Regulatory perspectives on CQAs, CPPs, and Risk Analyses for Combination Products.

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TRACK #2 Achieving Drug Product Quality: Novel Approaches and Applications
Session 5. Drug/Device combination products: Quality

Douglass Mead, Senior Director, Regulatory Affairs CMC,
Medical Devices and Combination Products

Janssen Research & Development, LLC

PQRI Product Quality Research Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

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Topics

- Primer on Combination Product Regulations
- How do drug and device guidances on Risk Management and Quality differ?
- How are these guidances applied to CQAs and CPPs for Combination Products?
- Q & A

Combination Product Regulations – the Basics

US FDA

A Combination product is defined as a "combination" of a drug and/or device and/or biologic (any two or all three) that is "marketed together." (21 CFR 3.2) For a drug PMOA:

- "**Single-entity**" or "integral" (e.g., prefilled syringe/injector; MDI)
- "**Co-packaged**" or "kitted" (e.g., Vial with syringe and needles)
- "**Cross-labeled**" (e.g., branded drug and separately supplied device intended for use together with mutually conforming labeling)

EU EMA/EC

Defines only: "Medicinal Products" (Drugs, Biologics, ATMPs), or "Medical Devices" that are CE Marked.
Integral drug-device combinations (e.g., prefilled pens, MDIs) are **also** "**Borderline Products**" (MDD/MDR MEDDEV 2.1/3) regulated as medicinal products. Follows the MPD plus conformance to the Annex I Essential Requirements of the Medical Device Directive (Medical Device Regulation)

Other Markets

Drug-Device combination products generally assigned as drug/biologic product or a medical device; Few formal regulations – requirements negotiated; Some markets have clearer guidances

Not…

Fixed-combination (drug-drug) prescription drugs regulated as drugs (21CFR 300.50), or drugs & devices used concomitantly

Combination Product Quality Regulations

- New (2013) "Combination product" cGMP rule (21 CRF Part 4) provides for a "streamlined" Quality System for drugs using a foundational Part 211 system plus elements from Part 820:
  - § 820.20. Management responsibility.
  - § 820.30. Design controls.
  - § 820.50. Purchasing controls.
  - § 820.100. Corrective and preventive action.
  - § 820.170. Installation & § 820.200. Servicing.
- These new GMPs have significantly changed pharmaceutical development practices, commercial operations, and partnership/supplier relationships.

Design Controls drive combination product development

- Design and Development Planning (Device/Combination Product Development Plan)
- Design Inputs (What does the user/patient require of the device? What technical and "suitability" characteristics are required of the device? How do you consider design inputs related to a **biopharmaceutica**l?
- Design Outputs (design phase - performance acceptance criteria, specifications, drawings) May be used to specify off-the-shelf products. Some **biopharmaceutical** specifications are also Design Outputs
- Design Verification [bench performance tests to confirm specifications (Outputs) are met] Confirmation that the specific device(s) are suitable with a specific **biopharmaceutical**.
- Design Validation [Establishing by objective evidence that the device(s) meets user needs and intended uses (Design Inputs); user/clinical/human factors studies with testing of the IFU, process validation, functional stability] Tested with the target population (and for/with **biopharmaceutical**, where necessary).
- Design Changes: document/approve design changes and reasons during development. Provides for device changes postapproval.
- Risk Analysis is required periodically during the development process.

Quality related ICH, ISO and FDA Guidances

- ICH M4Q - Container Closure – "The suitability of the container closure… "reproducibility of the dose delivery from the device when presented as part of the drug product." (3.2.P.2.4 and 3.2.P.7)
- ICH Q6A Specifications: Test Procedures and Acceptance Criteria: "…parenteral formulations packaged in pre-filled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system." (3.2.P.5)
- ICH Q1A (R2) Stability Testing: including "functionality tests (e.g., for a dose delivery system)" (3.2.P.8)
- ISO Standards: Particular requirements
  - **ISO 14971**:2012, *Medical devices — Application of risk management to medical devices*
  - ISO 20072:2009, *Aerosol drug delivery device design verification — Requirements and test methods*
  - ISO 11608 – Current series on **injection systems**
- FDA Guidances:
  - Container Closure Systems (May 1999) - Associated Components: **suitable/protect/compatible/safe/function properly**; Guidances on **cGMPs, Human Factors**, PFS/Injectors/MDI/DPI/nasal sprays/patches, etc.

Regulatory Requirements for Drug-Device Functionality

- ICH Q8(R2) "Pharmaceutical Development (2009)":
  - "**Critical Quality Attributes** (CQA) (3.2.P.2.2): "CQAs for other delivery systems can additionally include more product specific aspects, such as **aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches**."
  - "Drug Product Container Closure System (3.2.P.2.4): "If a dosing device is used (e.g., **dropper pipette, pen injection device, dry powder inhaler**), it is important to **demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions that, as far as possible, simulate the use of the product.**"
  - "Identifying (through, e.g., prior knowledge, experimentation, and **risk assessment**) the material attributes and process parameters that can have an effect on product CQAs"
  - Annex:
    - **Quality Target Product Profile –** "The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:" "Intended use in clinical setting, route of administration, dosage form, **delivery systems**;" "Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., **dissolution, aerodynamic performance**) appropriate to the drug product dosage form being developed."

Regulatory Requirements for Drug-Device Quality

- ICH Q9 "Quality Risk Management" (2005)
  - Primarily addresses: "principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality"
  - Q9 does not contain the word "device."
  - Relies on ISO/IEC Guide 51:2014 for many definitions; References ISO 14971 *Medical devices — Application of risk management to medical devices*
- ICH Q10 "Pharmaceutical Quality System" (2008)
  - Provides guidance to "establish, implement, and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.
  - Scope includes: "Delivery system development (where relevant)" among other drug development activities

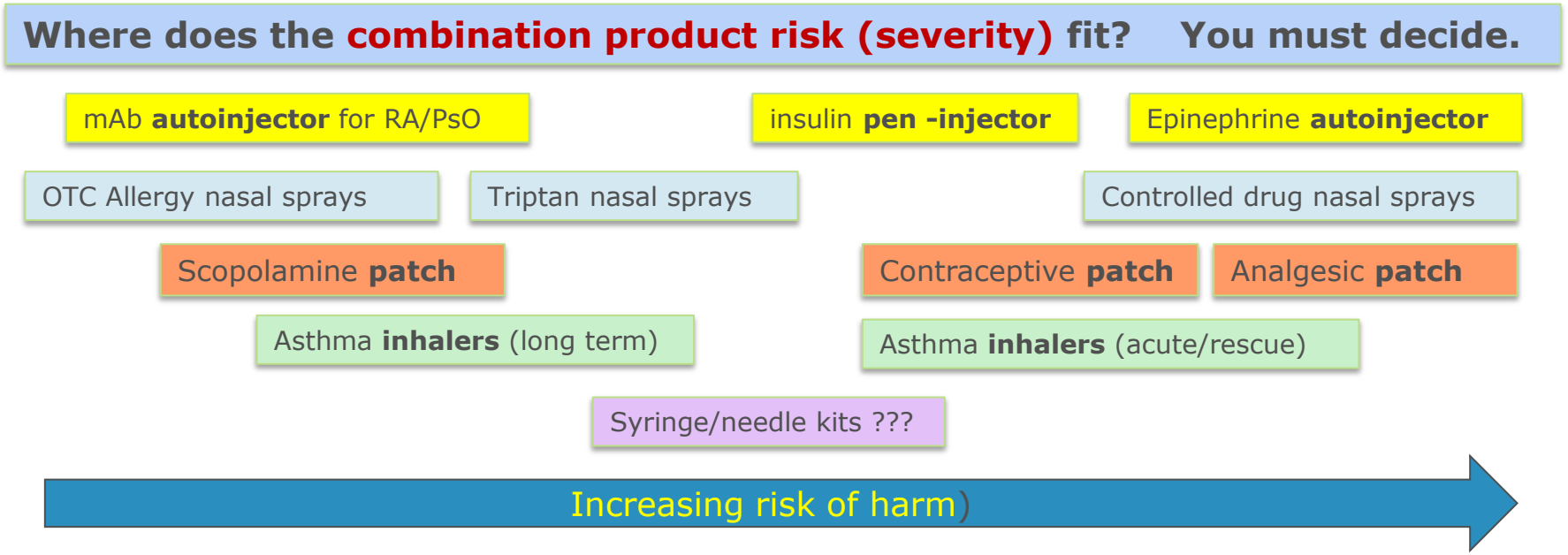
How are ICH Q9 and ISO 14971 Different?

- Q9 introduces the concept of human harm ("ultimately link to the protection of the patient") as the basis of "quality risk management" but then details the properties and processes that impact product quality. In practice, risks include patient safety, regulatory compliance, product supply and other risks.
- ISO 14971 addresses all device risks in terms of patient harm. Faults (design, process, user) create Hazards that can cause Harm. Hazards and Harms have severities and probabilities. Mitigations reduce risks to humans.
  - Key concept: "Reasonably foreseeable sequences or combinations of events that can result in a hazardous situation…"

Other Combination Product (drug and device) differences

- Drug properties remain static after approval; Devices can change/improve over the product's lifecycle.
- Drug specifications are derived from batch records; Device specifications are derived from user requirements, then specified, verified and validated.
  - Drug Critical Quality Attributes come from a controlled manufacturing process; devices depend more on design controls – i.e., final assembly process is less critical.
- Drug requirements are data driven; devices can be supported with engineering rationale or features that are described.

Combination product risk assessment and control strategies combine Q9 and ISO 14971 approaches with added focus on drug risks to patients



- Objective: The team's deliberation, risk prioritization (severity & probability for each hazard), and mitigations implemented matter most.
- Goal: Determine a level of acceptable "residual risk"

What drives CPP control strategies for drug-device combination product manufacturing?

Biologic Process

Starting Materials: Master Cell Bank; media; disposables

Drug Substance: Preculture > expansion > Harvest / capture > Viral inactivation > chromatography > Concentration > Storage

Drug Product: Thawing > pooling/mixing > filtration > aseptic filling > storage

Drug Process

Starting materials: Precursors; solvents; reactors

Drug Substance / API: Chemical synthesis, etc. > Storage

Drug Product: Blending > granulating > Drying > excipients/fillers > tableting > blistering

Device Assembly

Subassemblies & Injection molded components and drug in primary container

Automated assembly of components with primary package (e.g., PFS)

IPC strategy: 100% machine vision inspection/rejection

What IPCs apply to the drug versus the device?

For drugs and biologics, the "process is the product." For assembled combination products, the "design is the product (device constituent part)"

Mapped General Concepts for Development

Device constituent part development

Design Controls

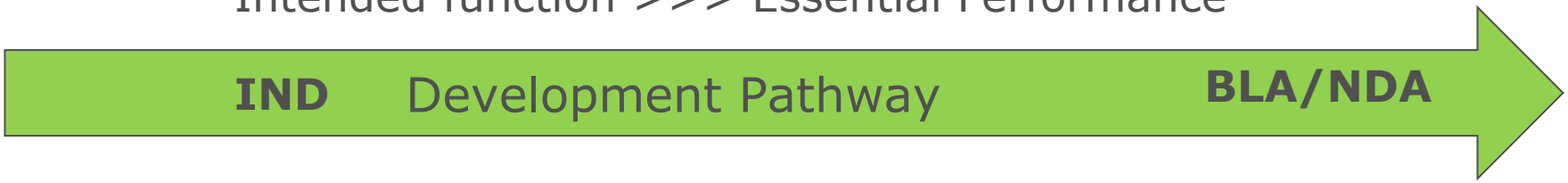
Shelf Life

Risk analysis – ISO 14971

Design V&V

User Reqs. > Tech. Design Reqs.

Intended function >>> Essential Performance



Drug-device Combination product development

Part 4 cGMPs

Lot release tests

CQAs

Process Development & Validation

CMAs

Human factors studies (DMEPA)

CPPs

qTPP

ICH Q8, Q9, Q10

Functional Stability

What are Combination Product and Delivery Device Control Strategies?

- Is Designs Controls itself a control strategy?
- What control strategies are needed for devices and combination products that are investigational?
- Where are device control strategies described in a submission dossier?
- What if there are no "critical" process parameters for device assembly?
- What does "critical" mean? Critical to patients, Quality, Use, regulatory approval?
- Are IFUs and Labeling critical?
- Does drug contacting v. non-contacting matter?

What are Combination Product and Delivery Device Critical Quality Attributes?

- There are thousands of part dimensions, multiple material (CMAs) choices, performance specifications. How do we boil these down to key release tests?
- For these potential example CQAs or CMAs, what does criticality mean?
  - Prefilled syringe (PFS) piston expulsion/breakloose forces?
  - PFS silicone/tungsten content
  - Kit component (luer) inter-connectivity
  - Choice of needle insertion depth
  - Spray patterns and droplet size for sprays and inhalers
  - Multidose dose counters; electronic features

What are Combination Product and Delivery Device Critical Quality Attributes

- What are "Essential Performance Requirements"?
  - A new term you may see in Health Authority requests for information. Distinguish between "intended function" and "essential performance."
- Do CtQ and QbD concepts work for devices?
  - Generally yes - but with some gaps compared to Design Controls (Part 820.30).
- Can "Design Spaces" (specifications and acceptance criteria) for a drug process apply to devices?
  - Generally yes – design validation and process validation have used the same principles.

Q & A