COMBISOLVE

Regulatory Compliance for Combination Products

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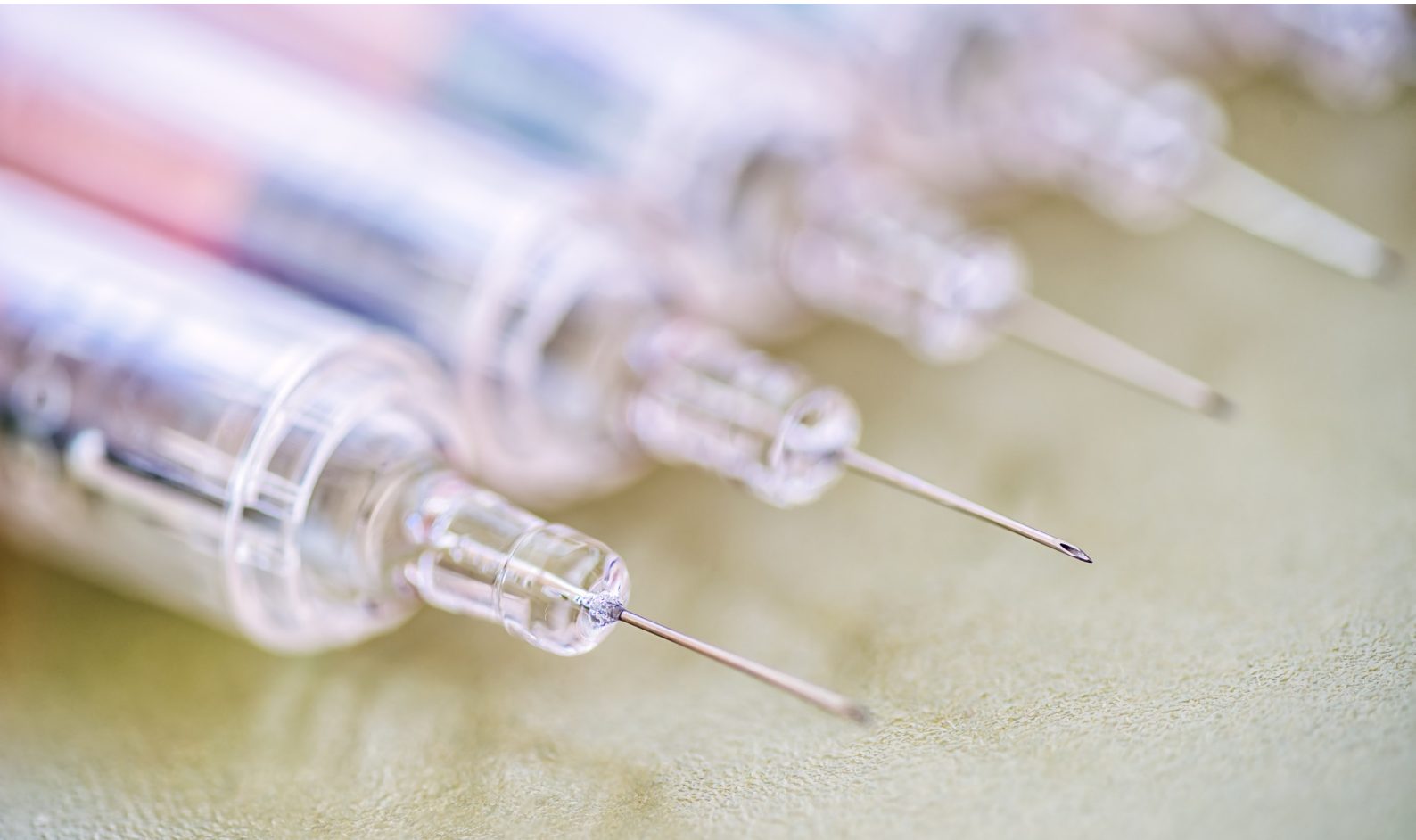
Combisolve is specialized in regulatory compliance and quality assurance for combination products. Our focus is on the medical device component, including the medical device interrelations between the biologic, drug and medical device in the combination product, and concerns the US combination products regulatory compliance requirements.

Companies who market or want to market a combination product in the US face specific challenges to get and keep their products regulatory compliant. Although no new requirements are added, the scope for conforming with the requirements has changed.

- What unfamiliar compliance requirements will traditional pharma companies face?
- And what unfamiliar compliance requirements will traditional device manufacturers face?

With 21 CFR 4 FDA introduced cGMP requirements for combination products. A combination product is a combination of two or three different types of the following regulated products: a biological product, a drug, or a medical device. In 21 CFR 3 FDA recognizes four types of combination products: single entity, co-packaged, cross-labelled, and (investigational) cross-labelled. FDA's Office of Combination Products (OCP) classifies combination products for regulation, coordinates the regulations within FDA and is a resource for the industry.

Examples of combination products are prefilled syringe, insulin injector pen, metered dose inhaler, transdermal patch, drug eluting stent, pacing lead with steroid coated tip, catheter with antimicrobial coating, condom with spermicide, bone graft implant, and photodynamic therapy.



For manufacturers in general there are two ways to conform with the regulations:

1

Ensure conformity of the combination product by

Applying all cGMP regulations applicable to each of the parts

2

Ensure conformity of the combination product by

Only applying the drug cGMP regulations
(21 CFR 210 and 21 CFR 211)

or by

Only applying the biologic cGMP regulations
(21 CFR 600-680)

or by

Only applying the device cGMP (QS) regulations
(21 CFR 820)

or by

Only applying the current good tissue practice requirements including donor eligibility requirements for HCT/P
(21 CFR 1271)

However, manufacturers must ensure the following. If parts - drug, biologic, device, and HCT/P (human cell, tissue, and cellular and tissue-based product) - are combined in a combination product, each individual part keeps its own cGMP requirements for conformance. The idea is that if any conflict or ambiguity appears, you follow the most specifically applicable regulation.

Depending on the primary mode of action (PMOA), the drug or device constituent of a combination product now got another regulatory and quality assurance status. FDA assigns a manufacturer's combination product to one of the following FDA divisions for taking the lead in approval, inspection, etcetera:

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)

The assignment of a combination product is based on its PMOA, which is the most important therapeutic action of a combination product.

Our solutions comprise the specific expertise and activities required for application in combination products pre-market and post market situations.

Market Access Solutions

We support regulatory compliance and market access for your new combination products, including post-market QS requirements. Main services: regulatory compliance, clinical evaluation, global registration, training. Combination product manufacturers should address many points, such as:

1. Any entity that undertakes any of the following activities in the manufacture of a combination product is considered to be a manufacturer : designing, fabricating, assembling, filling, processing, testing, labelling, packaging, repackaging, holding, storage of a combination product.
2. What is the best strategy and approach towards FDA? How clear is the FDA combination product assignment process and what about the cooperation between the Centers? When and how to communicate with what FDA division? Now for drugs their focus on risk management is during manufacturing, while for devices their focus is during the development phase. How to have a single risk management view of the final combination product?
3. How to choose the right approach and how to integrate cGMPs and QSRs into combination products? You must justify what you choose to follow, especially in areas where they conflict. Companies who traditional are more pharmaceutical companies must decide how to integrate specific medical device 21 CFR 820 QS requirements such as design controls and CAPA/medical device reporting (MDR). Companies who traditional are more medical device companies must decide how to integrate the pharmaceutical 21 CFR 210 and 211 cGMPs such as stability and theoretical yield.
4. The depth and breadth of the design history file (DHF) for a device in a drug-device submission should be scaled to the complexity and risk associated with the product.
5. If you want to market your combination product in the US and the EU, what differences must be taken into account and how to avoid wasting time and money?

Remediation Solutions

We support regulatory compliance and QS requirements for your current combination products. Also your QMS will be upgraded for handling future combination products. Main services: regulatory compliance, clinical evaluation, quality assurance, auditing, training. Combination product manufacturers should address many points, such as:

1. You do not want to apply and implement the regulations with duplication of effort or resulting in a non-compliant QS. Often there is no need to create all new procedures. And it is possible to integrate the two regulations to have one compliant QS.
2. If you approach gaps in your current QS and want to implement and maintain a successful and compliant QS for combination products then consider the following. Review your current combination products portfolio and develop a risk-based strategy that give you the opportunity to identify critical areas to devote more attention and resources, instead of spreading the same amount of resources across the entire supply chain, where deficiencies might be missed.
3. Prevent that corrections have more widespread implications than initially thought and new gaps may occur or existing gaps may no longer be completely addressed. Quality systems are linked and remediating one may lead to the need to update other QS elements as well.
4. Ensure knowledge exchange between drug and device experts that have traditionally not interacted, such as between software engineers, industrial designers and medical experts.
5. Purchasing controls must include risk management techniques for selecting suppliers and addressing remedial and corrective actions for noncompliant products.
6. Other requirements to reconsider for combination products are in the area of CAPA, change control, packaging and labelling, laboratory controls, retention and holding, and stability and reserve samples.

Process Improvement Solutions

We improve business processes for your combination products. We implement best practice processes, information systems and organizations. And if you want we - temporarily - run specific processes for you. Main services: process implementation, information system application, interim management, staffing, outsourcing, training. Combination product manufacturers should address many points, such as:

1. To ensure knowledge exchange between drug and device experts that have traditionally not interacted, a realignment of organizational structures, processes or technologies may be necessary. This can be a major change initiative in a (bio) pharmaceutical or medical device company and requires top management buy-in and approval.
2. Complaint handling requires a formal unit designated for combination product complaint handling. Documentation related to reportable events needs to be clearly identified and maintained in a separate portion of the compliant files. And the reporting of adverse events follows a different timeframe.
3. How to deal with differences in management responsibilities between drugs and devices? For devices management responsibilities are specifically detailed in the QSR and require having an adequate organizational structure and conducting periodic management reviews of the quality systems. For drugs management responsibilities are not explicitly described in the drug cGMP regulations, are general and require all employees to be qualified and trained for their job responsibilities.
4. Document control requirements differ between devices (QSR) and drugs (cGMP). The combination product manufacturer must consider how to manage internal documentation for compliance with applicable QSR and cGMP requirements. How to align your processes, information systems, organization and suppliers?

COMBISOLVE

Combisolve represents service providers who deliver these services. Our main partners are Qserve and Vormation.

Qserve

Qserve group, a global leading medical device consultancy group.

vormation

Vormation is an international business development, interim management and consultancy company.

For more information
please contact us:

info@combisolve.com
+31653396985
www.combisolve.com

Amsterdam (HQ), Arnhem
Boston, San Francisco
Beijing, Nanjing