Considerations for Developing an Autoinjector Control Strategy: A Case Study

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Overview

- What is a combination product?
- Development framework comparison
- CQAs and Essential Drug Delivery Outputs (EDDO)
- Control strategies for combination products
- Case study example

Combination Products

What are they and development framework comparison

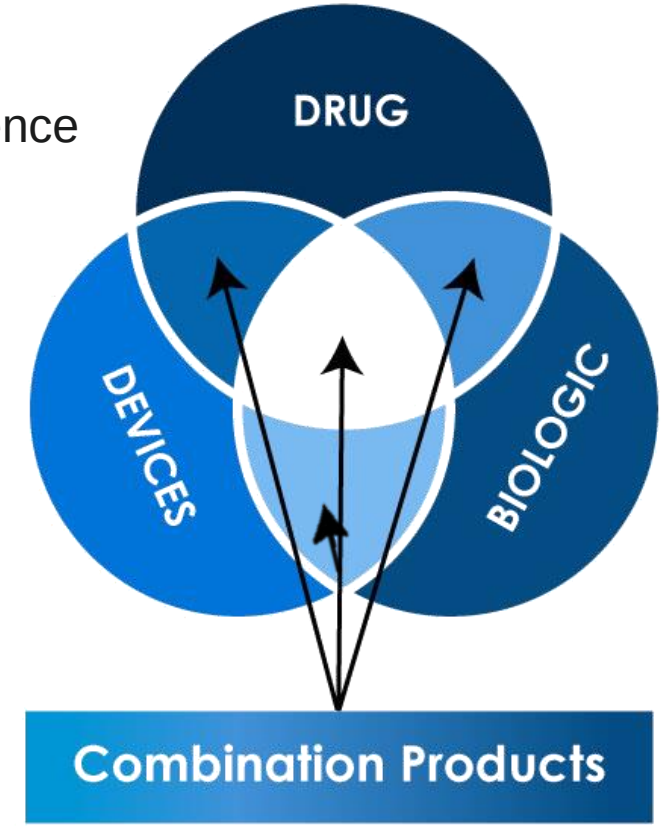
Combination Products

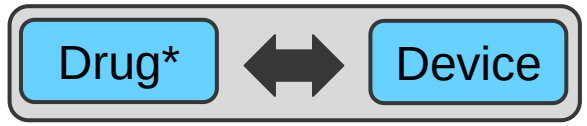
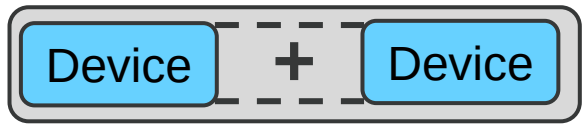
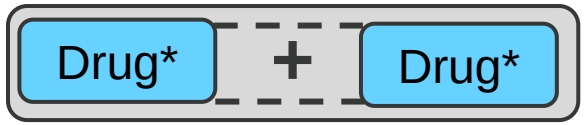
What?

- Combines two or more different constituents (drug, device or biologic)
- Regulatory definition varies by region/country; driven by the Primary Mode of Action (PMOA)

Why?

- Enhances therapeutic efficacy, safety and/or patient (user) convenience
- Growing demand for personalized medicine and self-administration
- Market differentiation (innovative in delivery systems)



Combined Products	US	EU
	**Combination Product** Single-entity, CD/BER (+CDRH)	**Integral drug-device combination**
	**Combination Product** Single-entity, CDRH (+CD/BER)	**Medical device with ancillary substance**
	**Combination Product** Pkg together, CD/BER (+CDRH)	**Medicinal product;** **Medical device**
	**Combination Product** Pkg together, CDRH (+CD/BER)	**Medical device;** **Medicinal product**
	**Combination Product** Cross-label, CD/BER +CDRH	**Medicinal product;** **Medical device**
	**Convenience Kit**	**Procedure/System Pack**
	**Fixed Dose Combination Product**	**Medicinal product(s)**

Legend: **PMOA** **Package**

*** Could be drug or biologic in this context**

Chipperfield and Chesworth, Regulatory Rapporteur – Vol 15, No 5, 2018 (modified)

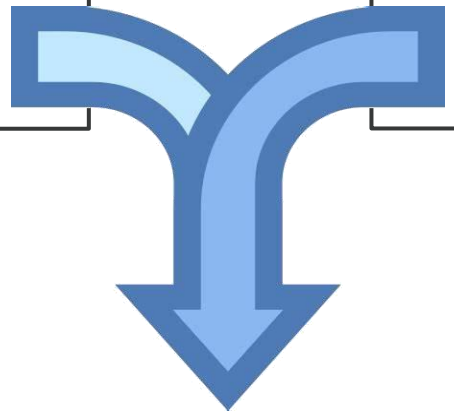
Development Framework Comparison

Biologic/Drug Constituent

- Quality by Design
- Design space based on process (inputs/parameters) as a function of impact on CQAs
- Impact of variability from product manufacturing (PROCESS)

Device Constituent

- Design Controls
- Design space based on physical aspects as a function of impact on device performance
- Impact of variability from physical and mechanical attributes (DESIGN)



Combination Products merge these concepts for an integrated approach to meet regulatory requirements

PDA Combination Product Development & Regulatory Best Practices: Drug/Biologic PMOA Perspective (modified); Suzette Roan; Mar 2019

CQAs vs. EDDOs

CQA Identification

- CQAs are identified based on the **severity of impact on quality, safety and efficacy** resulting from failure to meet that quality attribute
  - Identified before taking controls into account
  - May change as a result of further product knowledge during development

QbD process applies risk-based identification of potential CQAs and is coupled with quality risk management to develop the control strategy

Essential Drug Delivery Output (EDDO)

- By definition, EDDOs are design outputs necessary **to ensure delivery of the intended drug dose to the intended delivery site**

- These function-based EDDOs, similar to CQAs, feed into a risk-based control strategy (through Design Controls)

- Certain (drug) CQAs may be applicable for the device constituent of combination products

Examples of potential CQAs for device (delivery systems)

- aerodynamic properties for inhaled products
- sterility for parenterals
- adhesion properties for transdermal patches

Example: Is it an Autoinjector EDDO?

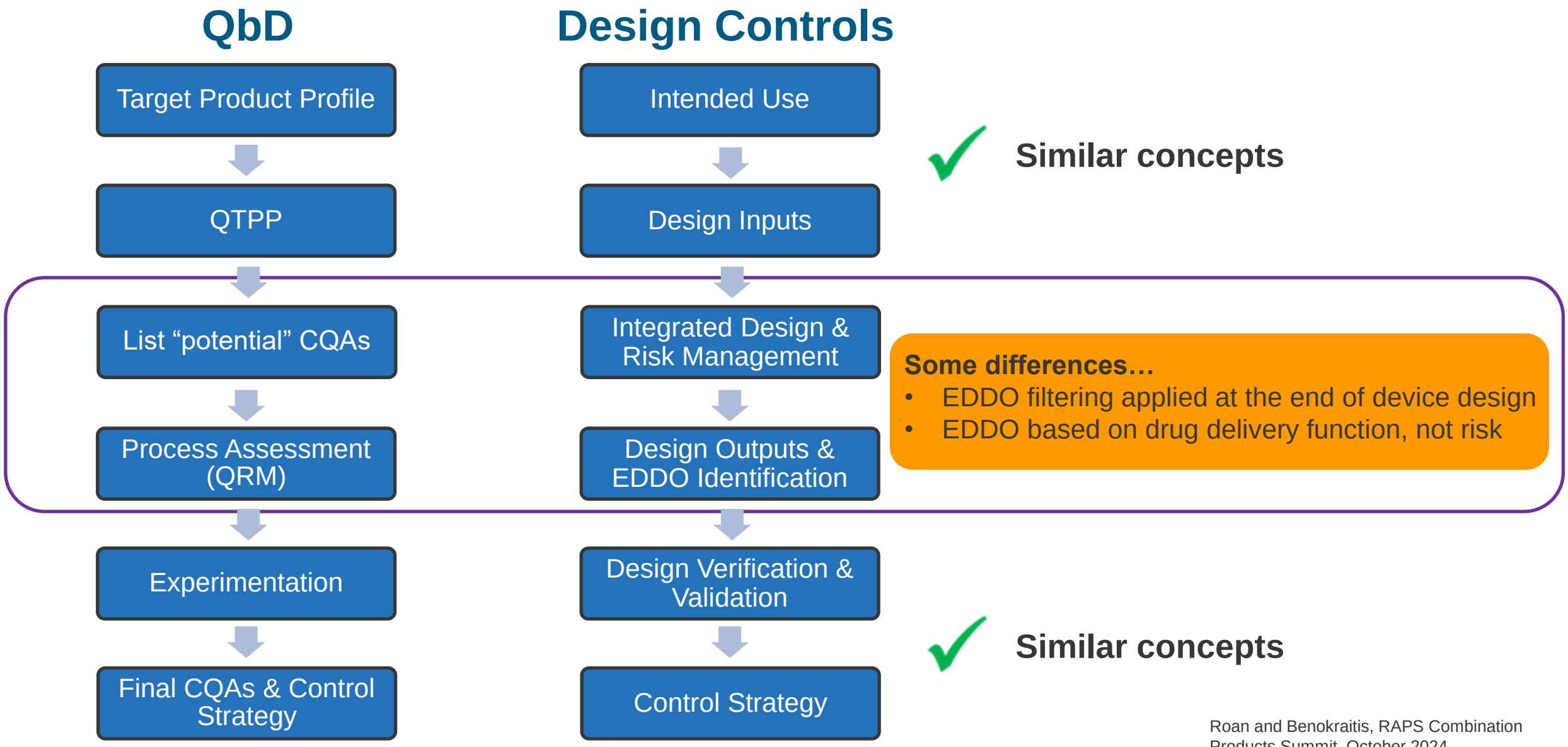
Yes

- **Extended Needle Length**
  - Ensures the needle is at the right depth and is dependent on the device
- **Injection Time**
  - Ensures the drug is delivered to the intended space within the appropriate time and is dependent on the device not the user

No

- **Needle Length (PFS*)**
  - It is a component level output because it influences but is subordinate to the extended needle length function
- **Breakloose / Glide Force (PFS*)**
  - It is a component level output because it influences but is subordinate to the injection time function

*** Prefilled Syringe is the primary container**



Roan and Benokraitis, RAPS Combination Products Summit, October 2024

Control Strategies for Combination Products

When developing a control strategy for an EDDO, it is important to consider the **attributes and manufacturing process steps that can influence the EDDO**, and describe why these attributes or process steps are the only ones that influence the EDDO.

Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products, Draft Guidance for Industry

Control Strategy: Types of Controls

- Design controls
- Purchasing/supplier controls
- Manufacturing controls
  - Upstream controls (incoming, in-process testing, etc)
  - Downstream controls (release testing)

A control strategy is used to ensure that the final finished combination product maintains its EDDO(s)

The type and number of controls implemented should correspond with product risk

Control Strategy … Strategy

- What design characterization/testing has been conducted?
- Why are the controls the right controls?
- Are the controls placed at the right point?
- Why is the acceptance criteria appropriate?

(Theoretical Example) Controls for Activation Force (EDDO)

Control Strategy "Approach A"
• Spring wire incoming inspection (COA) • Spring coiling process validated • In-process control (IPC) test at supplier for spring coiling process • Autoinjector sub-assembly release testing for spring compression force at supplier • etc

OR

Control Strategy "Approach B"
• Final lot release testing for Activation Force of finished product

Case Study: Autoinjector

Case Study (Example): Autoinjector Control Strategy

- Company XYZ is developing an Autoinjector for delivery of a novel drug
  - To be used in an upcoming Phase 3 study
  - Planned as a commercial device presentation for ease of use by patients
  - Intended for emergency use

- Elements involved in the design and process:
  - **Components:** provided by suppliers for the primary container and Autoinjector subassemblies
  - **Manufacturing the primary container (PFS):** filling and stoppering the syringes with drug
  - **Assembly of the Autoinjector:** enclosing the PFS into the Autoinjector subassemblies
  - **Final label and pack:** labeling and packaging of the finished product

Step 1: Identify EDDOs

Identified EDDO*	Functioning "Step"	Why?
Dose Accuracy	Delivery of intended dose	The automated dose delivery is necessary to ensure appropriate drug delivery.
Extended Needle Length	Delivery to the target site	It ensures the needle is at the right depth and is dependent on the device.
Cap Removal Force	Product preparation	Cap removal in emergency use case needs to be completed before the injection can be administered and it is dependent on the device.
Activation Force	Initiation of dose delivery	It initiates drug delivery and is dependent on the device not the user.
None identified	Dose delivery progression	N/A
Injection Time	Dose delivery completion	It ensures the drug is delivered to the intended space within the appropriate time and is dependent on the device not the user.

As noted in FDA draft guidance, depending on the design and use, there may be alternate or additional EDDOs

Step 2: Identify attributes and process steps which may impact EDDOs

Identified EDDO	Influencing attributes and manufacturing process steps
Dose Accuracy	• PFS component dimensions • Fill/finish process and stopper position • Insertion/placement of PFS in autoinjector subassembly
Extended Needle Length	• Needle/PFS component dimensions • Insertion/placement of PFS in autoinjector subassembly
Cap Removal Force	• Cap/PFS component dimensions
Activation Force	• Interaction of autoinjector subassemblies (dimensions, assembly, etc)
Injection Time	• Spring component force specification • Break loose and glide force (PFS)

Step 3: Assess design, risk and process characterization

- Purchasing Agreements with critical component suppliers
- Tolerance stack analysis of (dimensional) attributes influencing EDDOs
- Design verification testing
- Identify upstream / downstream controls
  - The number and type of controls implemented should correspond with risk
  - Understand and justify if any downstream processes do not impact EDDOs

Step 4: Control Strategy for Clinical (Development)

	Upstream Controls		Downstream Controls	
	Purchased Components	**Drug Product (Fill/Finish)**	**Autoinjector Assembly**	**Labeling & Packaging**
Dose Accuracy	• CoC empty syringes and plunger stoppers	• IPC: extractable volume and stopper position • Release testing: expelled volume (PFS)	• Release testing: injection indicator (plunger rod position)	• Release by final manufacturer made based on upstream testing (PFS, assembled autoinjector, etc). • Justification for why attribute is not impacted by labeling and packaging processes.
Extended Needle Length	• CoC functionality visual inspection	• Justification for why attribute is not impacted by this process	• Release testing: extended needle length	
Cap Removal Force	• CoC for autoinjector subassembly	• Justification for why attribute is not impacted by this process	• Justification for why attribute is not impacted by this process	
Activation Force	• CoC for autoinjector subassembly	• Justification for why attribute is not impacted by this process	• Justification for why attribute is not impacted by this process	
Injection Time	• CoC empty syringes and plunger stoppers • In-process testing of spring compression	• Release testing: DP concentration	• Release testing: injection time	

As noted in FDA draft guidance, depending on the design and use, there may be alternate or additional EDDOs and controls necessary

What if…

- There is prior knowledge (i.e.; device is the same design/technology used for other products within company's portfolio)

- Potential control strategy changes between clinical and commercial
  - Is the manufacturing process changing?
  - Is there additional characterization testing (across lots)?
  - etc

Key Takeaways

- Development frameworks for drugs and devices have similarities, but also differences
- **EDDOs** are based on drug-delivery function, not risk
- **EDDO controls** ensure the product **meets the device drug-delivery function quality standards**
- Number and types of controls implemented **should correspond with risk**