Device Development

Control Elements Gone Wild:

Mastering Combination Product Requirements for a Product-specific CSS

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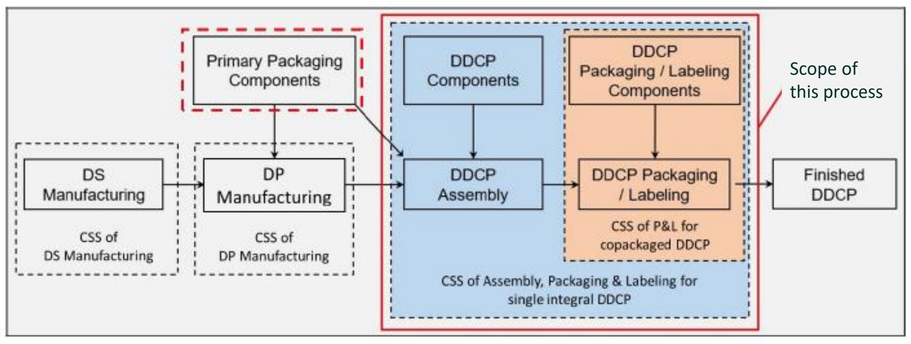
The Poster describes the structured approach to identify control elements for the **assembly of single integral Drug Device Combination Products (DDCPs)** on the one hand, and **the packaging and labeling of both single integral and co-packaged DDCPs** on the other hand.
It defines how
- Critical Functions (CFs) of the DDCP are identified,
- Critical to Quality (CtQ) sub-system functions are identified,
- Essential Design Outputs (EDOs) are derived from CtQs,
- Essential Performance Requirements (EPRs) of a DDCP are established,
- Primary Functions (PFs) of a DDCP are obtained.

Scope:



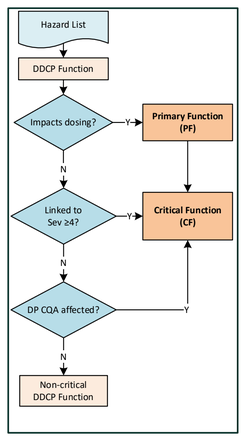
Hazard List

Critical Functions

Primary Functions

Hazard list:
The Hazard list is established within the Risk Management process and provides **the Critical Functions (CFs)** that form the basis of the control elements for a DDCP. **Primary Functions (PFs)**, performance/dosing related functions, are also listed.

Hazard	Hazardous situation (examples)	Specific Harm	Severity	Associated DDCP Function	Associated DP CQA	Primary Function	Critical Function (S4, S5, EP, PF, or DP CQA)
Haz01-02 No injection possible. No medication/ drug delivered for treatment - unrecognized	no drug released to body	Reduced efficacy resulting in continuation of disease. Requires additional medical intervention.	S3	Dosing	n/a	PF	CF
Haz03-01 Pathogenic germs (Pathogen exposure)	Pathogens penetrate body	local infection/ reddening of skin	S1	Maintainance of sterile barrier	Sterility	no	CF
Haz04-01 Sharp edge/ needle (sharps injury)	skin is penetrated while exposed to sharp object	irritation, minor pain	S1	Freedom from sharp object*	n/a	no	no
Haz04-06 Small parts (choking/inhalation)	Small part is put in mouth and leads to choking	untreated asphyxia, resulting in death	S5	n/a	n/a	n/a	n/a



The following criteria are used to identify Critical Functions:
- **Performance at the point of use**: A DDCP Function that could have an impact on the performance at the point of use (e.g. dosing), becomes a Primary Function (PF). PFs are critical and therefore automatically become CFs.
- **Severity of harm**: Severity classes, ranging from low to serious, are defined in the Risk Management Plan. Each harm listed in the Hazard List is assigned with a certain severity. DDCP Functions that are critical to safety can be identified using the associated severity of harm that can occur resulting from their failure. DDCP Functions linked to hazards that are of serious harm (e.g. severity class S4 or higher) become CFs.
- **DP CQA:** The pharmaceutical and drug product related CQAs (DP CQAs) are identified in the criticality assessment of QAs of the drug product. If a DDCP Function impacts a DP CQA, the DDCP Function also becomes CF. Therefore, the identification of CF also incorporates ICH Q8 pharmaceutical control strategy principles and ICH Q9 quality risk management for the finished combination product.

Critical Functions are functions and/or attributes that ensure safety, efficacy, and functionality of the final DDCP.
Primary Functions are functions or operational steps of a DDCP, when not performed correctly, would directly result in a failure to accurately deliver the medicinal product via the correct route of administration and/or result in unacceptable harm to the patient. (ISO 11608-1:2022)

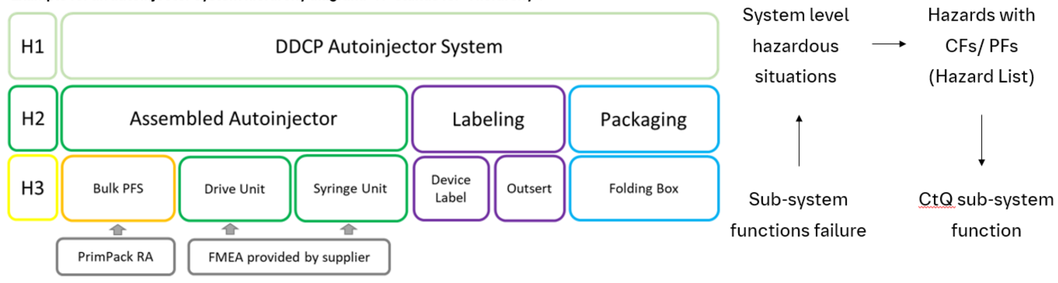
System Risk Analysis

H2 Level CtQ Subsystem Functions

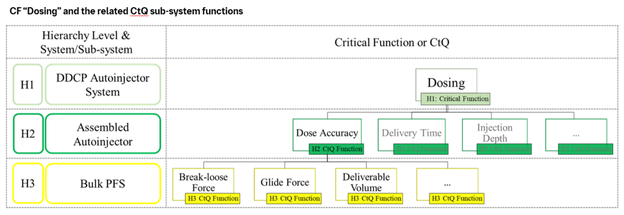
EPRs

System Risk Analysis:
The System Risk Analysis analyzes, controls and evaluates design-related risks of the DDCP. It is also used to identify Critical to Quality (CtQ) sub-sytem functions. The System Risk Analysis is structured in hierarchical levels, where the finished DDCP is divided into lower-level subs-systems. The aim is to increase the undestanding of the DDCP and how failures of individual components effect the functionality of the whole DDCP. Failure modes of the lower-level sub-systems are connected to failures on the DDCP system level using a hierarchical structure. The DDCP system level (H1) represents the System Risk Analysis, where failures are connected to hazards from the Hazard List. Thereby, failures of the DDCP are linked to CFs (including PFs) on the DDCP system level. Following the cascade down the hierarchy from the system level to the lowest sub-system level will identify sub-system functions, that contribute to the system level failure linked to a CF. These sub-system functions become critical to quality and are hence **CtQ sub-system functions**. These functions are identified on each level of the hierarchy. So each DDCP has H2-CtQ sub-system functions, H3-CtQ sub-system functions, etc. connected to the CFs. Each sub-system level consists of a dFMEA for the specific subsystem. The primary packaging risk assessment and supplier documents (e.g. FMEAs) can be used as direct inpuct document for the lowest subsystem levels.

Example for an autoinjector system hierarchy diagram. "H" stands for "Hierarchy".

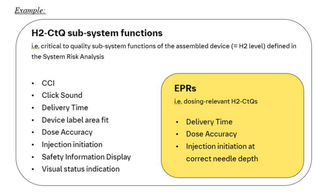


CF "Dosing" and the related CtQ sub-system functions



- EPRs are the dosing-related H2-CtQs sub-system functions

Example:



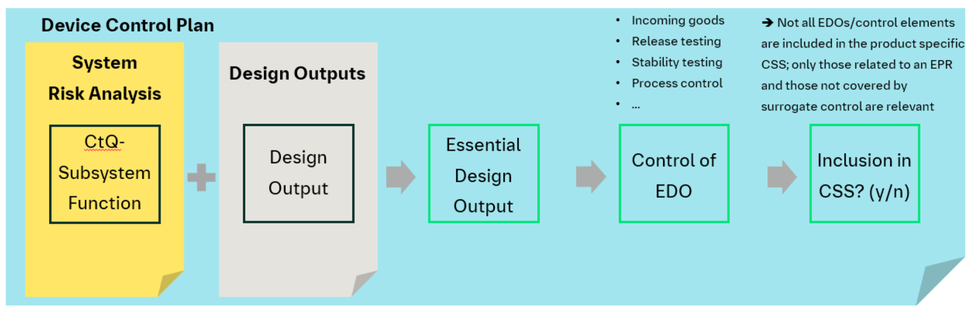
Critical to Quality is a DDCP sub-system function and/or attribute that contributes to a Critical Function of the final DDCP.
EPRs are those H2-CtQs sub-system functions relevant to accurately deliver the medicinal product via the correct route of administration at the point of use.

Device Control Plan

EDOs

Device Control Plan:
The Device Control Plan lists the identified CFs, PFs, EPRs, and CtQ sub-system functions. To establish a Device Control Plan, the CFs and CtQ sub-system function must be linked to a DO, which then becomes an Essential Design Output (EDO). As EDOs are critical to quality, an adequate and effective method of control shall be established for each EDO. Methods of control can be, for example, release testing, incoming goods inspections, or manufacturing controls. However, not all EDOs have to be inlcuded in the product specific CSS. In the Device Control Plan, a justification is given why control elements are included or not.

Device Control Plan – Process overview: 1. Identify EDOs 2. Control of EDO 3. CSS Relevance

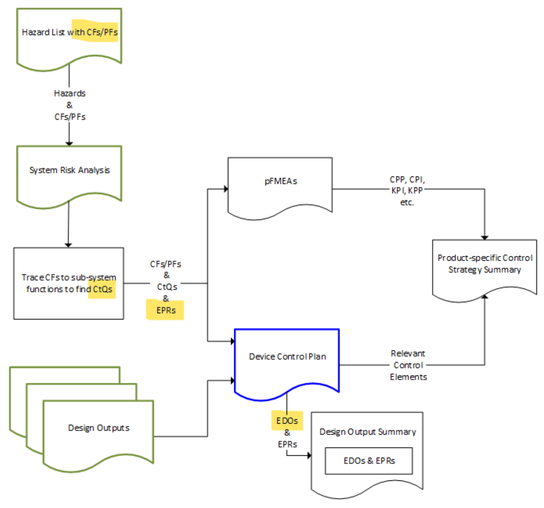


EDOs are all device attributes whose control is necessary to ensure safe and proper functioning of the DDCP.

Example:

Information from System Risk Analysis				Information from Design Output document					Information to be established by the team within this document.			
CF/PF on H1 DDCP System Level	H2 CtQ Function	H3 CtQ Function	H3 Subsystem	Design Output (DO)	DO related to EPR? (y/n)	DO-ID	Essential Design Output	EDO ID	Control	Control Category	CSS? (y/n)	Justification / Comment
Combination Product Stability	Drug solution visibility	Syringe appearance	PFS	Syringe color	no	DO-PP-030	Colorless glass	Appendix 2, § 5.3	Incoming Goods Inspection	Incoming goods	No	Syringe appearance is a CMA in the primary packaging risk assessment and therefore is already included in the CSS via the primary packaging risk assessment as Level 1 source document.
Dosing	Dose accuracy	n/a	n/a	Deliverable volume	yes	DO-NIS-130	≥ 2.0 mL	see DO-ID	Implement control of Dose Accuracy/Deliverable volume during release testing and stability of DDCP	Release Testing and Stability	Yes	n/a
Dosing	Dose accuracy	Filled stopper position (PS1)	PFS	Plunger stopper position (PS1a)	yes	DO-PFS-040	6.5 – 10.3 mm	see DO-ID	in process control during fill & finish of the PFS.	IPC	No	Already included in the CSS via the process controls of the fill & finish process.

General overview:
The overview on the right shows the entire process for incorporating all critical elements into the control strategy summary.



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