Design Control and Control Strategy

How to reach a state of control for combination product manufacturing and release

Introduction

The development, manufacture and release of drugs combined with- or using medical devices is highly regulated. Furthermore, the regulations are different in different parts of the world. Any company wanting to launch a product in a drug delivery device or aid, such as a syringe, injection pen, spray, and so on, is advised to seek guidance on the current regulations for that type of product and the market in which to launch.

That said, there are a number of steps to take which will help the development of the product into a state of control at launch regardless of the type of product, or what regulation to apply. Here we will briefly lay out some basic strategies to apply during the product development and subsequent manufacture.

Device Development

Any medical device or combination product development is advised to follow the FDA design control guidance for medical device manufacturers. This guidance explains the principles of design control and the importance of documenting the user needs, translating those into design inputs to which the design development will work. The resulting design outputs will be verified and the resulting product validated against the user needs and intended uses.

The documented evidence of design control activities and the risk management files are collected in the design history file of the product. As the development of the product nears its end, a design transfer needs to take place during which the design is transferred to manufacturing specifications and to the commercial supply organization. Part of this transfer is formulating and implementing a control strategy for the manufacture and release of the product.

A critical part of the product (device) development process is to identify the critical quality attributes (CQA's), which for the device constituent parts may be called the essential performance requirements (EPR's). For a medical device or a combination product the EPR's can be defined as follows:

- Limited to the device functions
- Affects the clinical performance at the point of use
- Essential to meet the intended use

EPR's, at minimum for a syringe will include:

- Delivered volume / dose accuracy
- Break loose & glide force
- Needle cover removal force (if time sensitive injection)

EPR's, at minimum for an auto-injector will include:

- Delivered volume / dose accuracy
- Injection depth
- Activation force (needle cover depression)

- Button activation force (if button activated)

In addition, the following may be considered

- Injection time
- Needle cap removal force (e.g. for critical interventions such as epinephrine)

Defining the Control Plan

The control plan should be largely driven by the risk management process during the development of the product. In particular, the process failure mode and effect analysis (pFMEA) is needed to identify those process and material parameters that have an impact on the CQA's (and EPR's). Those parameters are typically called critical process parameters or critical material attributes (CPP's and CMA's). The final control plan will eventually contain the following elements:

- Identified CPP's impacting CQA's and EPR's
- Process controls
- Process monitoring, including:
    - In process controls
    - Environmental monitoring
    - Incoming goods tests or controls
- Established procedures and instructions (site SOP's & Work Instructions)

Manufacture and release

Batch release needs to include the device EPR's, as well as the drug product CQA's. For a company planning to produce and release a combination product (drug product with device component) this will likely lead to additional test capabilities needed in the QC labs or in manufacturing suites, such as force measurements.

Since a lot of the testing required to release these products is destructive in nature, including testing the EPR's, there are significant gains to be made by planning how best to carry out the tests. Sampling plans are required to be statistically justified, which means that variable testing is preferred over attribute testing due to the lower number of test items required to achieve statistically significant results. This improves yield, both through reduction of loss (samples needed) and increased through-put (fewer analyses needed for release).

Significant efficiency gains can be achieved by including highly automated in- or at-line testing of the EPR's, rather than having to collect test items at line and bringing them to a QC lab for generating the results. By keeping the testing close to the assembly line results can be generated faster thus supporting parametric (real-time) batch release.

The Automationspartner SA41 test unit has been designed with the goal of supporting combination product batch release. This is a fully automated test unit able to carry out a suite of tests on each sample within a time of 15 – 25 seconds, depending on device and number of tests required. Test samples are loaded using a rack through a drawer, and the machine produces a test report once it is done. The machine is designed for installation in a controlled environment (ISO class 8) and with a compact footprint and is thus well-suited for operation in the manufacturing suite.

Conclusion

The successful development and launch of a combination product is a complex endeavor typically spanning several years. In order to reach a commercially viable state the project teams are advised to view existing regulations and standards as tools and not as hurdles. The definition of user needs and essential functions is critical as they will be used to guide the project throughout the development, verification, and validation of the product. The risk management work will inform the project on the risks of using and manufacturing the product, and thus also what to control in order to achieve the desired quality and safety. Finally, the application of the regulations and guidelines will greatly improve the regulatory approval process and thus facilitate and expedite the availability of the product and the therapy for the gain of patients and of society.

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