facing documents to support transparency of the assessment by FDA. These public-facing documents are e.g. 510(k) summaries, SSED, and approval orders.

These summaries should include, as appropriate, planned modifications; testing methods, validation activities, performance requirements, and means of user communication.

Although it is specifically mentioned that trade secrets and confidential commercial information are excluded from disclosure, having your roadmap of product modifications publicly available to your competitors may not always be attractive.

What EU can learn from the PCCP approach

Although I was professionally raised as MDD auditor and file reviewer, and worked for 20 years in industry under MDD, I always liked the robust, predictable approach of the FDA. While the self-certification under Annex II of MDD gave manufacturers optimal flexibility, the flipside of it was that lack of knowledge, bad intent, and/or inferior Notified Bodies made this self-certification process vulnerable for derailing.

The current MDR implementation in Europe has turned into a disaster for industry, Notified Bodies and the public health system. It is inevitable that the MDR must be reformed in the coming years in order to make it cost-affordable for society, and to ensure timely availability of the latest safe and effective technology to treat patients.

While cleaning up the MDR will take years there are things that can be done short term and this draft PCCP guidance documents shows clearly lessons to learn from.

Below I list my two most urgent recommendations to whoever wants to listen in Europe to improve the current MDR practice:

1) Create a formal path for manufacturers to consult Notified Bodies as early as possible in the planning phase of changes and submissions, The Q-submission program of FDA can serve as the blueprint. This will avoid waste of time and money in industry and at Notified Bodies. And when there is distrust towards Notified Bodies, I would say that Notified Bodies that cannot separate duties in a responsible manner should not have been accredited by Competent Authorities in the first place.
2) Modify the MDCG guidelines to include the possibility of a PCCP process for planned significant changes. The criteria are already given by FDA. This will lead to the ability of manufacturer to self-certify implementation of Notified Body approved PCCPs, of which they implementation can be verified during surveillance audits. You may even consider allowing to add new product codes as part of a PCCP (e.g. line extensions, customized procedure packs).

There is so much to learn from FDA, which I consider the far-out best regulatory framework in the world now the European MDD has expired. It is just a matter of willing to harmonize, which requires political courage.

Kees den Besten, 26 August 2024