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4 Things You Need to Know About Combination Drug Compliance

Four essential insights for navigating the complex world of combination drug compliance.

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Combination products are a fascinating area of the pharmaceutical industry and present great future promise. The segment is projected to reach $115 billion in global sales by the end of 2019. It has grown solidly at a rate of 7.9% CAGR since 2013, and is projected to continue at that rate through 2019.[1]

Some of the key factors driving this growth include: higher levels of patient compliance, demand for minimally invasive surgeries, opportunities for precise pain relief, quicker healing and governments and non-governmental organizations (NGO) embracing combination drugs for their ease of administration.

Combination products defined in 21 CFR 3.2(e)[2] are therapeutic and diagnostic products that are composed of any combination of a drug, device, or biological products, with the intention of creating safer, more effective, precisely targeted and easier to administrate therapies.

While the technologies and innovations driving the combination product market deliver a great deal of value to patients and to the medical community, the novelty of these products is often challenging for drug developers and regulatory agencies. The marriage of two different disciplines – drug and medical device – creates a complex regulatory process that must be well managed. In addition, evolving regulations as the combination product segment matures can present challenges for older, legacy combination products.

What is 21 CFR Part 4?

In October 2004, the FDA released draft guidance, Current Good Manufacturing Practices for Combination Products. The final rule was published as 21 CFR Part 4 in January 2013 and became effective July 22, 2013.

While 21 CFR Part 4[3] did not create new requirements, it did clarify which cGMP rules need to be enforced based on how the product is produced, packaged and marketed.

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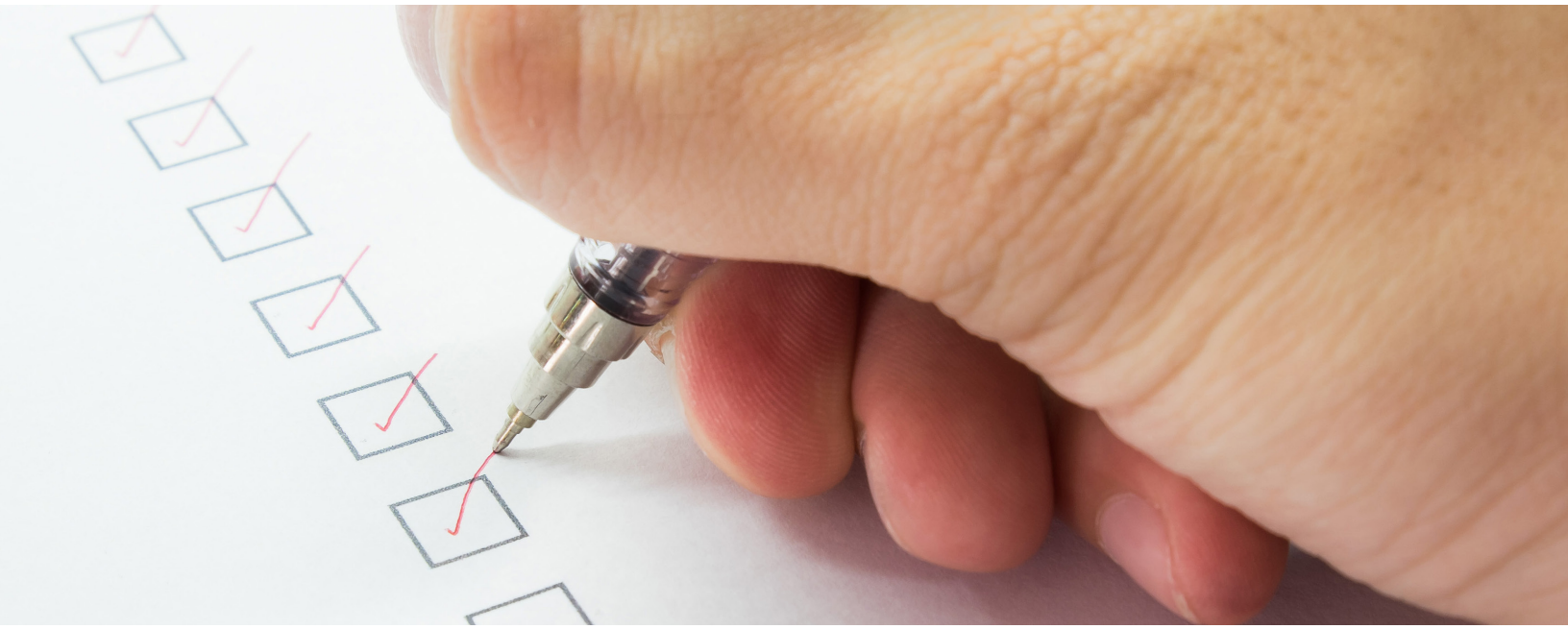
Specifically, if the constituent parts are manufactured and marketed separately, as may be the case for constituent parts of cross-labeled combination products, they remain separate for purposes of applying the cGMP regulations.

On the other hand, single-entity and co-packaged combination products are more complex. As much as possible, the final rule worked to utilize existing regulations for the component parts of combination drugs. The existing cGMP rules that apply to combination products are:

- 21 CFR 210[4] and 211[5] for finished pharmaceuticals
- 21 CFR 820[6] for devices
- 21 CFR 600-680[7] for biological products
- 21 CFR 1271[8] for human cell, tissue, and cellular and tissue-based products

21 CFR 4.1 – 21 CFR 4.4.4(e) specifies the regulatory rules and constructs for the individual components of a single-entity and co-packaged combination product, including a course of action for rectifying potential conflicts within the above listed regulations for the product's component parts.

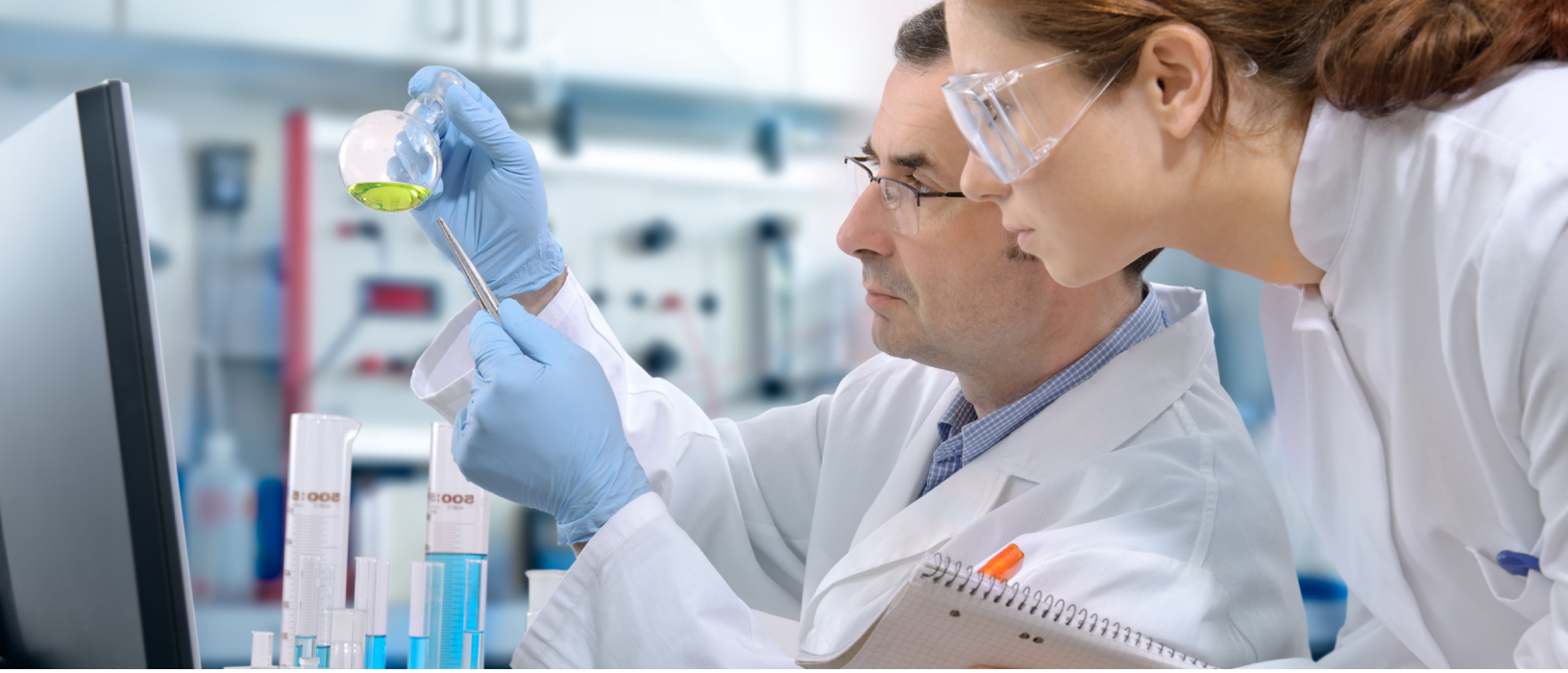


Understanding the Role of the FDA's Office of Combination Products

The importance of the FDA's Office of Combination Products (OCP) cannot be underestimated. This FDA office is a resource for agency reviewers and industry, assigns the lead center (CDRH, CBER or CDER) and designates the primary mode of action (PMOA).[9]

The PMOA is the action "expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." To clarify, the PMOA is the means by which the product is expected to have the greatest therapeutic impact, and in most cases is the action contributing the greatest risk.

A product's PMOA is presented within a Request for Designation document that explains the product's intended use, therapeutic benefits, how the product works and recommends the lead center assignment. A combination product is ultimately reviewed by CDRH, CDER, or CBER. However, as stated above, the OCP determines the lead center.



Bringing Legacy Combination Products into Compliance with 21 CFR Part 4

Regulation for combination products has been a lengthy journey, starting with the final rule for Medical Device GMPs made effective on December 18, 1978. Definitions of and jurisdictional questions for combination products started to be formally addressed in the early 1990s and ultimately formalized into law as 21 CFR Part 4 in January 2013.

Given the span of this regulatory journey, how do manufactures best ensure legacy product compliance with 21 CFR Part 4?

To begin to analyze legacy combination products for compliance with current law, a manufacturer needs to gather historical documents. Risk management and design verification analysis needs to be performed and any potential compliance gaps uncovered. The good news is we have existing tools for combined product risk management:[10]

- ISO 14971: 2007 – Medical Devices – Application of Risk Management
- 21 CFR 820.30(g): Risk Analysis – requires the identification of risks associated with the drug/device design, its manufacturing processes, and intended uses
- ISO 10993: Biological Evaluation of Medical Devices – tool for evaluating and demonstrating risks associated with biocompatibility.

Ultimately, manufacturers must have a Continued Design Verification mindset – essentially that the product is a state of design control. Evidence for the appropriate state of design control is recorded, per 21 CFR 820.30(j), in the Design History File.

"Bringing Legacy Combination Products into Compliance with 21 CFR Part 4," a presentation recently delivered at the CASSS CMC Strategy Forum, goes into greater detail on these issues. The primary initiatives manufacturers of legacy combination products should undertake include:10

- Quality system gap assessment
- CAPA - acknowledge gaps, create high level plan to remediate
- Update policies and create SOPs
- Prepare design and development plan and define high level milestones
- Create Design History File and index
- Create user-needs requirement document
- Compile and conduct risk analyses
- Prepare design input and output documents
- Compile historical design control verifications
- Verify proper design transfer
- Review change controls for design changes
- Conduct design review/verification meetings per 820.30(e)
- Conduct risk-based remediation(s)
- Prepare Design Verification Traceability Matrix (DVTM)
- Finalize the design and development plan and close the Design History File

Streamlined Approach for Review and Approval of Some Combination Products

The final rule, 21 CFR 4.4 (a), requires that a single entity or co-packaged combination product must meet all GMP requirements for the combination product's constituent parts (the specific rules applying to constituent parts are listed earlier in this article).

However, a manufacturer does have two different compliance options. The first is, as stated above, be fully compliant with the regulation for the product's constituent parts. However, the agency did acknowledge the similarities of the constituent parts GMP requirements. Therefore, a streamlined option4 was made available for products where the drug and device components have "arrived at, or are being manufactured at the same facility."

In these cases, a manufacturer could use 21 CFR 210/211 as their umbrella quality system provided they also incorporate the following provisions from the Quality System Regulations (21 CFR 820) within their quality system: design controls, purchasing controls, corrective and preventive action (CAPA), management responsibility, installation, and servicing.

Summary

The future of the combination drug product category is exciting as new technologies and innovative marriages of current technologies continue to come online. These advancements have tremendous potential, but will create ongoing regulatory complexity and the need for adaptive regulatory constructs. The expertise of the entire industry including manufacturers, regulatory agencies, suppliers, and supporting consulting organizations will be required to assure the tremendous promise for patients is fulfilled.

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SOURCES

1. Transparency Market Research, “Drug Device Combination Products Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 - 2019”

2. “Combination Product Definition,” FDA, 21 CFR 3.2(e)

3. “CGMP Requirements for Combination Products – Final Rule,” FDA, 21 CFR 4

4. “Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs; General,” FDA, 21 CFR 210

5. CGMPs for Finished Pharmaceuticals,” FDA, 21 CFR 211

6. “Medical Devices Quality Systems Regulation,” FDA, 21 CFR 820

7. “Biological Products,” FDA, 21 CFR 600-680

8. “Human Cells, Tissues, and Cellular and Tissue-Based Products,” FDA, 21 CFR 1271

9. “Frequently Asked Questions About Combination Products,” FDA website

10. “Bringing Legacy Combination Products into Compliance with 21 CFR Part 4,” Tracy TreDenick, BioTechLogic, CASSS CMC Strategy Forum presentation, July 2016