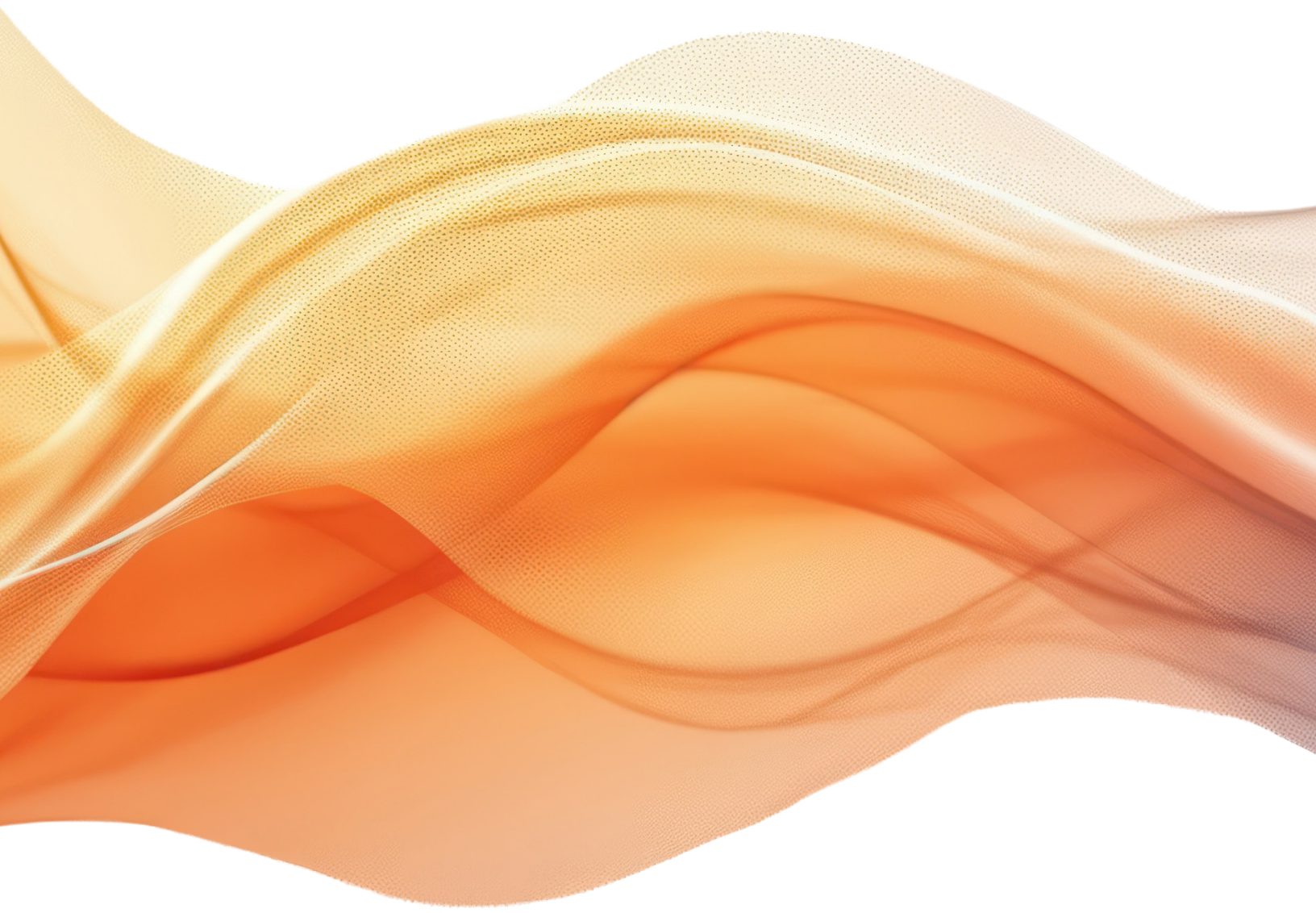
QualityHub Brief

DRUG-DEVICE COMBINATION PRODUCTS & QMSR COMPLIANCE

FDA Expectations for Device Constituent Parts



Foundational Overview

Pharmaceutical companies can find themselves on unfamiliar ground when developing combination products. It's not unusual for significant progress to be made on a product before realizing that even prepackaging a well-established drug or biologic in a standard, off-the-shelf syringe can significantly alter the regulatory landscape. As a result, pharma manufacturers must be aware that, in addition to compliance with the traditional US Food and Drug Administration (FDA) drug regulations, they are also subject to the agency's rules governing specific design and manufacturing aspects of medical devices.

Outlined below are key considerations for pharmaceutical companies, particularly those with a nascent understanding of combination product development and manufacturing.

Combination Product Determination per 21 CFR Part 3.2(e)

Combination Product Types	Product Examples
1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity.	• Prefilled syringes • Antibiotic impregnated meshes • Drug-eluting stents
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products.	• Convenience kits • Drug packaged with a delivery device
3. A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose).	• Photosensitizing drug and activating laser or light source • Iontophoretic drug delivery patch and controller

The fourth type of combination product is an investigational drug, device, or biological product packaged separately that, according to its proposed labeling, is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Regulatory Requirements for Device Constituents

The FDA requires companies that market combination products to comply with the Good Manufacturing Practices applicable to both drugs (cGMPs) and medical devices (Quality Management System Regulation, or QMSR), as outlined in 21 CFR Part 4.4. It is important to note that the FDA doesn't require compliance to all requirements for both drugs and devices.
For pharma companies currently manufacturing product in accordance with drug cGMP requirements, the FDA requires compliance with the following additional requirements of the QMSR, which is aligned with international quality systems standard ISO 13485:

Area	**QMSR (ISO 13485) Clause**
Management Responsibility	Clause 5
Design & Development	Clauses 7.1 (Risk) and 7.3
Purchasing & Supplier Controls	Clause 7.4
Complaint Handling	Clause 8.2.2
CAPA	Clauses 8.5.2 (Corrective Action) and 8.5.3 (Preventive Action)
Production & Service	Clause 7.5

The Production & Service provision generally doesn't apply to most combination products, but the remaining clauses can pose a challenge for pharma companies that aren't familiar with medical device regulations. Below is a high-level view of what each of the areas listed above requires from makers of combination products.

The medical device QMSR requirements made effective in February 2026 emphasize the application of risk management and risk-based decision-making across the entire quality system. This is very much in alignment with drug requirements in the ICH Q9 guideline on Quality Risk Management. The many points for application of risk in drug product GMP processes should be extended to the same Quality Management System (QMS) subsystems for the device constituent.

Points to consider in the application of risk to combination products include, for example:

- Supplier management based on the risk of the commodity or service supplied;
- The extent of investigations of deviations, nonconformances, complaints, and corrective and preventive actions (CAPAs) so it's commensurate to risk associated with the event in question;
- Escalation of quality events to higher levels of management review for key decisions on corrective actions;
- Justification of Acceptable Quality Limits (AQLs) in quality control inspections;
- Justification of confidence and reliability targets for process validation; and
- Risk mitigation in design to address product and usability hazards.

Management Responsibility

Management Responsibility requirements apply to the entire quality system, including the device constituent part and its integration with the drug or biologic. Top management must establish a quality policy, define roles and responsibilities, ensure adequate resources, and conduct regular management reviews that incorporate risk management, complaints, and CAPA across the whole product lifecycle.

In practice, this means leadership is accountable for ensuring the device-specific requirements are properly integrated into the overall combination product cGMP framework and not treated as a separate or siloed system.

A QualityHub auditing team with expertise in both pharmaceutical and medical device quality systems can conduct an assessment to identify a company's gaps and weaknesses in Management Responsibility requirements.

Design & Development

Design & Development activities are often the greatest challenge for pharma companies that are new to combination products. Manufacturers must establish controlled design processes, including design inputs and design outputs, verification and validation, design transfer, and change control, while incorporating risk management throughout the design lifecycle per international risk standard ISO 14971.

The FDA requires companies to ensure that all design aspects of the device constituent part, including the physical attributes, performance attributes, and quality attributes, are predetermined and controlled. Design & Development requirements cover the lifecycle of the device constituent, from initial development through post-market surveillance.

Purchasing & Supplier Controls

Pharmaceutical companies recognize the importance of using qualified suppliers and having strong supplier systems in place, but the Purchasing & Supplier Controls demanded by the QMSR may include specific requirements not present in a drug firm's current Supplier Management Systems. These requirements often require more stringent auditing and evaluation of suppliers.

Makers of combination products must qualify, monitor, and reevaluate suppliers using a risk-based approach; ensure purchasing requirements are clearly defined; and verify that incoming products and services meet specified requirements. The need for robust Purchasing & Supplier Controls becomes even more critical when significant aspects of the device constituent are outsourced, as noted on page 5 of this QualityHub Brief.

Complaint Handling

Manufacturers of combination products are required to implement procedures for handling complaints, including their receipt, evaluation, and investigation. They must also assess whether complaints are reportable and ensure they are integrated with risk management and CAPA processes.

Complaints must be evaluated for both device and drug/biologic failure modes, including use errors, device malfunctions, and labeling issues. Companies must also ensure appropriate regulatory reporting (e.g., Medical Device Reports [MDRs] or Field Alert Reports [FARs]) and maintain complete complaint records with documented investigations and conclusions. Complaints must be assessed holistically – considering the entire combination product – to ensure safety signals are properly identified, trended, and addressed.

CAPA

Whereas the intent of corrective and preventive actions are interwoven throughout the operational processes of most pharmaceutical companies, the QMSR's CAPA clauses explicitly define the requirements. CAPA serves as a central mechanism to drive continuous improvement and ensure that recurring or systemic issues are eliminated across the entire combination product lifecycle, not just isolated to one constituent part.

Manufacturers must investigate nonconformities, determine root causes, implement corrective actions, and evaluate their effectiveness using a risk-based approach linked to product safety and performance. A CAPA system must also incorporate inputs from complaints, production data, internal audits, supplier issues, and post-market surveillance to ensure a complete understanding of system-wide risks. Actions must be proportionate to the severity and likelihood of harm, and changes must be controlled to prevent unintended impacts on either the device or drug/biologic constituent.

A rigorous gap analysis is prudent to ensure all the requirements are adequately met, or to identify the need for additional procedures to ensure compliance.

Contract Manufacturing of Device Constituents

It's not unusual for a pharmaceutical company to use a contract manufacturer to help assemble and manufacture the device elements of their combination products. Ultimately, however, the responsibility of quality system compliance remains with the company that registers the finished combination product and cannot be delegated to the vendor. Some key areas to consider when using a contract manufacturer for device constituents include:

Supplier Audits

Strong supplier audits are important, not simply for the purpose of regulatory compliance, but because they also make good business sense. The loss of a critical contract manufacturer could be perilous for a business. A company should never assume that its vendor is in compliance, but rather take every step to ensure they are properly meeting all the regulatory requirements to work on your product, including the QMSR, ISO 13485, and ISO 14971.

Simply being registered with the FDA, or even previously passing an FDA inspection or Notified Body audit, is not a substitute for auditing a vendor's capabilities to manufacture a specific combination product constituent. An experienced third-party auditor can be helpful because a large number of pharmaceutical firms do not have in-house expertise in medical device compliance.

Design Transfer

Even if your pharmaceutical company is purchasing a standard, off-the-shelf item from a device component supplier, the responsibility for design controls is not transferred to the contract manufacturer. Specifications for the product they're making must be controlled from a drug manufacturer's internal design control processes, and the company retains responsibility for compliance of their contractor's manufacturing methods.

Areas where design transfer should connect to a contract manufacturer include:

- Materials and components,
- Qualified equipment,
- Validated processes,
- Appropriate verification activities,
- Work instructions and procedures,
- Test methods, and
- Operator training.

Production and process controls should be authorized and approved by the pharma company because it has ultimate responsibility for a product's quality. Changes to production and process controls should be discussed and approved by the drug manufacturer.

Design Changes

Any change to the device component of a combination product, no matter how small, must be handled in accordance with a pharmaceutical company's internal design control requirements. These include changes to:

- Labeling,
- Component designs,
- Materials or raw material suppliers,
- Test methods, and
- Manufacturing processes.

Problems can occur when contract manufacturers make changes to its manufacturing process without the knowledge of the finished combination product maker. The device component may not be visibly different following the change, but it must still be reviewed and documented through Design & Development procedures.

A pharma company must make sure that quality agreements with contract manufacturers have adequate language to ensure visibility and control over any, and all, changes that involve combination products.

Assessing New Contract Suppliers for Device Constituents: Key Considerations

There is no substitute for having strong controls in place for contract manufacturers, but there are some helpful things to consider when evaluating a new device component supplier for a combination product.

- **Use a contract manufacturer whose primary competency is in making medical devices or combination products.** Recognize that even though a company may have a long history of success in making circuit boards or other products that provide a similar function to the device component of a new combination product, they might lack QMSR, ISO 13485, or ISO 14971 expertise.
- **Ensure the contract manufacturer is cleared in the EU and with the FDA.** Ask for copies of all Notified Body audit reports for at least five years, as well as any FDA-483 inspectional observation forms, warning letters, Establishment Inspection Reports, and all FDA correspondence. These could indicate issues that could impact the contract manufacturer's ability to manufacture a combination product.
- **Do not rely solely on the results of previous FDA inspections to assess a contractor's current state of compliance.** Inspections provide only a snapshot in time and may not cover all aspects of the QMSR relevant to a new combination product.