Navigating the Regulatory Landscape for Connected Combination Products: Challenges, Gaps, and Forward Strategies

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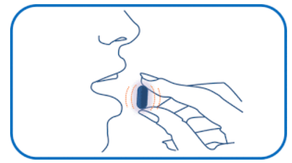
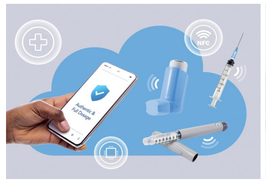


1. INTRODUCTION

- **Combination products** are **therapeutic** and **diagnostic** products that combine two or more regulated components (drug/device/biologic), as defined under **21 CFR 3.2(e).**
- **Connected combination products** incorporate **digital technologies** (e.g., sensors, software, wireless connectivity) to monitor or enhance product function.
- The rise of **digital health** tools—especially AI-enabled apps and IoT-connected devices—has blurred regulatory lines and introduced novel compliance and safety challenges.
- These products require interdisciplinary regulatory strategies, involving **CDRH, CDER, CBER**, and the **Office of Combination Products (OCP).**

📊 **Global Market Insight:** The connected combination product market is projected to grow at **CAGR > 10%** by 2030 due to increasing demand for personalized, real-time therapeutic interventions.



2. REGULATORY FRAMEWORK OVERVIEW

Classification & Pathways

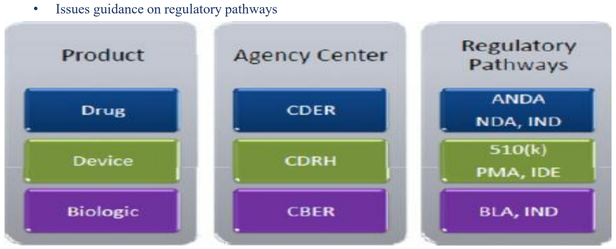
- FDA assigns regulatory responsibility based on the Primary Mode of Action (PMOA).
- **Key submission pathways:**
- 510(k) (devices)
  PMA (devices)
  NDA/ANDA (drugs)
  BLA (biologics)
- 21 CFR Part 4 governs CGMPs for combination products.

Guiding Regulations

Component	Key Regulation	Relevance
Drugs	21 CFR Parts 210/211	Drug GMP
Devices	21 CFR Part 820	QMSR
Software	21 CFR Part 11	e-signature, data integrity
Combination	21 CFR Part 4	CGMP convergence

Role of Office of Combination Products (OCP)

- Oversees PMOA assignments
- Coordinates review between centers
- Issues guidance on regulatory pathways



3. KEY CHALLENGES IN REGULATORY OVERSIGHT

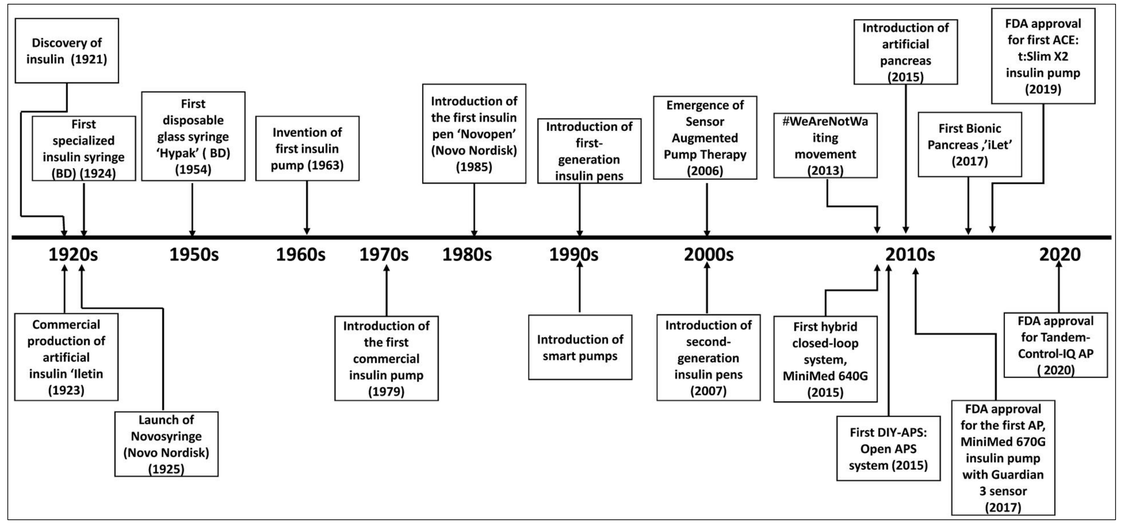
1. **Fragmented Review Responsibilities**
   Intercenter communication delays between CDER/CDRH/CBER
   Redundant or inconsistent documentation expectations
2. **Unclear Classification Criteria**
   Difficulty applying PMOA when software significantly influences device performance
   Lack of specific pathway for AI-driven components
3. **Cybersecurity & Data Privacy Concerns**
   Insufficient guidance for connected drug-delivery systems
   Overlap between FDA, FCC, and HHS regulations
4. **Software Validation Burdens**
   Rapid iteration of connected software requires new risk management models
   No harmonized expectations across software updates, patches
5. **Human Factors and Usability Issues**
   Complexity of user interfaces in connected systems
   Challenges in risk mitigation and labeling

5. CASE EXAMPLES

📍 **Smart Insulin Pens**
Device: Digital insulin delivery with Bluetooth tracking
Challenge: Connectivity failure → delayed dosing
Regulatory Gap: No clarity on cybersecurity labeling and over-the-air update validation

📍 **Digital Inhalers**
Combination: Drug + sensor + app
Gap: Divergent data storage rules and patient consent protocols

📍 **Ingestible Sensors (e.g., Digital Pills)**
Function: Monitor ingestion compliance via sensors
Challenge: Risk of surveillance misuse; unclear benefit-risk modeling for approval



4. CURRENT GAPS IN THE FRAMEWORK

⚠️ **Guidance Gap:** No FDA guidance specific to connected combination products integrating mobile apps, wearables, or cloud computing.

⚠️ **Global Misalignment:** Regulatory inconsistency between FDA and EU MDR (especially with UDI, GSPR, and cybersecurity).

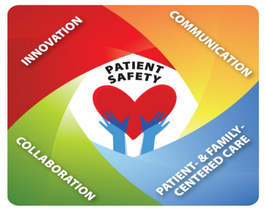
⚠️ **Disjointed GMP/QMS Expectations:** Device QMS (ISO 13485) vs Drug GMP (21 CFR 210/211) vs Software Life Cycle Processes (IEC 62304) often conflict.

⚠️ **Post-market Gaps:** Challenges in capturing real-world evidence (RWE), software performance in home settings, and adverse event reporting for digital elements.

6. FORWARD-LOOKING STRATEGIES

1. **Regulatory Improvements**
   Develop product-specific guidance for connected systems
   Create a Connected Product PMOA Decision Tree
   Issue Software Update Management Protocols (SUMPs)
2. **Intercenter & Industry Collaboration**
   Cross-functional FDA working groups to streamline hybrid product reviews
   Collaborative research programs (CDRH + CBER/CDER + Digital Health Center of Excellence)
3. **Global Alignment**
   Support IMDRF efforts toward harmonized frameworks for connected technologies
   Advocate for mutual recognition agreements for software validation
4. **Innovation Enablement**
   Encourage use of Real-World Evidence (RWE) in regulatory submissions
   Define AI/ML training dataset governance requirements
   Promote use of modular submissions for frequent software changes

7. CONCLUSION



The rapid advancement of connected combination products where drugs, devices, and digital technologies converge—signals a new era of personalized, data-driven healthcare. These innovations promise improved therapeutic outcomes, enhanced patient engagement, and more efficient healthcare delivery. However, current regulatory frameworks have not evolved at the same pace, creating uncertainties and compliance risks for industry stakeholders.

The challenges span:

- **Inconsistent regulatory pathways** and classification confusion.
- **Limited guidance** on digital component validation, updates, and cybersecurity.
- **Gaps in post-market surveillance** for integrated software-device-drug platforms.
- **Global misalignment**, creating market entry delays and increased development costs.

Without regulatory agility, there is a risk of stifling innovation and delaying access to life-changing technologies for patients. To fully realize the potential of these advanced therapies, a **collaborative, risk-based, and forward-thinking regulatory strategy** is essential.

Call to action: Let's shape the future of connected healthcare together.

Join the movement to build smarter, safer, and more agile regulatory frameworks.

8. REFERENCES

FDA. (2017). Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products FINAL GUIDANCE. https://www.fda.gov/media/90425/download

Principles of Premarket Pathways for Combination Products Guidance for Industry and FDA Staff DRAFT GUIDANCE. (n.d.). https://www.fda.gov/media/119958/download

Title. (2014). https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf

Software and Digital Health Policies Issued by FDA. (2023). Akin Gump Strauss Hauer & Feld LLP - Software and Digital Health Policies Issued by FDA; Akin Gump Strauss Hauer & Feld LLP. https://www.akingump.com/en/insights/blogs/ag-data-dive/software-and-digital-health-policies-issued-by-fda

General Principles of Software Validation; Final Guidance for Industry and FDA Staff This document supersedes the draft document, "General Principles of Software Validation, Version 1.1, dated June 9, 1997. U.S. Department Of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health Center for Biologics Evaluation and Research. (2002). https://www.fda.gov/media/73141/download

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Advancing connected healthcare through regulatory innovation, collaboration, and compliance strategy.