Risk Management Activities during Development & LCM of a Drug Device Combination Product

Alice Maden

Associate Director, Regulatory Affairs, BD

Agenda

1/ Established US & Under Construction EU Combination Products Frameworks

2/ Risk Management through US & EU Texts

3/ Risk Mitigation By Design: the System Approach

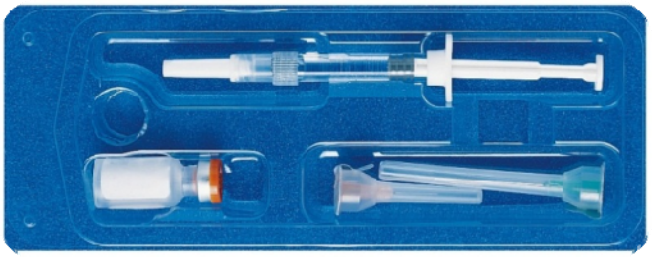
1/ Established US & Under Construction EU

Combination Products Frameworks

Definition of a combination product

- As defined in 21 CFR 3.2(e)

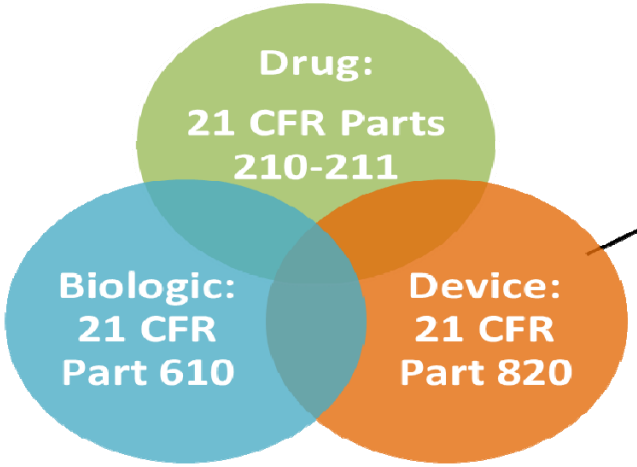
Single entity
(combined into one)



Co-packaged (sold together)

Cross labelled
(dependent)

Food and Drug Administration 21 CFR Part 4
cGMP for Combination Products & Final Guidance



- Management Responsibility (820.20)
- Design Controls (820.30)
- Purchasing Controls (820.50)
- Corrective/Preventive Action (820.100)
- Installation (820.170)
- Servicing (820.200)

Drug Device Combination Product: DDC was born…

"in situations where the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, **the medical device is not assessed by a Notified Body and assessment of all of the above aspects, including compliance with Annex 1 to the MDD, is conducted as part of the assessment of the application for marketing authorisation.**

Draft Concept paper
November 2016,
EMA/CHMP/QWP/BWP/66
1488/2016, (CHMP)

EU MDR, April 2017

"the marketing authorisation dossier shall include[…] **the results of the assessment of the conformity of the device part with the relevant general safety and performance** requirements"

"the authority shall require the applicant to provide **an opinion** on the conformity of the device part with the relevant general safety and performance requirements […] **issued by a notified body"**

"Council Directive 2001/83/EC will be amended to include a specific requirement for medicines marketing authorisation applications to include a **Notified Body report on the conformance assessment of integral device components** to comply with the general safety and performance requirements of Annex I of the new MDR"

Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products
Version 1.0
September 2017

PDA
Parenteral Drug Association

2/ Risk Management in Main US & EU Texts

EU OVERVIEW OF DDC Risk Management

Draft Concept paper EMA/CHMP/BWP, November 2016 *Human Medicinal Products (CHMP)*

Medical devices supplied as integral to a medicinal product, such as pre-filled syringes, inhalers, and auto-injectors, are more complex than container-closure systems […] Complex DDCs have the highest risk of inappropriate usage. DDC fitness for the intended purpose (e.g. administration of a medicinal product) needs to take into account the Quality aspects of the device in itself and its use with the particular medicinal product, as well as the complexity of the device component, the patient characteristics, the caregiver characteristics where relevant and the clinical situation in which the DDC is to be used.

Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products *MHRA, September 2017*

"The risk of medication error due to the device component should be considered in the Risk Management Plan for medicinal products incorporating an integral medical device"

"For drug delivery devices with well-established platforms […]a simplified approach, e.g. risk-based usability assessment rather than formal usability engineering studies may be acceptable, based on the intended user group and environment of use."

FDA Guidance cGMP's for combination products

« manufacturers must perform risk analysis where appropriate, which should **begin early in the design process and continue throughout the lifecycle for the product.** Risk analysis should enable identification of unacceptable risks so that they can be mitigated. It **influences other aspects of design control [**…] Although existing **risk analysis for products used as constituent parts** of the combination products **may be relevant,** risk analysis should **include considerations for the combination** product as a whole […] **Some** risks may be identifiable during **initial design development and addressed in design inputs,** while others may become apparent **later** in **product development, during premarket review, or based on postmarket experience** (including adverse event reporting) and used to determine whether any aspect of the design should be modified. "

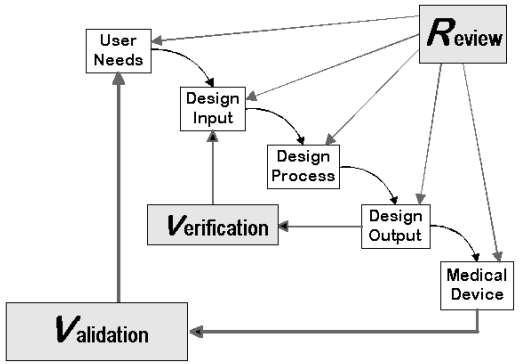
Design Control Guidance for MD Manufacturers CDRH, 1997

[…] **begins with the development of the design input requirements**. As the design evolves, new risks may become evident. To systematically identify and, when necessary, reduce these risks, the **risk management process is integrated into the design process**. In this way, unacceptable risks can be identified and managed earlier in the design process when **changes are easier to make and less costly**."

" Congressional concern that **device manufacturers were carrying out product corrections or removals without notifying FDA** or not doing so in a timely fashion. Congress explained that industry's failure to report corrections and removals, particularly those undertaken to **reduce risks associated with the use of a device, "denies the agency the opportunity to fulfill its public health responsibilities by evaluating device-related problems and the adequacy of corrective actions"** and "has seriously interfered with the FDA's ability to take prompt action against potentially dangerous devices"

"FDA believes that **correction and removal reporting and record keeping for combination products containing a device constituent part is necessary to protect the public health** as envisioned by Congress, by ensuring that the Agency has current and complete information regarding those actions taken by applicants to reduce risks to health caused by their products."

Combination Products Risk Management: the device related part



Development

Iterative, periodic and integrated process of Risk Management

New design/specs

Post Market

Unidentified and/or modified failure mode?
Adjusted Severity?
Out of trend deviation?

- Need for a formal, periodic & agile process
- Strengthened partnership with suppliers: integrated approach along:
  - **New Product Launch**
  - **Post market surveillance**
  - What about Life Cycle Management?

Life Cycle Management through Risk Assessment

"Level of risk to public or animal health and the impact on the quality, safety and efficacy of the medicinal product concerned."

"Potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product."

Criteria to assess Importance of change according to Health Authorities

"ICH Q9: Risk Management: Change management/change control:

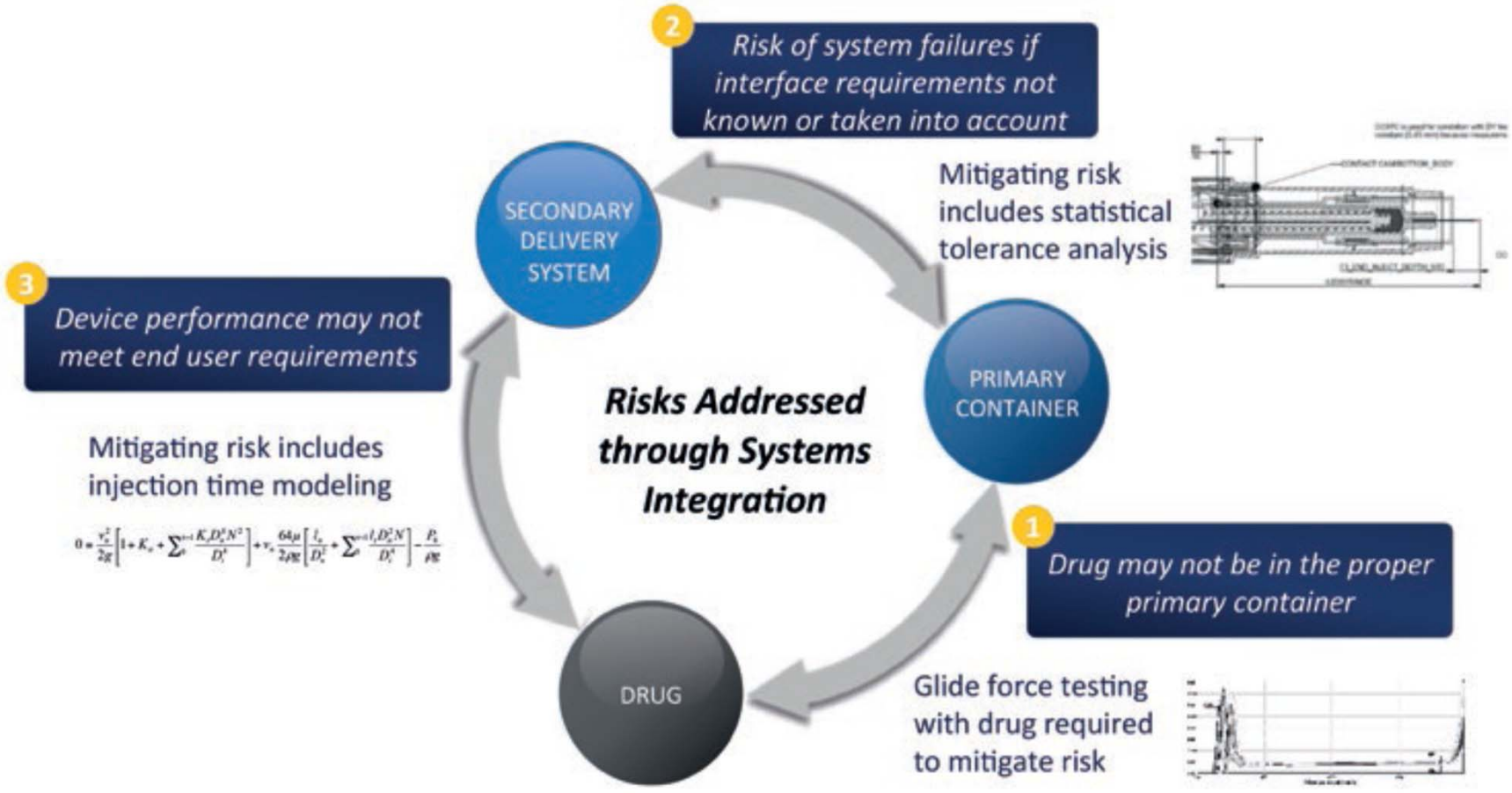
⇒ To evaluate the impact of the changes on the availability of the final product

⇒ To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process, or technical transfers

⇒ To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation, or communication with regulators"

What if the glass supplier changes? What if silicone in my syringe is slightly different?

3/ Risk Mitigation By Design: the System Approach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Risk of system failures if interface requirements not known or taken into account
Mitigating risk includes statistical tolerance analysis
SECONDARY DELIVERY SYSTEM
3
Device performance may not meet end user requirements
Mitigating risk includes injection time modeling
Risks Addressed through Systems Integration
PRIMARY CONTAINER
1
Drug may not be in the proper primary container
DRUG
Glide force testing with drug required to mitigate risk

Risk Mitigation: THE VALUE OF INTEGRATION

Pharmaceutical Companies who purchase components separately take on additional risks that can be significantly reduced by selecting an integrated system instead.

System integration provides value to pharma and patients at several levels:

⇒ A well integrated system anticipates and mitigates system performance risks early in development.

⇒ Single supplier can perform system validation and design verification testing on established reference systems, challenging system performance at the limits of process capability.

⇒ Single supplier can also anticipate where problems can arise throughout the development process and how to troubleshoot them effectively.

⇒ Single supplier has a unique appreciation of nuances in meeting ISO standards.

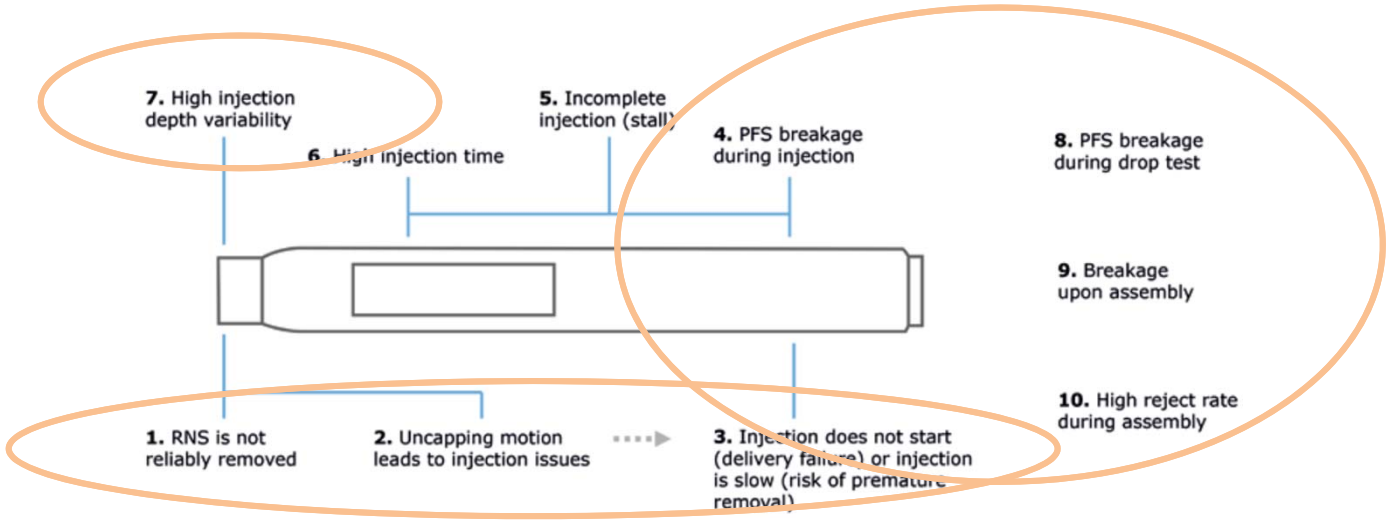
High degree of supplier accountability & strengthened partnership for a successful Drug Device Combination Product development

Real-world challenges faced with non-integrated components from different suppliers

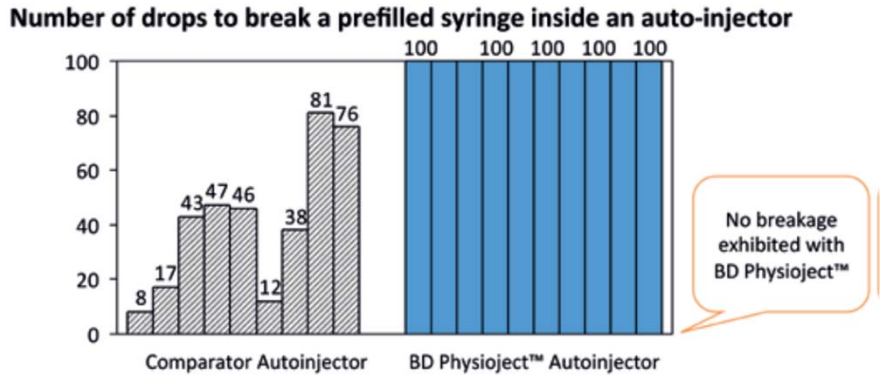
Cap Removal Malfunction & Wasted Drug: When patients remove the cap from an auto-injector, rigid needle shield (RNS) not always be pulled from the needle. The result could be an uncapping motion that damages the needle and the drug delivery device.

Needle Extension Variability: Needle depth not always well-controlled or understood when the auto-injectors and prefillable syringes are combined. unexpected clinical outcomes when bridging from syringe injection to auto-injection.

Primary Container Defects: Component dimensional variability not always well accounted for in the design of the auto-injector assembly process. Higher reject rates and possible primary container breakage during assembly



Case Study: PFS +AI Integrated System Solution



Comparison of auto-injectors with 1.0 mL prefilled syringes, filled with water. The same type of syringe was used inside all auto-injectors tested. Each bar represents one auto-injector. Auto-injectors were dropped (ISO 11608) a maximum of 100 times, or until prefilled syringe exhibited breakage. All BD Physioject™ samples confirmed intact by X-ray analysis. (BD internal study.)

⇒ Proprietary prefillable syringe (PFS) component specifications
⇒ Critical dimensions to assembly which incorporate both BD Physioject™ and PFS
⇒ Aligned assembly process design & guidance provided for system assembly

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