Maintaining an Integrated Control Strategy Over the Combination Product Lifecycle

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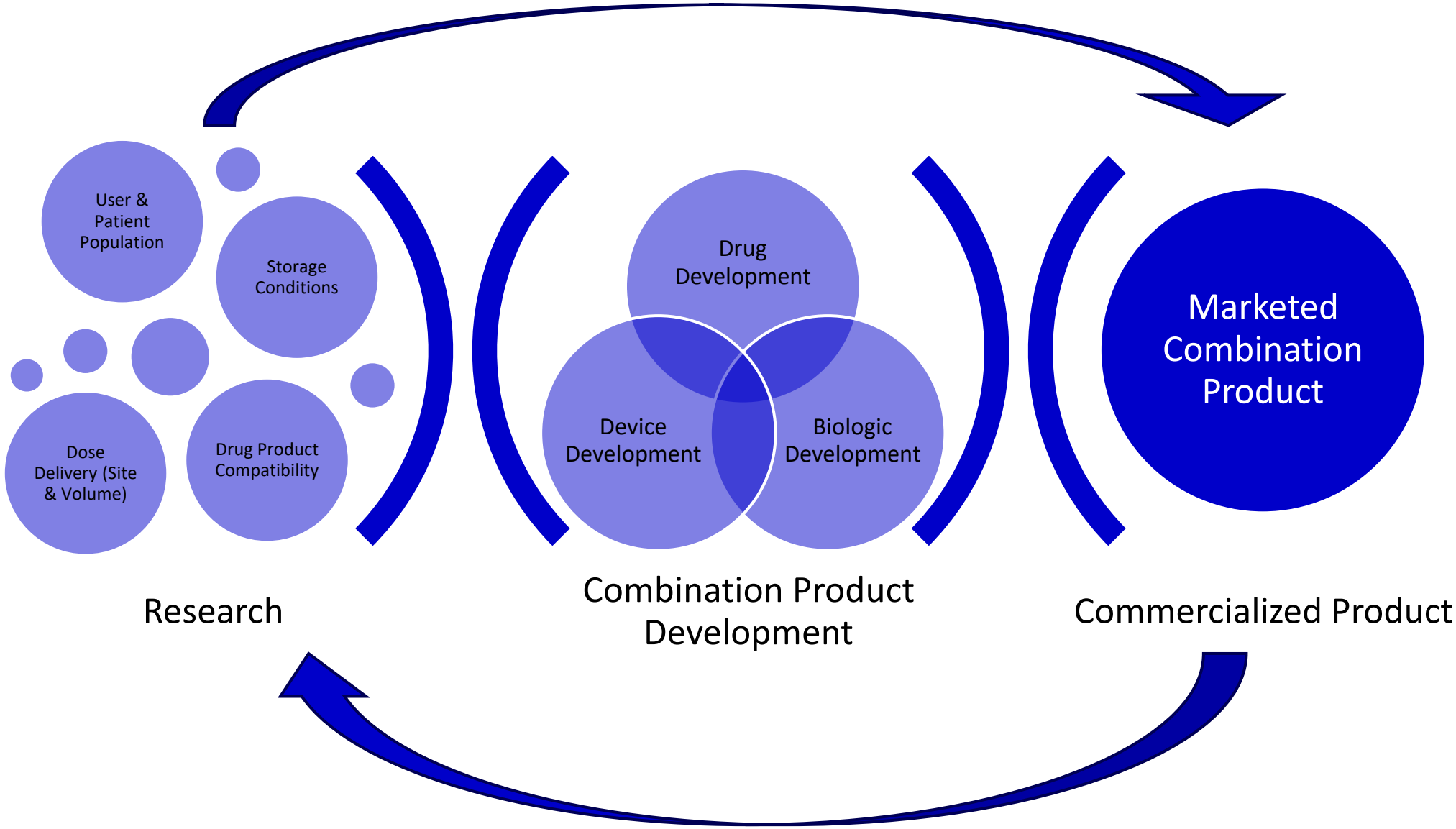
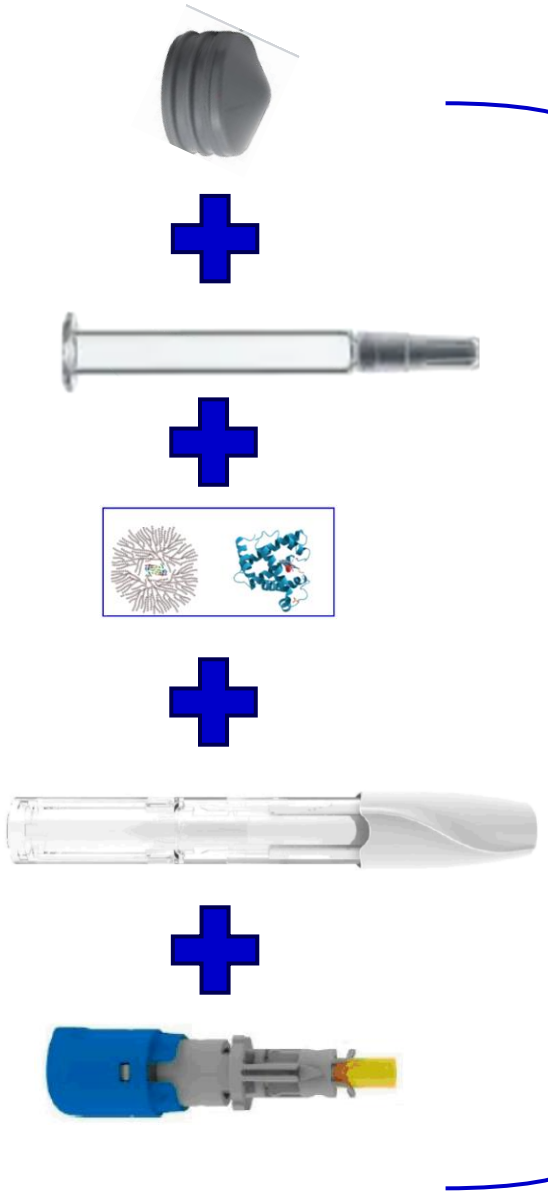
Combination Product Lifecycle Management – Simplified View



Potential Changes that might occur after commercialization



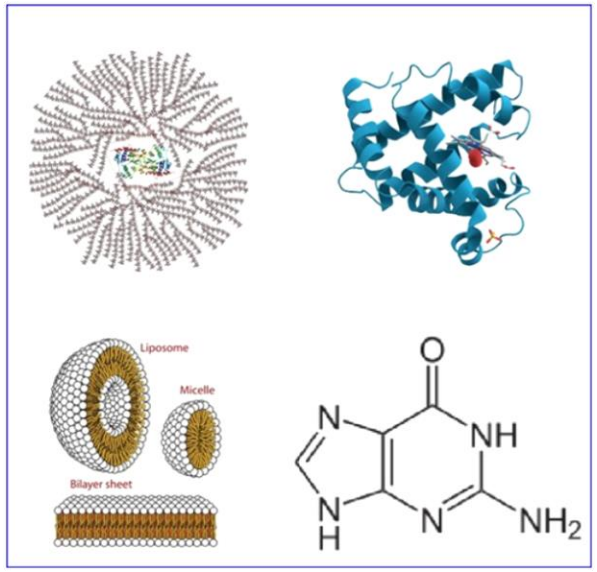
Marketed Prefilled Pen (PFP) for subcutaneous delivery

New Concentration PFP

Potential Pediatric Variant PFS

Component Changes

Understanding the Interfaces between Drug and Device



Drug product solution:
CQA and non-CQA

Components:
Syringe barrel & plunger stopper

Development of Primary Container

Formulation
Interfacing Drug CQA
Drug Stability
Delivered Volume
Concentration

Compatibility
Drug Stability
Contact surface
Siliconisation
Biocompatible, E&L

Syringe Driven Quality Attributes
BLEF
Needle
Drug Viscosity
Injection rate
Fill volume

CCI and Fit to Device
Dimension and metrology
Barrel Properties

Development of Device Combination Product

Interfacing Device Attributes
Device Stability/Shelf-life
Biocompatible, E&L
Delivered Volume/Volume of Injection
BLEF/Injection Rate
CCI

Grounding Changes in Risk Management and Existing Control Strategy Framework

What Are the Risks?

- What are risks to drug product quality (i.e ICH Q9)?
- What are the risks to device functionality (i.e ISO 14971)?
- What are the risks to the patient/user (i.e ISO 14971)?

What are the impacts?

- What the critical attributes are potentially impacted by the is change (consider both drug and device attributes)?
- What prior knowledge (i.e process understanding, device characterization, etc) informs this change?

Control Strategy Changes?

- What changes to attribute control or process control are required (consider both drug and device control strategies)?

New Strength in the Same Volume

Initial Marked PFP

New Concentration

What Are the Risks?

- Increased concentration may correspond with increased solution viscosity impacting performance. Increased concentration may have worse physical stability (i.e aggregation, etc).
- Potential User Impact: Increased injection time leads to use error/compliance.

What are the impacts?

- Drug Product Attribute Impacts: Solution Properties/Material Compatibility
- Device Attribute Impacts: Injection Time (PFP); Extrusion Force (Syringe)

Control Strategy Changes?

- While complex change may require confirmation of product on stability, fundamentally the identified impacted attributes may have a suitable control strategy already defined.

Reduced Volume to Reduce Overall Dose

Initial Marked PFP

Supplemental Pediatric Variant

What Are the Risks?

- Introduction of a reduced dose in a new patient population requires evaluation of the new dose volume as well as patient centric specifications given change in population.

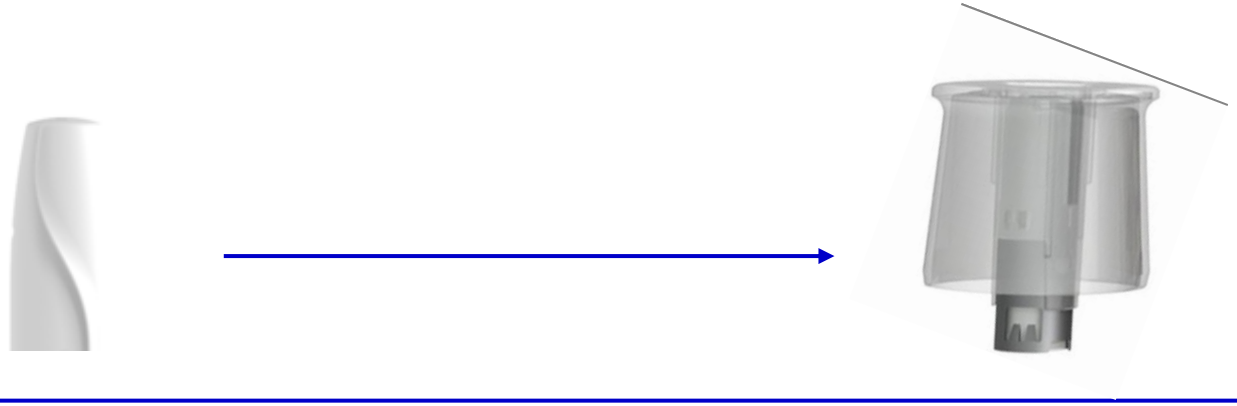
What are the impacts?

- Drug Product Attribute Impacts: Fill Volume (Syringe; PFP)
- Device Attribute Impacts: Delivered Volume (PFP); Needle Depth (PFP); Activation Force (PFP)

Control Strategy Changes?

- Evaluation of needle depth for population change; if required, modification of control strategy to account for adjustment (re-design; etc)
- Activation Force Considerations

Cap Design Change



What Are the Risks?

- Introduction of a new cap design (i.e dimension change, material change, etc), which has no drug product contact.
- Potential User Impact: New User interface with the cap

What are the impacts?

- Drug Product Attribute Impacts: N/A – non product contacting
- Device Attribute Impacts: Cap Removal Force

Control Strategy Changes?

- Cap Subassembly Controls (new dimensions, etc)
- Cap Removal Force Considerations

How and Where to Tell the Story of Holistic Drug/Device Control Strategy

Control Strategies for a specific Quality Attribute often encompass several different elements, which details may be spread out across several sections within Module 3. If change impacts a quality attribute and control strategy many sections could be impacted.

(Example) Control Strategy for Glide Force/Injection Time may be presented in several elements:

Understanding requirements – i.e specification limits? – P.2 Intro - QTPP

- User population – P.2.4
- Autoinjector design – spring force – P.2.4
- Justification of Specifications – P.5.1

Viscosity

- Molecular design – intrinsic property of molecule – P.2.2
- Concentration of protein/API – P.2.2
- Formulation excipients – P.2.2

Syringe (cartridge) – control of components

- Needle inner diameter – P.2.4, P.7
- Plunger / barrel lubrication – P.2.4

Test methods

- Speed relevant to time (duration of injection) – P.2.4, P.5
- Variability, reporting of results – P.2.4, P.5

Design Verification

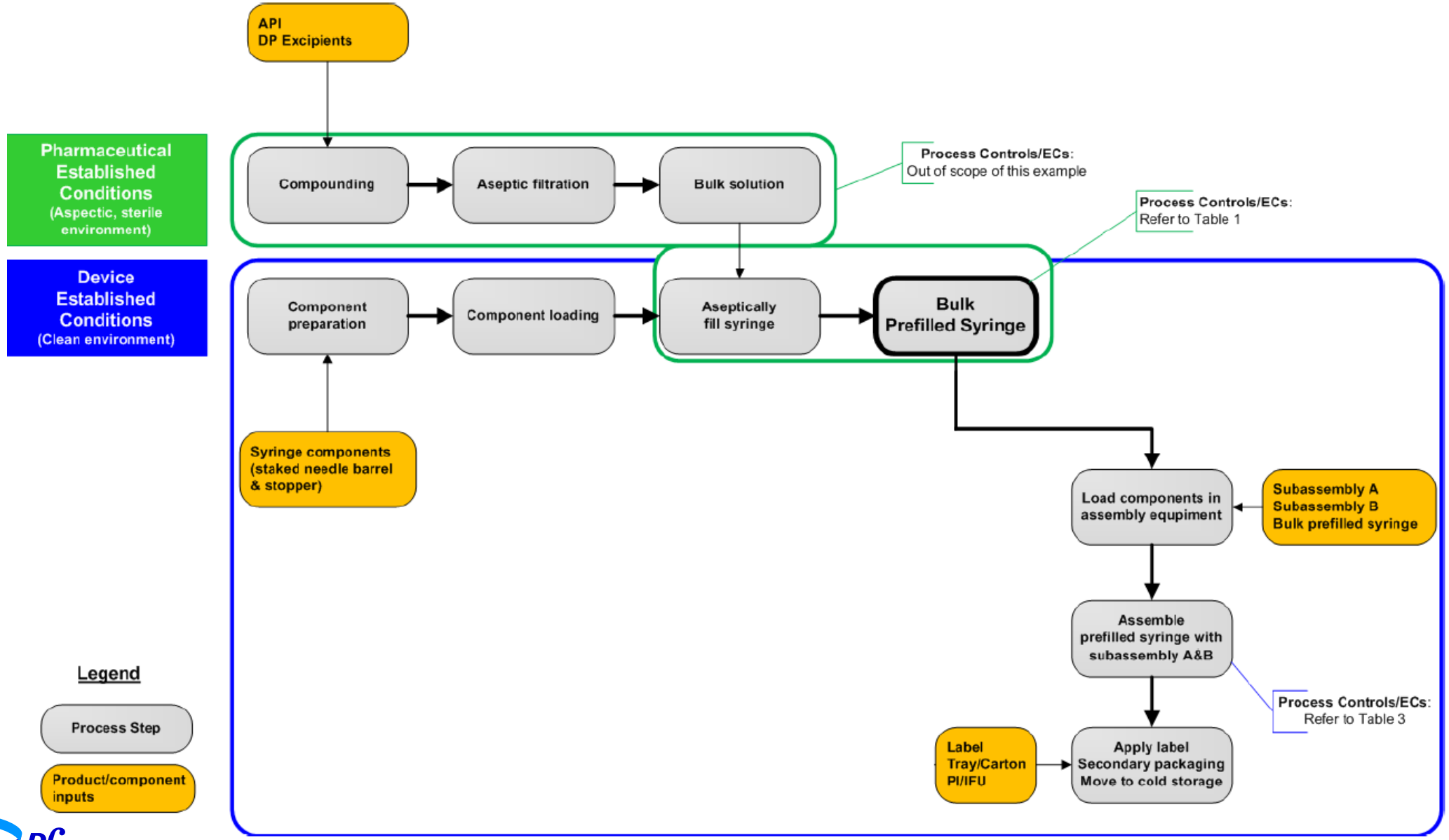
- Reliability – P.2.4
- Confidence in assessment – P.2.4

Stability – P.2.4, P.8

Process Validation – P.3.5

Routine Controls – P.3, P.5

Regulatory considerations for Lifecycle Management (ICH Q12) – What's the mechanism to implement the change?



Summary

A patient-first and risk-based control strategy provides the foundation for a robust product and process development to ensure the combination product quality throughout the product lifecycle

Understanding drug-device interfaces can inform where there is potential for risk as well as what additional work may be required

Be mindful initial regulatory filing approach and what conditions (both pharma and device) are considered established to inform how changes, including control strategy changes should be processed