Considerations in Combination Product Risk Management

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ABSTRACT

Drug-device combination products are rapidly increasing in use based upon the numerous benefits they provide. Successful development and commercialization requires demonstration of performance and regulatory compliance. This article is a brief review of a webinar that discussed approaches to achieving both.

BACKGROUND

This article is a review of select aspects of the webinar *Creating an Effective Combination Products Risk Management Program: Special Considerations for Control and Analytical Testing Strategies Development*. (1)

Drug-device combination products (CP's) are an ever-increasing presence in the pharmaceutical landscape. Benefits include more convenience for patients, lower costs from fewer/eliminated hospital/clinic visits, fewer steps in usage as drug product may not need to be withdrawn from a vial, better safety with automatic needle retraction, and better compliance through connectivity such as smartphone apps. As with any pharmaceutical product, commercial offering requires demonstration of performance and compliance with applicable regulations. (2)

The FDA defines a CP as comprising two or more components and classifies them into four types: (3)

- Drug + Device
- Drug + Biologic
- Biologic + Device
- Drug + Biologic + Device

Each component retains its regulatory status. For example, a CP composed of a drug and a device must meet the regulatory requirements of both the drug and the device. Table 1 lists the applicable regulations.

TABLE 1: Regulatory Requirements for Components of Combination Products (4)

		Drug	Device	Biologic
Regulations		Drug cGMP 21 CFR 210 & 211	Quality System (QSR's) 21 CFR 820 (a)	Biological Product 21 CFR 600-680, 1271
FDA Lead Center (e)		CDER (b)	CDRH (c)	CBER (d)
Types	Drug + Device	√	√	
	Drug + Biologic	√		√
	Biologic + Device		√	√
	Drug + Biologic + Device	√	√	√

(a) FDA recognition of ISO 1345 is pending, (b) Center for Drug Evaluation and Research, (c) Center for Devices and Radiological Health, (d) Center for Biologics Evaluation and Research, (e) FDA center with primary jurisdiction for pre-market review and post-market regulation

There are three categories of CP's. (5).

- Single Entity: A product comprised of two or more regulated components … that are physically, chemically, or otherwise combined or mixed and produced as a single entity [21 CFR 3.2 (e) (1)]
- Co-Packaged: Two or more separate products packaged together in a single package or as a unit [21 CFR 3.2 (e) (2)]
- Cross-Labeled: 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 product [21 CFR 3.2 (e) (3)(4)]

Examples are given in Table 2.

TABLE 2: Examples of Combination Products

Single Entity (drug delivery)	**Single Entity** (medicated device)	**Co-Packaged**
pre-filled autoinjector	drug-coated catheters	convenience kits • injection pen with user-loaded pre-filled cartridge • liquid medication with dose dispenser (e.g., cup, pipette, spoon) • surgical tray with anesthetic and surgical scrub • vial and syringe package
drug-eluting contact lense	antibiotic bone cements	
dry-powder inhaler	spermicidal condoms	
iontophoretic delivery system	drug-coated pacemaker leads	
metered dose inhaler	drug-coated stents	
pre-filled nasal sprayer	antimicrobial surgical gloves	
pre-filled pen injector	antimicrobial wound dressings	
pre-filled on-body delivery systems	antibiotic-impregnated surgical mesh	
pre-filled syringe	**Cross-Labeled**	collagen sponge with bone morphogenic protein
transdermal patch	photodynamic therapy (light-emitting device and a drug activated by that light	
Single Entity (drug-biologic)		
antibody-drug conjugates		
progenitor cells with a drug		

A CP is distinguished from a *combination therapy*. A combination therapy is composed of either two or more drugs, or two or more devices. The components of the combination therapy are governed by the same regulation. In contrast, the components of a CP are governed by two or more regulations.

REGULATIONS

Each CP has multiple modes of action; these are based on the intended use or therapeutic effect of each of its components. The primary mode (PMOA) is the most significant in contributing to the overall intended use. This is illustrated by the examples below.

CP	Primary mode of action		Secondary mode of action	FDA lead center (*)
Drug-eluting stent	Device	Opens artery to treat arteriosclerosis	Drug prevents inflammation and restenosis of artery	Center for Devices and Radiological Health
Drug-eluting disc	Drug	Treats brain tumor (chemotherapy)	Disc enabled localized delivery of drug	Center for Drug Evaluation and Research
(*) FDA center with primary jurisdiction for pre-market review and post-market regulation				

The PMOA determines the FDA lead center that has primary jurisdiction for pre-market review and post-market regulation.

The FDA offers two options for regulatory compliance. The first is the *full-compliance* approach [i.e., demonstrating full compliance with all applicable regulations for each component (constituent part) of the combination product]. See Table 1. The second is the *streamlined* approach. In this approach, the FDA recognizes there are common elements among the regulations while also calling out specific regulatory elements for the constituent parts that are uniquely interpreted. A market authorization holder (MAH) (legal manufacturer in device terminology) fully implements its base quality management system (QMS), and supplements that QMS with the called-out QMS elements for the additional constituent part(s). For example, a pharmaceutical company with a drug cGMP-based QMS, which is the MAH for a drug-device combination product, would demonstrate full compliance to all the elements of the base drug cGMP QMS requirements. In addition, the company would need to demonstrate compliance to the device quality system regulation (QSR) call-outs applicable for the device constituent part of the CP. The call-outs specified under 21 CFR§4A, Combination Product cGMPs, are listed in Table 3. (6)

TABLE 3: Called-out Provisions of 21 CFR under the Streamlined Approach (21 CFR §4A) (6)

Device QSR Provisions	
§820.20	Management Responsibility
§820.30	Design Controls
§820.50	Purchasing Controls
§820.100	Corrective and Preventative Action
§820.170	Installation
§820.200	Servicing
Drug cGMP Provisions	
§211.84	Testing and Approval or Rejection of Components, Drug Product Containers, and Closures
§211.103	Calculation of Yield
§211.132	Tamper-Evident Packaging Requirements for Over-the-Counter (OTC) Human Drug Products
§211.137	Expiration Dating
§211.165	Testing and Release for Distribution
§211.166	Stability Testing
§211.167	Special Testing Requirements
§211.170	Reserve Samples

Biological Product Provisions	
§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 Preparation / Limits of Potency
§610.30	Test for Mycoplasma
§610.40-48	Testing Requirements for Communicable Diseases
§610.50	Date of Manufacture
§610.53	Dating Periods for Licensed Biological Products
§610.60-68	Labeling Standards
§1271	Human Cells, Tissues and Cellular and Tissue-Based Products

PERFORMANCE

Successful CP development and commercialization relies on risk management through all phases, i.e., early development, late development, and lifecycle management. This comprises risk management of the components and the CP. Accomplishing this requires a focus on establishing and demonstrating essential performance requirements (EPR's). EPR's can be generally considered as design input requirements essential to effective use of a CP and components that are achieved at an acceptable level of risk.

There are a variety of tools available to support risk analysis, e.g., failure modes and effects analyses (FMEA's), fault tree analyses (i.e., Ishakawa diagrams), human factors studies, and stability studies. This can include cross-functional involvement and be a very involved process. As an example, Table 4 lists selected EPR's that could be considered for a self-injection system employing a syringe. It must be demonstrated that the drug is effective. It must also be demonstrated that the device protects the drug, is compatible with the drug, functions properly, and is usable by intended users in the use environments (i.e., has an effective user interface).

TABLE 4: Selected Essential Performance Requirements for a Self-Injection System Employing a Syringe

Drug / Biologic				
purity	stability	volume	viscosity	structure
elution profile	particle size	concentration	acute / chronic exposure	
dose ranging / finding		chemistry, manufacturing, and controls (CMC)		
pharmacokinetics (PK)		local / regional / systemic toxicities		
Device (Protection)				
container closure integrity		permeability	microbial ingress	
dimensional tolerances		component inter-connectivity		
Device (Compatibility)				
biocompatibility	particles	extractables / leachables	loss of API via absorption or adsorption	
contaminants (tungsten, silicone oil)		surface interactions, adverse chemical reactions, particle formation		
Device (Performance)				
drug viscosity	injection rate	permeability	siliconization	shelf-life
coating integrity	clarity of units of measure		break-loose / extrusion force	
back-pressure	needle gauge / length / insertion		clarity of dose completion	

A robust approach to demonstrate successful performance is a test plan based on recognized guidances and standards. Examples are:

- USP <87> *Biological Reactivity Extraction Solvents Tests, In Vitro*
- USP <381> *Elastomeric Closures for Injections*
- USP <382> *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems*
- USP <660> *Containers – Glass*
- USP <661> *Plastic Packaging Systems and Their Materials of Construction*
- USP <787> *Sub-Visible Particulate (SVP) Matter in Therapeutic Protein Injections*

- USP <788> *Particulate Matter in Injections*
- USP <790> *Visible Particulates in Injections*
- USP <1184> *Irritation and Skin Sensitization*
- USP <1207> *Package Integrity Evaluation - Sterile Products*
- Ph. Eur. 3.2.9 *Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders*
- Ph. Eur 3.2.1 *Glass Containers for Pharmaceutical Use*
- JP 7.01 *Test for Glass Containers for Injections*
- JP 7.03 *Test for Rubber Closure for Aqueous Infusions*
- ISO 10993 *Series Biological Evaluation of Medical Devices*

The test plan may require considerable effort. For example, consider the evaluation of a CP comprising a prefilled syringe. In the Figure is shown the ISO 11040 series of standards that form the basis of performance evaluation. (6)

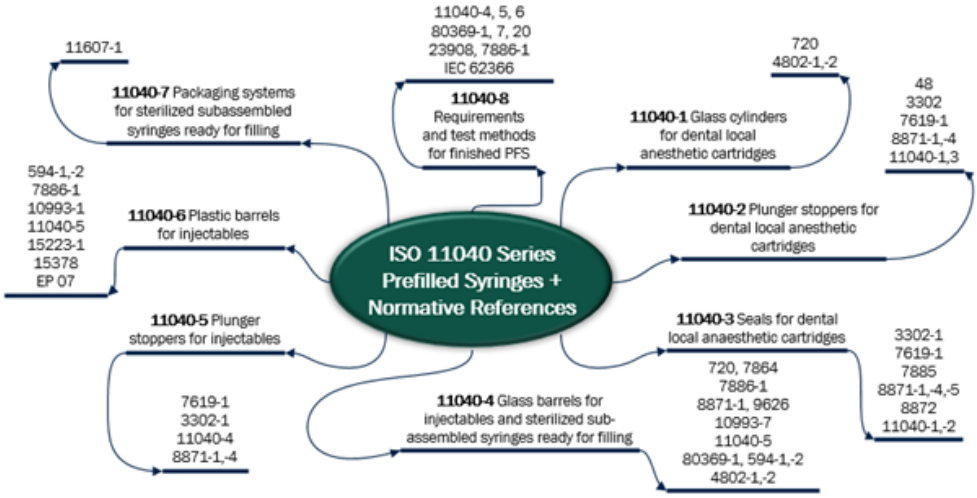

FIGURE: ISO 11040: Prefilled Syringes – Sections and Normative References

SUMMARY

Development and commercialization of combination products requires demonstration of essential performance requirements and compliance with applicable regulations. This requires a test plan informed by applicable guidances/standards and an intimate understanding of regulations; neither of which is a small task. Time to market can be reduced through partnership with an organization intimately familiar with both aspects.

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