Drug Device Combination Products: Evolving Global Regulatory Landscape

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• Regulatory requirements presented may differ from actual regulatory requirements imposed by Health Authorities for specific combination products.

• Content and examples discussed are hypothetical and do not reflect any specific product or class of product.

• Most material used is sourced from Health Authority presentations and communications in public forums.
Agenda

- Combination Products Growth
- Combination Products and the US FDA Regulations
- Control Strategies and Integrated Development
- Evolving Global Regulations
  - European Regulatory Environment
  - Opportunities for Harmonization
- Summary
Combination Products Growth

Adapted from Special Report Combination Products: Development, Regulation & Key Technologies; Medical Alley Association 2016
Combination Products Growth

Multiple Growth Factors

- Growth in development of clinical drugs and devices for advanced medication delivery
- Dosage consistency and simplification
- Better Patient Outcomes
  - Tolerance levels, pain levels, symptoms
- Increased demand for portable medical devices
- Preference for minimally invasive procedures
- Healthcare cost efficiencies
- Health Authority intervention to ensure high patient safety and proper and consistent regulation, e.g., US FDA Office of Combination Products (OCP)

Containers and Closures vs. Combination Product

The United States FDA distinguishes between mere drug **containers and closures** versus containers and closures that are also **devices**.

**Drug container-closure:**
Vial contains and protects the drug

Subject to drug cGMPs as a container or closure

**Combination Product (Single Entity):**
Syringe serves both as a drug container-closure **AND** as a device which delivers the dose

Subject to drug cGMPs as a container or closure
**AND to the device**
Quality System Regulations

**Combination Product (Co-pack):**
Vial = container-closure
+ Piston syringe = delivery device

Subject to drug cGMPs as a container or closure
**AND to the device**
Quality System Regulations

**21 CFR § 3.2(e)**
A product comprised of **two or more regulated components**, physically, chemically, or otherwise **combined or mixed and produced**.
US Combination Products Regulations & Guidance

78 FR 4307
Combination Products
cGMPs Final Rule
Jan ‘13


SINGLE ENTITY

DRUG
DEVICE

CO-PACK

DRUG
DEVICE

CROSS-LABEL

DRUG
DEVICE

Pre-Market
Post-Market

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United States
Combination Products cGMPs

Option 1
Demonstrate compliance with the entire regulation for each constituent part of the Combination Product.

DRUG
DEVICE
BIOLOGIC and HUMAN CELL TISSUE PRODUCTS

21 CFR Parts 210 & 211
21 CFR Part 820
21 CFR Part 600-680
21 CFR Part 1271

Cross-labeled combination products must demonstrate compliance only with cGMP regulations applicable for the constituent part.

Option 2
“Streamlined Approach”

• Leverage common elements between the regulations.

• Demonstrate compliance with either the entire Drug (or Biologic) cGMP, or the entire QSR, as well as specific sections of the regulations applicable to the other constituent part(s).

21 CFR Elements
Uniquely Interpreted in Device QSRs
21 CFR Elements Uniquely Interpreted in Drug cGMPs

If the Combination Product (CP) includes a biological product, the cGMP requirement for biological products in 21 CFR Parts 600 through 680 also apply; if the CP includes any HCT/Ps, 21 CFR Part 1271 requirements also apply.

FDA Combination Product Regulations: Streamlined Approach

Device QSR Requirements
§ 820.20 : Management Responsibility
§ 820.30 : Design Controls
§ 820.50 : Purchasing Controls
§ 820.100: CAPA
§ 820.170: Installation
§ 820.200: Servicing

Drug cGMP Requirements
§ 211.84 : Testing/approval/rejection of comp.
§ 211.103: Calculation of yield
§ 211.132: Tamper-evident packaging
§ 211.137: Expiration dating
§ 211.165: Testing and release for distribution
§ 211.166: Stability testing
§ 211.167: Special testing requirements
§ 211.170: Reserve samples

Biologic GMP Requirements
§ 600.2-3: General Provisions
§ 600.10-15: Establishment Standards
§ 600.20-22: Establishment Inspection
§ 600.80-81: Post Marketing Reporting
§ 600.90: Waivers
§ 610.1-2: Release Requirements
§ 610.9-18: General Provisions
§ 610.20-21: Standards Prep./Limits of Potency
§ 610.30: Test for Mycoplasma
§ 610.40-48: Testing Reqs. Communicable Disease
§ 610.50: Date of Manufacture
§ 610.53: Dating periods for licensed Bio. Products
§ 610.60-68: Labeling Standards
§ 1271: Human Cells, Tissues and Cellular & Tissue-Based Products

Control Strategies to Safeguard Patients

Cornerstones

– Combination Product Integrated Development

– Risk Management:
  • Essential Performance Requirements/Critical Control Points
  • Human Factors
  • Reliability
  • Change Controls
  • Purchasing Controls
Combination Products Integrated Development

Part 4, and evolving Global CP Regulations

- ICH Q8: Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality Systems
- Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry
- Post Marketing Surveillance & Safety Reporting

Proactive and Active...

RISK ASSESSMENT  RISK CONTROL  RISK REVIEW  QUALITY RISK/BENEFIT ANALYSIS

- 21 CFR 820: QSRs (Design Controls, Change Control, Purchasing Controls)
- ISO 13485: QMS
- ISO 14971: Risk Management
- IEC 62366-1: Usability Engineering
- FDA Draft Guidance Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development
- Post Marketing Surveillance & Safety Reporting


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Typical Integrated Development Process

**Pro-Active Risk Management Underpinning**

**Research**
- Basic Research
- Prototype Design & Discovery
- Preclinical Development

**Early Development**
- Phase 1 Clinical
- Pre-IND Meeting

**Late Development**
- Phase 2 Clinical
- EOP2 Meeting
- Phase 3 Clinical

**Lifecycle**
- Pre-NDA/BLA Meeting
- NDA/BLA Submission

**Drug & Device Functionality & Interaction**

**Combination Product User Interface: Human Factor Studies**

**Combination Product Design Control/Quality by Design/Risk Management**

**Design-Build-Test-Refine**
- Design Outputs
- Design Verification
- Design Transfer
- Design Validation

**Concept Feasibility & Evaluation**
- User Needs/Design Inputs

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For Constituent parts, their interactions, and the Combination Product as a whole.

User Needs and Requirements

Product Requirements/Intended Functions (CtQs and CQAs)

- Focus on both **SAFE** and **EFFECTIVE** use of the combination product
- Essential for the proper functioning of the device, the drug, and the combination product
- **Essential Requirements**: Subset of Intended Functions needed to achieve freedom from unacceptable harm and/or for acceptable delivery of the dose

*CtQ: Critical-to-Quality; CQA: Critical Quality Attribute*
CtQ Cascade and Controls Strategy

For Constituent parts, their interactions, and the Combination Product as a whole.

User Needs and Requirements

Product Requirements/Intended Functions (CtQs and CQAs)

Process Requirements (CPPs & CMAs)

Risk Mitigation Strategies and Controls
- Human Factors
- EPRs/Critical Control Points
- Reliability
- Change Controls
- Purchasing Controls

Verification and Validation

CtQ: Critical-to-Quality; CQA: Critical Quality Attribute; CPP: Critical Process Parameter; CMA: Critical Material Attribute; EPR: Essential Performance Requirement
What goes wrong in Combination Products?

Transdermal patch adhesion is not robust...only lasts a few hours instead of days....drug released adequate?

Nurse was supposed to dose patient with 0.25mg liquid and instead ... she drew up 2.5 mg and nearly administered to the patient.

Caregivers could not assemble dosing kit and draw out the correct dose.

Nurses removed the plunger from the syringe and reinserted it before injecting dose.

Pre-filled Syringe: upon lifting device away from patient's skin, the needle was still exposed, it did not retract into the device.

https://www.youtube.com/watch?v=nvwR74XpKUM
Product Risk Management

Risk Management is the process of...

- Identifying hazards
- Evaluating associated risks
- Mitigating/controlling the risks
- Monitoring the effectiveness of the controls

Product Risk Management

Hazard, Hazardous Situation, Harm

Hazard

Hazardous Situation

Harm
Failure Analysis

Root Cause → Failure Mode → Hazard

Device Risk Control

Failure Mode & Effects Analysis (FMEA)
- Identifies failure modes, their causes/effects, and supports PRA to drive mitigation efforts
- Bottom-up analysis focused on identifying causes and establishing risk control measures
- FM are typically local to the process or component (fails to meet spec, lack of function, defect, etc.)
- Probability of the root cause leading to failure mode and hazard

CtQ Cascade: Control Strategies Foundation
*(design, process, use, etc.)*
**Combination Product and Delivery Device Critical-to-Quality Attributes**

*...some examples*

**Formulation:**
- Drug stability
- Dose Volume
- Particle Size
- Concentration
- Viscosity

**Funcionality**
- Injection force profile/
  - Piston expulsion/
  - Break-loose forces
- Needle gauge and length
- Drug viscosity
- Injection rate
- Barrel siliconization
- Tissue backpressure
- Needle insertion depth

- Clear units of measure
- Multi-dose dose counters;
  - Electronic features
- Spray patterns and droplet
  - Size for sprays and inhalers
- Clarity of dose completion
- Product Differentiation
- Adhesion strength
- Permeability

**Compatibility**
- Drug stability
- Contact Surfaces
- Silicone oil/ Tungsten Content
- Leachables
- Adhesion (transdermal)

**Container-Closure Integrity and Fit to Autoinjector**
- Dimensional tolerances
- Stopper and tip-cap
- Barrel barrier properties
- Kit component (e.g., luer)
  - Inter-connectivity

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Combination Products Device CtQ/Drug Criticality Integration

CtQ Flowdown based on FDA Combination Product cGMP Guidance Document Example of PFS
Combination Products Device CtQ/Drug Criticality Integration

CtQ Flowdown based on FDA Combination Product cGMP Guidance Document Example of PFS
Product Risk Management Integration

Failure Analysis
*(design, process, use, etc.)*

- **Root Cause**
- **Failure Mode**
- **Device Risk Control**
- **Hazard**

**Failure Mode & Effects Analysis (FMEA)**

- Identifies failure modes their causes/effects and supports PRA to drive mitigation efforts
- Bottom-up analysis that is focused on identifying the causes and establishing risk control measures
- FM are typically local to the process or component (fails to meet spec, lack of function, defect, etc.)
- Probability of the root cause leading to failure mode and hazard

**Risk Analysis**
*(what happens in use setting)*

- **Sequence of Events**
- **Hazardous Situation**
- **Risk Control in the Environment**
- **Harm**

**Product Risk Assessment (PRA)**

- Identifies potential hazards of the PRODUCT (drug + device) that could harm the patient
- Top-down analysis that focuses on interactions and/or sequence of events that lead to Harm
- Probability of the Harm to the User
**Product Risk Management Integration**

**Risk Analysis**  
*what happens in use setting*

- Hazard \(\rightarrow\) Sequence of Events \(\rightarrow\) Hazardous Situation \(\rightarrow\) Risk Control in the Environment \(\rightarrow\) Harm

**Product Risk Assessment (PRA)**
- Identifies potential hazards of the PRODUCT (drug + device) that could harm the patient
- Top-down analysis that focuses on interactions and/or sequence of events that lead to Harm
- Probability of the Harm to the User

**CtQ Cascade: Control Strategies Foundation**
- Formative & Summative Human Factors/Usability Engineering
- Clinical Studies
- Design Validation
- Linkage to Post Marketing Safety Reporting

**Design Controls & QbD CTQ Cascade Flow Down**

- Voice of Customer
- Functional
- System Specifications
- Subsystem Specifications
- Subassembly Reqs. Process & Equipment
- Component Specifications Raw Materials

**V&V Management**
- Clinical Tests
- Validation Tests
- Test Results
- Verification Tests
- Test Results

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Product Risk Management Integration

Hazards and Harms Analysis and Risk Evaluation:
Who is the User? What are predictable mis-uses?

- FDA Guidance: Applying Human Factors and Usability Engineering to Medical Devices (2/16)
- FDA Draft Guidance Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (2/16)
- Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry (4/16)
Combination Products Risk Considerations

Use Environment Considerations:

- **Storage** (e.g., refrigeration, away from children, shelf-life, use away from home)
- **Human Factors:**
  - **Who is the user?** Pediatric? Elderly? Caregiver? Training adequacy?
  - **What is the complexity of the environment?** User stress levels and distractions? At home?
  - **What is the user interface?** Clear Labeling, e.g., Instructions for Use (IFU)
  - **What is the consequence for user error?**
  - **What are the physical/sensory requirements?** Self-injection?
  - **What are the cognitive requirements?**
  - **What are the user habits and expectations?** Adherence to dose regimen that is not daily (e.g., weekly? Bi-weekly? Monthly?)

## Failure Modes and Effects Analyses (FMEAs)

User FMEA (uFMEA)  
Design FMEA (dFMEA)  
Process FMEA (pFMEA)  
Drug Criticality Analysis

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>ISO 14971 Based</strong></td>
<td><strong>IFU Task/Design Feature/Assembly Step</strong></td>
<td><strong>Hazard Types</strong></td>
<td><strong>Harm to patient with a deviation</strong></td>
<td><strong>Severity for each Harm</strong></td>
<td><strong>Probability or frequency</strong></td>
<td><strong>Detectability pFMEA only</strong></td>
<td><strong>Risk Score</strong></td>
<td><strong>Mitigations</strong></td>
<td><strong>Severity</strong></td>
<td><strong>Probability or frequency</strong></td>
<td><strong>Detectability pFMEA only</strong></td>
<td><strong>Post Mitigation Risk Score</strong></td>
<td></td>
</tr>
<tr>
<td><strong>User FMEA</strong></td>
<td>IFU steps</td>
<td>Needle stick, re-cap needle (multiple)</td>
<td>Cross infection (multiple)</td>
<td>High</td>
<td>Medium</td>
<td>NA</td>
<td>High</td>
<td>Design, IFU warning</td>
<td>High</td>
<td>Low</td>
<td>NA</td>
<td>e.g., ALAP</td>
<td></td>
</tr>
<tr>
<td><strong>Design FMEA</strong></td>
<td>Design Feature</td>
<td>Needle stick – miss line</td>
<td>Cross infection</td>
<td>High</td>
<td>Medium</td>
<td>NA</td>
<td>High</td>
<td>Safety interlock</td>
<td>High</td>
<td>Low</td>
<td>NA</td>
<td>e.g., Tolerable</td>
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</tr>
<tr>
<td><strong>Process FMEA</strong></td>
<td>Assembly step</td>
<td>Missed dose, mis-assembly</td>
<td>Lack of drug effect</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>Vision detection</td>
<td>Medium</td>
<td>Very low</td>
<td>Very high</td>
<td>e.g., Acceptable</td>
<td></td>
</tr>
</tbody>
</table>

Image Credit: D. Mead, Janssen

**Generic example – typical tables for each FMEA type can run 10-20 pages**
Product Risk Management Integration
Combination Products Control Strategies

- Focus on both **SAFE** and **EFFECTIVE** use for the proper functioning of the **device**, the **drug**, and the **combination product**

<table>
<thead>
<tr>
<th>Essential</th>
<th>Functions and components that have potential to harm the patient or affect the mechanics of the clinical performance of the product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Essential</td>
<td>Remaining functions and components that are not considered to be essential</td>
</tr>
</tbody>
</table>

- Risk-based evaluation and application of routine controls
- Emphasize greater controls on essential functions and the aspects of the components which contribute to essential performance
Combination Products Control Strategies

Cascade controls for **EACH** Essential Performance Requirement

**Purchasing/ Supplier Controls**
- Material Specs
- Supplier Specs
- **Supplier Quality Agreements**
- Component manufacturer controls
- In-process controls
- Release testing

**EM Controls**
- External Manufacturer Controls
- In-process controls
- Release testing

**Incoming Controls**
- Incoming inspection & release procedures
- Incoming Specifications
- Deviation Disposition
- Statistical Justification(s)

**Mfg Control Plans**
- Incoming inspection & release procedures
- Incoming Specifications
- Deviation Disposition
- Statistical Justification(s)

**Packaging & Labeling Controls**
- Control of packaging and labeling of materials across component and suppliers

**Final Testing and Release Controls**
- Incoming inspection & release procedures
- Incoming Specifications
- Deviation Disposition
- Statistical Justification(s)
Evolving Global Regulations

Establishing regulatory frameworks to drive successful practices and control strategies throughout the combination product lifecycle, to assure public health.
Combination product regulations are relatively recent, and specific regulations only exist in certain markets.

Focus is on **successful practices and control strategies** throughout the product lifecycle to assure **public health**, ensuring **risk is commensurate with product complexity and patient needs**.
Evolving Global Combination Products Regulations


Brexit

26 November 2016

Evolving Global Regulations

Some Current Challenges

Combination Product:
• Inconsistent, ambiguous definitions

Regulatory Framework:
• Inconsistent designations
• Inconsistent filing requirements
• Little uniformity in application and assessment of clinical trials registration process

Manufacturing Controls:
• Practical challenge in application of the relevant GMP (Good Manufacturing Practice) code, regulation or standard to production of separate device, diagnostic, or medicinal constituents of a Combination Product
• Challenge in the determination of the combined requirements which apply to those parts of the production process that involve the integrated components
• ISO 13485 certification of Quality System? Inconsistent requirements across markets.
• Inconsistent audit practices of regulatory authorities relative to applicable manufacturing standards

Technical Dossiers:
• Confusion as to dossier contents and formats for submission in rapidly shifting environment

Post-market Requirements:
• Nature of assessment and reporting of events differs for constituent parts
• Efficient and effective communication pathways between authorities for visibility, and assessment of reportable postmarket events? …Of post market change management?
Evolving Global Regulations

- **Primary Mode of Action** and **type of Combination Product** (e.g., single entity, co-pack, or cross-label “set”) largely drives regulations, submissions procedures, pathway to market and post marketing safety reporting in most markets.

**PRIMARY MODE OF ACTION:**

“...the single mode of action of a combination product that provides the most important therapeutic action ... The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects…”

(US FDA 21 CFR Part 3.2(m))
EU Medical Device Directive

- EU MDD (93/42/EEC)
- Active Implantable Medical Devices Directive (90/385/EEC)
- In Vitro Diagnostic Medical Devices (98/79/EC)
  - EU Directives set certain aims, requirements or end results that must be achieved by every member state.
  - National authorities must create or adapt laws to meet the goals of a given directive, but are free to decide how to do so.

- Under MDD 93/42/EEC, Article 1.3, the relevant essential requirements of Annex 1 to this Directive shall apply as far as safety and performance related device features are concerned.

ERC – Essential Requirements Checklist

PHARMA

Marketing Authorisation Application (MAA)

AGENCY

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European Regulatory Environment

**EU Medical Device Directive**

- **EU MDD (93/42/EEC) and**
- **Active Implantable Medical Devices Directive (90/385/EEC)**

  - EU Directives set certain aims, requirements or end results that must be achieved by every member state.
  - National authorities must create or adapt laws to meet the goals of a given directive, but are free to decide how to do so.

**EU Medical Device Regulation** (published May 2017)

- Regulation (EU) 2017/745: Governs how manufacturers of medical devices produce and sell products in EU [26 May, 2020]
- Regulation (EU) 2017/746: Governs In vitro diagnostic medical devices (IVDR) [26 May, 2022]

Also impacts non-EU countries that leverage CE (European Conformity) Mark

- **EU Law: BINDING legal force throughout every member state, on par with national laws.**
- National governments do not take action themselves to implement EU regulations, but DO ensure their national law does not define the subject matter any further.
- Will be consistently implemented across the EU and enforced nationally.
Annex I Requirements

MDD: 23 Articles, 12 Annexes

- Essential Requirements (ERs)
  - 13 Clauses
  - ~94 individual requirements

MDR: 123 Articles, 17 Annexes, Increased Applicability

- General Safety Performance Requirements (GSPRs)
  - 23 Clauses
  - ~178 individual requirements

EU Medical Device Directive
EU Medical Device Regulation (published May 2017)
**Drug Device Combination Products**

<table>
<thead>
<tr>
<th>United States</th>
<th>European Union</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug</td>
<td>• Term used loosely in MDR without legal definition</td>
</tr>
<tr>
<td>• Biologic</td>
<td>• A product is EITHER a Medicinal Product OR a Medical Device</td>
</tr>
<tr>
<td>• Combination Product</td>
<td></td>
</tr>
<tr>
<td>• Device</td>
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</table>

**Textual Details**

- Drug
- Biologic
- Combination Product
- Device

**Medicinal Product**
- MD incorporating 1° medicinal product
- Single-entity MD administering

**Medical Device**
- MD incorporating ancillary medicinal product
- ‘Other’ MD administering

**Images**

- Single Entity
- Co-Pack
- Cross-label
EU MDR Impact on Combination Products

EU MDR Article 117

Where, <device is integral>, the marketing authorization dossier shall include, where available, the results of the assessment of the conformity of the device part [...] allowing the manufacturer to affix a CE marking to the medical device

If the dossier does not include the results of the conformity assessment [...] authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I

Date of Application: 26 May, 2020

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- No longer acceptable for Pharma/Device Developer to self-assess the conformity to Annex I
- The internal ‘Essential Requirements Checklist’ model will no longer work
  - CE certificate or Declaration of Conformity (for Class I devices) for device constituent of the combination product
  - NEW REQUIREMENT: NB opinion/memo/report confirming compliance with relevant general safety and performance requirements for the device constituent of the medicinal product
EU MDR Impact on Combination Products

Combination Products developers have raised numerous questions regarding interpretation and implementation of Article 117 with EMA and European Commission.

- TOPRA/RAPS Inter-regulatory and Stakeholder Workshop – 20 Nov., 2018
  - Participants: EMA, National Competent Authorities (medicines and devices), EC (DG Sante and DG Grow), Notified Bodies, Industry (medicines and devices)
- EMA Q&A on Article 117 (27 Feb., 2018)
EU MDR Impact on Combination Products: Many Questions

Combination Products developers have raised numerous questions regarding interpretation and implementation of Article 117 with EMA and European Commission.

- TOPRA/RAPS Inter-regulatory and Stakeholder Workshop – 20 Nov., 2018
  - Participants: EMA, National Competent Authorities (medicines and devices), EC (DG Sante and DG Grow), Notified Bodies, Industry (medicines and devices)

- EMA Q&A on Article 117 (27 Feb., 2018)
EU MDR Impact on Combination Products

(STILL A NEED FOR ADDITIONAL GUIDANCE)

- Future Marketing Authorization Applications
- Impact on existing MA for products with a device constituent part
- Notified Body considerations
- MANY LINGERING QUESTIONS REQUIRING GUIDANCE
EU MDR Impact on Combination Products

Key Takeaways

• **Future Marketing Authorization Applications**
  
  − Prefilled, non-reusable, drug-device combinations in EU will continue to be regulated as medicinal products **BUT MDR encompasses all integral single-use combination products regulated as medicinal products** (e.g., Pre-filled syringes, pre-filled inectors, patches and kits with pre-filled syringes)
  
  − “**General Safety and Performance Requirements**” (GSPRs) (Annex I) will apply to device constituent
    
    • **Note:** Annex II, clause 4 of the MDR asks for documentation to demonstrate conformity to the GSPRs from Annex I that are applicable to the device, taking into account its intended purpose. This shall also include justification, validation and verification of the solutions adopted to meet those requirements.
  
  − CE marked device component of combination products are to be **CE marked per new MDR requirements**
  
  − **Non-CE marked device component** of combination products- **Notified Body opinion required** (depending on device classification: NB Opinion not necessary for Class 1 non-sterile or non-measuring devices)
  
  − **NB opinion strongly suggested to be included at the time of MAA submission**, starting May 26, 2020
  
  − **Eudamed and UDI** not applicable to Article 117 products or to their device components. Only applicable to CE marked co-packaged devices.
EU MDR Impact on Combination Products

Key Takeaways

• **Impact on existing MA for products with a device constituent part:**
  - Not clearly defined
  - Article 117 will not be applied retroactively, however NB opinion may be needed in case of a “significant” change of the device component of a drug approved prior to 26 May 2020 (what qualifies as “significant”?)…Combination Products approved prior to MDR will be grandfathered, but changes to them will not.
  - CE marked device component of combination products- **no grandfathering of CE mark awarded under MDD**.
    - When validity of CE mark expires, will updated CE marking require variation to MA?
    - If device is CE marked under existing MDD with certificate which is still valid after May 26, 2020, will NB opinion still be needed for device to demonstrate conformity to MDR Annex 1 GSPRs?
    - If device constituent is Class I and has a Declaration of Conformity issued by the legal manufacturer, does device have to be in conformity with MDR on May 26, 2020?
EU MDR Impact on Combination Products

Key Takeaways

- **Notified Body (NB) Considerations**
  - **NB capacity** to take on additional assessment work from Pharma Industry?
    - NB authorization to the overall MDR includes Article 117 reviews
    - Some are just now being authorized to review medical devices for CE marking under the MDR; there will be a backlog of companies/devices needing to be re-certified
    - Concerns about NB capacity, process questions, lack of scientific/technical guidance
    - To date, only one NB (BSI UK) has been designated to EU MDR (announced 21 Jan., 2019) (BREXIT?)
    - Will have test labs and Authorized Representative in EU (not UK)
  - Indication from NB that **labelling instruction** for medicinal products will apply. (Labelling requirements in MDR Annex I not applicable) (??)
  - “**General feeling**” Applicant does not need to have a separate QMS for Article 117 products. GMPs will apply since regulated as medicinal product, so do not anticipate QMS audits to be required for NB opinion. (??)
  - Format/content of submission unknown (??)
  - “**Do not believe**” there will be a special QS requirement or Clinical Evaluation requirement; Notified Bodies expect to see some risk-based clinical evidence in the technical file, but not dedicated clinical trials. Prior knowledge will be considered. (??)

- Note: For Investigational Medicinal Product Dossiers (IMPDs) for integral, single-use CPs, need to provide a statement as to conformity to Annex 1. Effective March 2018: **EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials**
EU MDR Impact on Combination Products

MANY LINGERING QUESTIONS REQUIRING GUIDANCE

- What is scope for the Notified Body (NB) conformity assessment? Limitations of the assessment? What will be format of the NB opinion?

- What about overlapping review issues (e.g., biological compatibility/leachables/extractables/Container Closure Integrity?)

- Allow parallel review e.g. by Day 80 of MAA review, OR allow opinion on non-final device?

- No NB Opinion required for investigational drug studies?

- Allow for a platform model?

- What if EMA is not in agreement with NB assessment?

- Are Combination Products Manufacturers expected to have a NB-verified ISO 13485 QMS for the devices?

- Drug product presented in an autoinjector is comprised of two integral single-use devices (PFS and Autoinjector) – would NB assessments be needed on both components as a single unit, or issue separate assessments for each component?
Next Steps

- Issues recognized at senior level of medicines and devices regulators (EMA and HMA) and work is ongoing to address them
- Biologics Working Party (BWP)/ Quality Working Party (QWP) draft guideline for drug device combination (DDC) products- expected end of Q2 2019
  - Quality aspects of the dossier requirements for DDCs for MAAs, Line extension applications and variations
  - EMA in dialogue with NBs
- Industry organizations (EBE, EFPIA, MTE) continuing dialogue with EMA and influencing through position papers

What should YOUR ORGANIZATION do?

- Familiarize and prepare to meet MDR and IVDR
- Identify Notified Body to work with to provide conformity assessments for device constituents, including pre-filled syringes
- Align with suppliers and service providers, ensure they are preparing.
- Be on the watch for EMA publication of guidance on transition period and answers to open questions.
Evolving Global Regulations

**Opportunity:** Develop internationally harmonized combination products Guidance.

**Align on definitions…and risk-based approaches**

**Some definitions:**

**Combination Product:**
Products with two or more separate medicine/biologic/medical device/diagnostic components integrally combined.

**Regulatory Framework:**
Usually requires a single regulatory submission, although may be subject to review from reviewers from multiple regulatory divisions under the leadership of a lead reviewer from the lead authority. Based on characteristics of the PMOA; where designation is unclear, apply risk-based approach to place product in jurisdiction according to which MOA presents greatest risks to the patient.

**Companion Product:**
Two separately supplied products that are co-dependent and cross-labeled. Usually requires separate regulatory submissions for each product, although reviews may be cross-referenced or coordinated.

**Kit or System:**
Two or more separate products which are co-packaged. May require separate regulatory submissions for each product plus a submission for the co-packaged kit or system.
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Some risk-based approaches:

**Regulatory Framework:**
- Consistent risk-based mechanism for determining PMOA for the purpose of assigning appropriate lead authority. Dedicated body to drive alignment?
- Cross communication between divisions responsible for regulatory review; Timely processing via parallel assessments by all participating authorities?
- Clinical practice applied (ISO 14155 or equivalent for devices, ICH GCP for pharmaceuticals) based on the Combination Product’s PMOA; ISO EN-62366 for Human Factors

**Manufacturing Controls:**
- Streamlined quality system; Maintain a quality system compliant either to a medical device (e.g., 21 CFR 820 or ISO 13485) or medicine (e.g., ICH GMP) quality system standard, but with additional elements to address requirements of MOA not covered by the primary quality system standard used.
- Audit practices to ensure manufacturers are compliant with relevant sections of all applicable manufacturing standards. Gap analyses and risk management reports in place to justify approaches taken to ensure compliance.
Some risk-based approaches:

**Technical Dossiers:**
- Minimize documentation burden by requiring one consistent set of documentation for submission to relevant health authorities.
- Product design and production information developed for both device and drug constituents of the product.
- Format of dossier dependent on Combination Product’s PMOA.
- Information on secondary MOA clearly identified and preferably arranged in a single location for review. Single dossier submitted and reviewed by lead authority, with input and correspondence as needed from other pertinent authorities re: secondary MOA.

**Post-market Requirements:**
- Reporting based on procedures for PMOA
  - Medicines- trends analysis and consideration of pharmacological mechanisms
  - Devices- investigate with engineering considerations for root causes and corrective actions
- Communication pathways between health authorities to ensure effective and efficient review of post-market events, and post marketing safety controls.
Summary/ Key Take Aways

• Innovation is occurring in combination products, with major industry growth anticipated in upcoming years.

• Combination product regulations are relatively recent and dynamic, and specific regulations only exist in certain markets. Opportunities for harmonization exist.

• The focus of evolving global regulations is on successful practices and control strategies throughout the product lifecycle to assure public health, ensuring risk is commensurate with product complexity and patient needs.

• The concept of primary mode of action has been adopted by many jurisdictions, however criteria for determination is not harmonized. Engage with competent authorities early on.

• You will need to demonstrate the suitability of the device for delivery of the drug
  – Cornerstones of effective combination product development, regardless of dynamic regulatory environment, entail integration of QbD, Design Controls, Human Factors, and Risk Management.
  – Understand your intended use, product configuration, intended user(s), risks and controls
  – Cascade controls for each essential performance requirement through the product lifecycle.
  – Effective Purchasing Controls and supplier quality agreements are a critical element of your combination product controls strategy.
Summary/ Key Take Aways

- The EU MDR adds to an already complex regulatory landscape, especially for Drug-Device Combination Products
  - Numerous questions have been raised regarding interpretation of EU MDR Article 117. Industry and Notified Bodies are awaiting Guidance.
  - Notified Body Landscape is moving, and capacity is strained.
  - Companies with integral, single use combination products expecting to file MAAs in 2020 should identify and select a Notified Body to provide conformity assessments for device constituents, inclusive of Prefilled Syringes. **Notified Body opinion is needed under Art.117 of EU MDR: This is needed for all integrated devices (syringes, autoinjectors, patch injectors, …) prior to submission**
  - Align with suppliers and service providers; ensure they are preparing.
Questions?

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