AAPS Open

RAPID COMMUNICATION

Open Access

Stability considerations for drug-device combination products-21 CFR part 4 update

Christopher Latoz[1*], Laure Larkin[2] and Kim Huynh-Ba[3]

Abstract

Combination products are therapeutic and diagnostic products that include two or more of the following: drug, biologic, and device. These products are needed for enhanced clinical outcomes and have more than one Mode of Action (MOA). Therefore, they require a more complex regulatory pathway and compliance with a minimum of two (2) sets of regulatory standards. In 2013, the 21 Code of Federal Regulations (CFR) Part 4 was published to clarify the applicable GMP regulations when drugs, devices, or biological products are included. The FDA (U.S. Food and Drug Administration) released additional guidance in 2017 to streamline the regulatory framework and provide transparency about demonstrating GMP compliance when multiple regulatory standards overlap. This paper summarizes the Current Good Manufacturing Practice (CGMP) requirements for drug-device combination products (Biologic combinations are not discussed in this paper). Emphasis is placed on considerations for structuring a compliant drug-device stability program, including the use of bracketing and matrixing the test schedule to support the establishment of the product expiry date and how legacy products can be evaluated to meet current standards.

Keywords Stability, Combination device, Drug-device, Design controls, Quality by design, Bracketing, Matrixing, FDA, CGMP

Introduction

Combination products are therapeutic and diagnostic products that include two or more of the following: drug, biologic, and device. The official definition per the U.S. FDA is "a combination product is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another)." (FDA 2015). These products generally have more than one Mode of Action (MOA), such as physical and chemical, and are needed for enhanced clinical outcomes. Therefore, they require a more complex regulatory pathway and compliance with a minimum of two (2) sets of regulatory standards.

*Correspondence:
Christopher Latoz
chrislatoz@yahoo.com
[1] Hollister Incorporated, Libertyville, IL, USA
[2] Ethicon Inc, Raritan, NJ, USA
[3] Pharmalytik LLC, Newark, Delaware, USA

In 2004, the FDA first released the draft guidance for combination products and published the final rule 21 CFR Part 4 in January 2013, which became effective in July 2013. While this document doesn't detail any requirements, it clarifies which GMP rules are applicable when drugs, devices, or biological products are included (CFR 2022). The FDA issued additional guidance in 2017 to streamline the regulatory framework and provide transparency about demonstrating GMP compliance when there are multiple regulatory standards and some requirements do not overlap (FDA 2015). For this article, only two types of combination products are considered: single entity and co-packaged. Cross-labeled combination product types exist but are not covered in this article.

Co-packaged combination products are two or more separate products stored in a single package or as a unit. In contrast, single-entity products comprise two or more regulated components (i.e., drug/device, biologic/drug)

that are physically, chemically, or otherwise combined into a single unit.

Among the most common combination products are drug-device. Drug-eluting stents and transdermal nicotine patches are two common examples of single-entity combination device products. In contrast, surgical kits containing drug and device constituents, such as a vial containing a drug product and a separate dispensing device, are co-packaged. Over the years, more and more drug and device manufacturers have become interested in developing combination devices, though many lack in-depth knowledge and expertise in the non-primary regulations. Looking at the similarities and differences between the design requirements of drug products and medical devices is a great starting point.

Comparison of Medical Device (Design Controls) and Drug (QbD)

"Design controls" for medical devices are required for designing, developing, and making design changes. The process of establishing design controls for medical devices, similar to the quality-by-design (QbD) process applied to traditional pharmaceutical products, begins in the Concept Design phase (Fig. 1). Here user and stakeholder needs are developed, which describe what the device should do and how it should function. Typically, a cross-functional team is assembled, and factors such as users and use environment, indications and intended use of the device, device and packaging functionality, and desired marketing claims related to the product use are considered. Focus groups and marketing research are invaluable tools in developing user needs. Stakeholders may have additional requirements related to the use of the product and user experience, which may need to be considered.

Once the user and stakeholder needs have been defined and agreed upon, design inputs (a device's physical and performance characteristics) are created from the user/stakeholder needs and used as a basis for device design. The design outputs are the established deliverables demonstrating that the device meets the design inputs and may include component specifications, packaging, labeling, production specifications, and drawings. After successful design verification and validation of the finished device, the design of the device is transferred into production during the Design Transfer phase.

All the Design Controls, including team members, roles and responsibilities, deliverables, and timing, should be captured in the Design and Development Plan (DDP). The DDP will be part of the overall design history file (DHF), which is required by both the International Organization for Standardization (ISO 13485) and the FDA (21 CFR 820). Changes from the established DHF must be documented and justified through a change control program to avoid unintended impacts on product quality.

The drug industry has adopted an approach of controlling process design with the Quality by Design (QbD) concept. In short, QbD employs statistical, analytical, and risk-management methodology in the design, development, and manufacture of pharmaceutical products. Figure 2 shows the relationship between the Design Controls used for medical devices and the QbD concept applied to pharmaceutical products. Combination device manufacturers must consider Design Controls to establish the critical quality attributes (CQA) for product development. Therefore, they must have a structured and solid design history file (DHF) to document the validation, verification, and transfer necessary for their products.

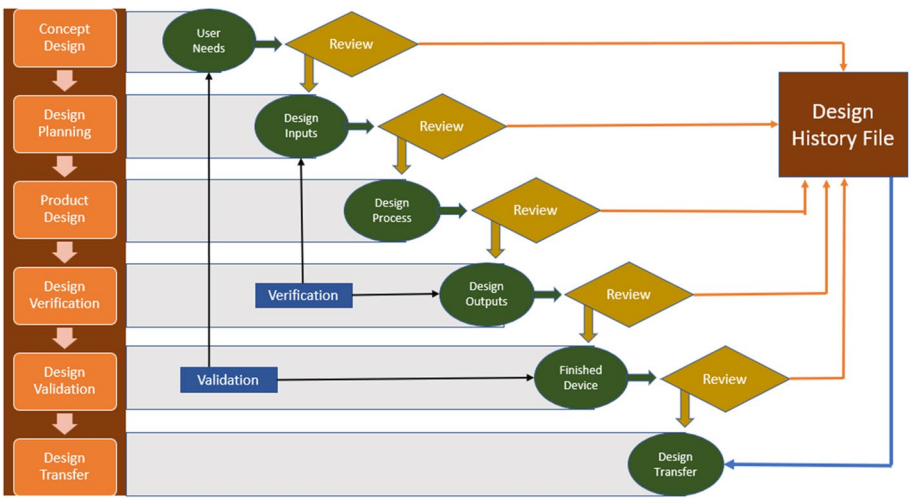

Fig. 1 Design Control Cycle for Medical Devices

Understanding how design controls are tied into combination product stability is critical to managing changes and maintaining product quality. Figure 3 shows the content of the design history profile that a drug-device combination product should maintain. Validation activities are initiated based on the user needs to gather information to develop the concept design. A design and development plan consists of the available design inputs and target goal for verification purposes. Data from product development are used to establish the critical attributes of the design. A validation protocol is developed to qualify the finished device based on the verification. The design will ultimately be transferred to manufacturing sites upon satisfactory

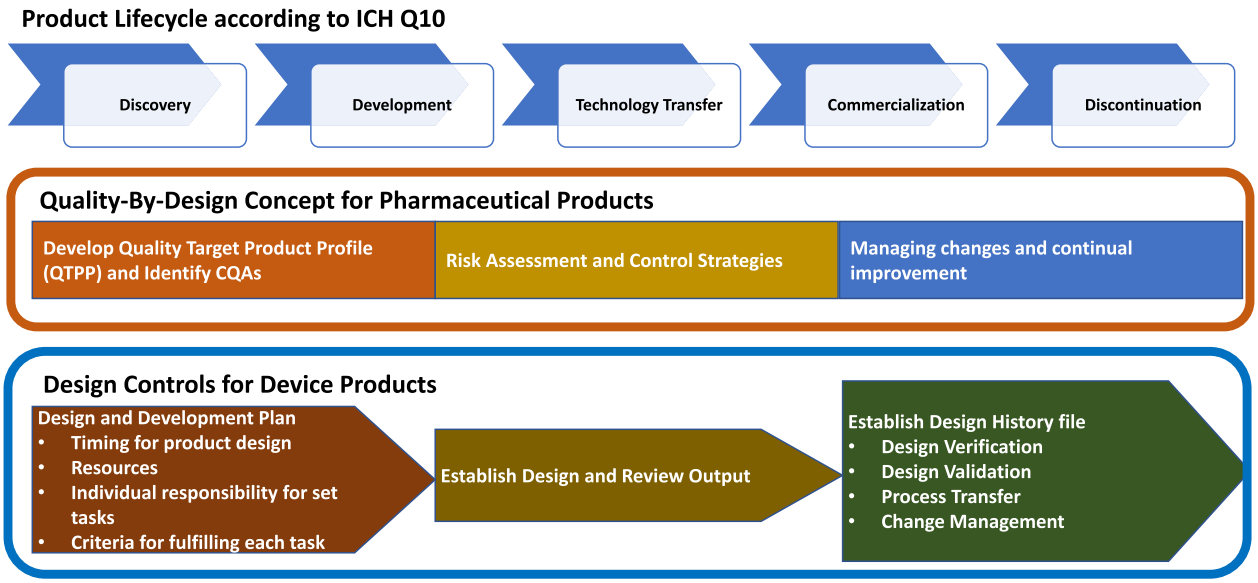

Fig. 2 Establishment of Design Controls based on QbD Concept

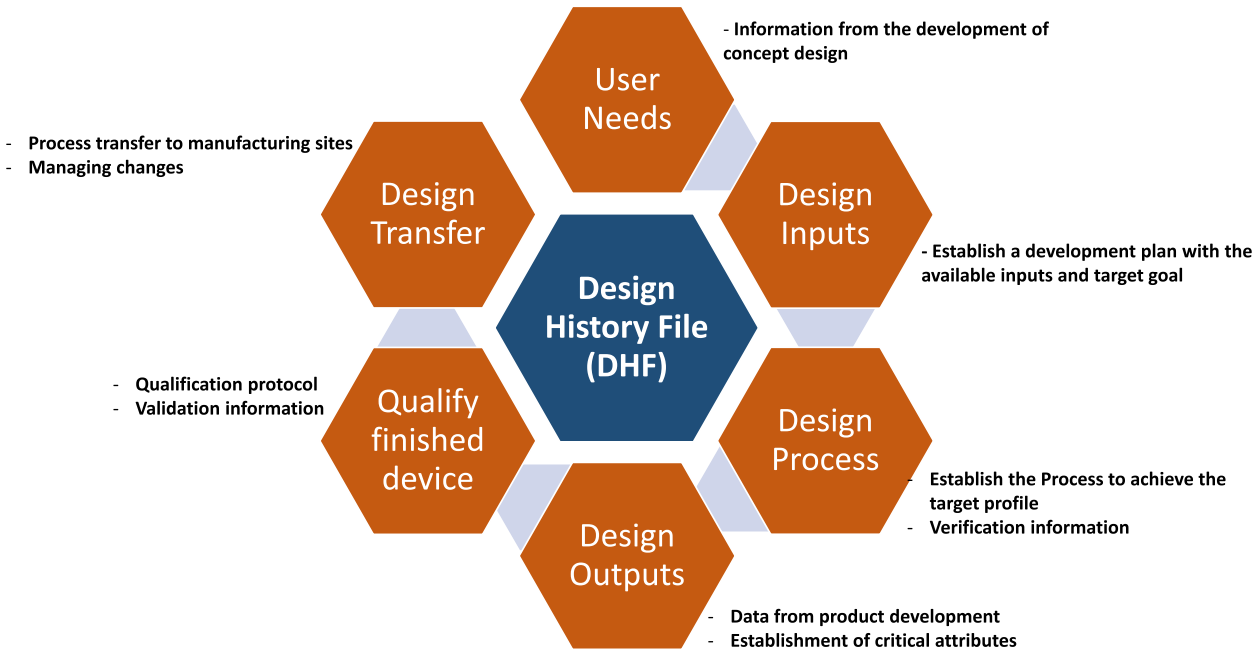

Fig. 3 Content of the Design History File

completion of validation. A change management system ensures the product quality continues to meet the user needs once it is commercialized. All data are retained in the design history file for the combination product.

Selecting which CGMP applies to a drug-device combination product

21 CFR Part 4 provides guidance as to which Current Good Manufacturing Practice (CGMP) requirements apply to co-packaged or single-entity combination products. For a combination product with a drug constituent, 21 CFR 210 and 21 CFR 211 apply. If the combination product includes a device constituent part, the Quality System Regulation 21 CFR 820 applies.

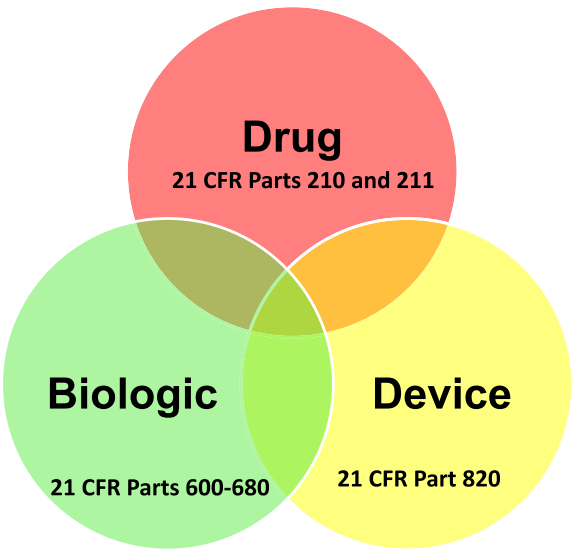

Fig. 4 Applicable 21 CFR Sections Based on Combination Product's Constituent Type

Figures 4 and 5 describes the 21 CFR sections that apply to combination products depending on the type of constituents (FDA 2015; CFR 2022). However, many CFR regulations overlap and can be applied to more than one product type. In those cases, the more stringent regulations will apply. The manufacturer must be aware of what regulations are applicable. If in doubt, a discussion with the agency is strongly recommended.

Current GMP and global regulations require that quality systems must be established. However, the "FDA acknowledged that there is no need for redundant CGMP requirements that are analogous between drug and device regs." (Amor 2016).

Consequently, combination product manufacturers are not required to have a Quality Management System that is fully compliant with both drug and device CGMPs. Instead, there are only select additional subparts of the medical device CGMP that need to be followed by drug manufacturing companies and select additional subparts of the drug CGMP that need to be followed by medical device companies venturing into combination drug-device products. It should be noted that there are globally recognized consensus standards specific to drugs or devices that are treated as requirements, specifically with regard to stability program requirements. They are discussed in later sections.

Summary of CGMP requirements for drug and device products

For a medical device manufacturer planning to manufacture a drug-device combination product, only the subparts from 21 CFR 211 shown in Table 1 below are required for the drug constituent. It should be noted that these are the key sections, and this list is not intended to be the complete list.

For a pharmaceutical product manufacturer planning to manufacture a drug-device combination product, the

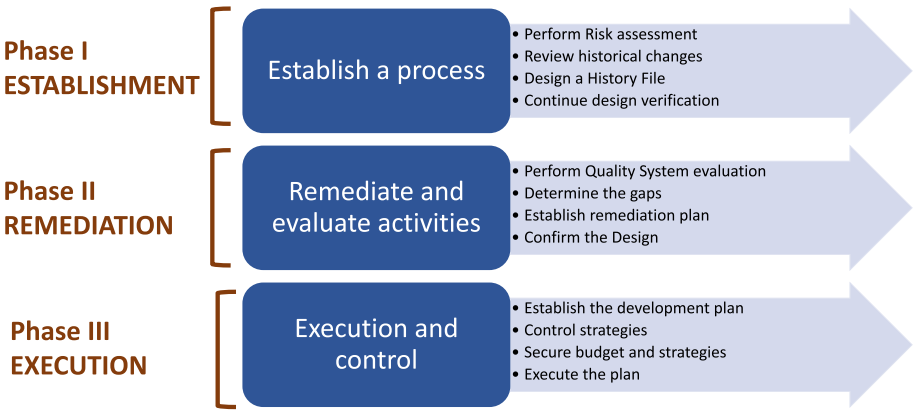

Fig. 5 Process to Bring Legacy Product to Meet Current GMP Compliance

subparts from 21 CFR 820 shown in Table 2 need to be added to their QMS scope.

Table 3 below summarizes the critical CGMP requirements for combination products with various constituent parts.

Ensuring legacy combination products meet current standards

Legacy combination products are defined as products that are no longer under development but have yet to be retired from the market. However, companies still need a plan to bring these legacy products up to current standards. A robust review should be executed for combination products marketed prior to the new regulations to determine compliance gaps. Any remediation changes need to be managed via the change management system. It is important to note that products marketed before June 1, 1997, are exempt from the new requirements.

Risk management and design verification analysis are very critical. The manufacturer can submit a request explaining the intended use, therapeutic benefits, and what lead center (the FDA center with primary jurisdiction for premarket review and regulation of the combination product) to review the application. This lead center will work with other centers as needed. The process of bringing legacy products to meet the current GMP Part 4 standard consists of three main steps.

Table 1 Additional 21 CFR Sections Applied to Combination Products with a Drug Constituent

Section Title	Summary of Section Content
21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures	Provides detailed requirements for a manufacturer to sample, test, examine, and accept or reject drug product components, containers, and closures. It is interesting to note that combination device manufacturers only need to demonstrate compliance with this section for device constituent parts or materials if the device constituent part is also the drug container or closure or a part thereof (FDA 2015)
21 CFR 211.103 Calculation of yield	Requires actual yields and percentages of theoretical yield to be determined at various stages of the manufacturing process**.** Verification of the calculated results is also required
21 CFR 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products	Applies to over-the-counter (OTC) drugs and how to demonstrate that they have not been tampered with before sale. OTC drug manufacturers must implement labels, tags, or other safety features that communicate that the drugs have not been modified or tampered with and remain safe and effective
21 CFR 211.137 Expiration dating	Helps ensure that drug products (or drug constituent parts) meet applicable standards of identity, strength, quality, and purity at the time of use. Expiration dating may be applied to the entire combination product or separately to the individual constituent parts of the combination product. For a co-packaged combination product with a single expiration date, the date is determined by the earliest expiration date (shortest shelf-life) for any constituent part. For the case of a drug-device combination product, the shelf-life is determined by the shortest estimated shelf-life of the following studies: drug stability, device aging, and packaging system (sterile barrier system) aging
21 CFR 211.165 Testing and release for distribution	Each drug product batch must be tested, conform to final specifications (including the identity and strength of each active ingredient), and be free of objectionable microorganisms before release. Any batch that fails to meet established standards or specifications must be rejected. Reprocessing is allowed, but the reprocessed material must meet the appropriate standards and specifications. For combination products, each batch must also be tested to ensure conformance to specifications for the drug constituent part. For single-entity combination products, laboratory testing must be performed on every batch of the combination product. In contrast, for co-packaged combination products, testing is only required for each batch of the drug constituent part
21 CFR 211.166 Stability testing	Requires a written stability program to assess the stability characteristics of drug products. The stability test results are used in determining storage conditions and expiration dates. Designing stability studies for combination products presents challenges as there may be vast differences in terms of stability requirements for drugs and devices. The selection of the number of batches, accelerated aging conditions, and the appropriate stability-indicating tests must be considered when establishing expiration dating for combination products. For a drug-device combination product, such as a drug-eluting stent, typical stability testing attributes may include appearance, assay/drug content, impurities/degradation products, drug release rate, particulate matter, and package integrity (FDA 2015). Matrixing and bracketing are encouraged; however, experience in this area is limited, especially with regions outside of ICH
21 CFR 211.167 Special testing requirements	Describes special testing requirements for drug products that are sterile and/or pyrogen-free, ophthalmic ointment, or a controlled-release dosage form
21 CFR 211.170 Reserve samples	Requires reserve samples to be included for every lot and sampled at twice the required quantity. For an active ingredient in a drug product, the reserve sample must be retained for one year after the expiration date of the last manufactured lot of drug product containing the active ingredient. Also included are special requirements for radioactive drugs and OTC drugs

Table 2 Additional 21 CFR Sections Applied to Combination Products with a Device Constituent

Section Title	Summary of Section Content
21 CFR 820.20 Management Responsibility	Requires management with executive responsibility (senior leadership) to be actively engaged in the oversight of the quality system. They are to establish and maintain an adequate organizational structure, establish key quality policies, and conduct a management review periodically to ensure that the QMS is effective
21 CFR 820.30 Design Controls	Requires the design and development process to be fully documented in a design history file (DHF). For a drug-device combination product, design control activities confirm that there are no negative interactions between constituent parts and ensure that their combined use results in a combination product that is safe, effective, and performs as intended
21 CFR 820.50 Purchasing Controls	Describes manufacturers' requirements to evaluate, qualify, continuously monitor, and control suppliers of materials and components. One way to facilitate purchasing controls is having well-defined supplier purchasing agreements. Combination product manufacturers must also comply with the testing requirements under 21 CFR 211.84 (above) for drug components, product containers, and closures
21 CFR 820.100 Corrective and Preventive Action	Requires device manufacturers to establish and maintain procedures for implementing corrective and preventive action (CAPA). Corrective action is taken in response to a specific event, nonconformance, or trend. It is intended to determine the root cause and prevent a recurrence while preventive action is taken to avoid the occurrence of a potential event, nonconformance, or trend. For combination products, the CAPA process should consider the implications of CAPA for all constituent parts and the entire combination product
21 CFR 820.170 Installation	Requires the manufacturer of a device requiring installation to establish and maintain adequate installation and inspection instructions and test procedures (where appropriate). As the FDA indicated, "installed and services devices will rarely be constituent parts of such combination products. If they are constituent parts of a combination product, they are more likely to be separately manufactured and marketed as constituent parts of cross-labeled combination products (FDA 2015)
21 CFR 820.200 Servicing	Requires each manufacturer to establish and maintain instructions and procedures to verify that the servicing meets the specified requirements. This only applies if the device has servicing as a specified requirement. In the case of combination devices, this will be similar to the comments above for 21 CFR 820.170

Table 3 Summary of the Essential CGMP Requirements that Apply to Combination Products with Various Constituent Parts

Product Type	Part 4 requirements
Combination Product includes a drug constituent part	The CGMP requirements identified under 4.3(a) will apply to the combination product, which follows 21 CFR 210–211
Combination Product includes a device constituent part	The CGMP requirements identified under 4.3(b) will apply to the combination product, which follows 21 CFR 820
Manufacture of a constituent part of a co-packaged or single entity Combination Product occurs at a separate facility	The CGMP system of the constituent part manufactured at that facility must comply with **all** CGMP requirements applicable to that constituent part
Combination Product contains multiple constituents	CGMP system must comply with the specifics of applicable provisions of all constituent parts, or based on the **P**rimary **M**ode **o**f **A**ction (PMOA), a streamlined approach can be utilized
If there are conflicts among the CFR requirements	The regulations most specifically applicable to the constituent will supersede the more general ones

Phase I – establish the design history file

For legacy combination products, a Design History File (DHF) is critical as a central repository for design verification. The DHF contains all the records demonstrating that the design was developed according to the design plan and its development. It provides an 'evidence-based' database to establish general requirements for design controls, purchasing controls, Corrective and Preventive Action (CAPA), management responsibility, installation, and servicing activities. A systematic risk management process can include risk assessment, control, communication, and review (FDA 2015).

Once the design history file (either electronic or paper-based) is available, existing documents should be reviewed against the current design controls to demonstrate that the product is manufactured and performs as intended. It is also beneficial in performing this assessment against the current quality system to address any procedural gaps (i.e., design control, purchasing control, risk management, risk analyses, etc.) A continuous and comprehensive design verification process will aid in understanding the original process development, qualification, and manufacturing processes so future improvements can be made.

Phase II – remediate the design and development plan

Once the assessment is complete, a cross-functional team should be created to establish a formal plan based on the gaps identified, which may include a quality plan or CAPA. For legacy products, the plan can be developed for a group or family of combination products based on risk assessment, design verification, and design validation, as appropriate.

The remediation plan should also summarize a review of policies and Standard Operating Procedures (SOPs) for compliance with the additional requirements and determine if changes to the current SOP are needed or if a new SOP should be considered.

This remediation plan should include critical milestones developed from the DHF and include key deliverables, activities, and specific criteria to meet established appropriate user-needs requirements.

Phase III – execute the plan

The plan can be executed by preparing design inputs and outputs. Steps must be taken to verify proper design transfer, change controls, and verification activities. Budget and resources must be obtained to implement effective control strategies, and product performance should be evaluated periodically and documented.

Challenges working globally

In the U.S., the regulatory approach for combination products is based on determining the PMOA of the product and submitting the application to the appropriate division of the FDA: Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), or Center for Biologics Evaluation and Research (CBER) based on the determination. The "leading center" is responsible for the review process and all subsequent communications with the applicant. While this approach is well-defined in the U.S., there are unique challenges when registering combination products in other countries.

In Brazil, for example, ANVISA (Brazilian National Health Surveillance Agency) defines a combined product as a "product that comprises two or more components that are regulated as products subject to sanitary surveillance, such as medicine/medical device, vaccine/medical device, which combines physically, chemically or otherwise, produced as a single entity." (Bosenberg et al. 2022). Brazil still has no specific legislation for registering and regulating combined products of different categories. To establish the pathway of drug-device, whether the device will be commercialized in drug packaging or separately needs to be considered. If separately, the device must comply with Resolution No. 185/2001, as amended by Resolution No. 340/2020, which establishes general conditions for the approval, marketing, and review of medical devices (Ribeiro et al. 2020).

For example, in the EU, there is no single definition of a combination product in the legal framework of medicinal products or medical devices. Drug-device combination products in the EU are regulated as medicinal or medical devices. The PMOA governs the regulatory pathway. Where the action of the medicinal substance is primary, the product is regulated under the medicinal products framework. The general safety and performance requirements (GSPR) of the Medical Device Regulations (Annex I of EU MDR 2017/745) apply to the device constituent. Where the action of the medicinal substance is secondary, the combination product is regulated as a medical device and must be CE-marked (Nasto et al. 2021). The drug constituent is reviewed by a drug authority, whose opinion will be provided to the Notified Body.

China defines drug-device combination products as "A product made up of drugs and medical devices and produced as a single entity (National Medical Products Administration 2021)." In August 2021, China's National Medical Products Administration (NMPA) updated registration requirements and processes for combination devices. Similar to the U.S., market applicants need to determine the PMOA of the combination product, which will determine the appropriate NMPA regulatory pathway for the product (Emergo 2021). Drug-led combination devices should be registered as drugs, and medical device-led combination products should be registered as medical devices (Emergo 2021). If the applicant is having difficulty in this determination, they can apply for designation determinations with the National Institutes for Food and Drug Control (NIFDC). Japan's definition of a combination product is much like that of the United States, "The products marketed as a single drug, medical device, or cellular and tissue-based product that combine two or more types of drug, device, processed cell, etc. that are expected to fall under the category of drugs, medical devices, or cellular and tissue-based products if marketed individually (PMDA 2014)." Unlike China, which stresses "single entity" in its definition, Japan and the United States allow for single entity, joint packaging, and cross-labeling combination products.

Other Asian countries like Russia, Singapore, India, and South Korea will regulate the product based on their own local interpretation of the Primary Mode of Action (PMOA). A product that is regulated as a device or a combination product in one country may be regulated as a single entity drug somewhere else. It is critical that the developer works with the regulating agency to understand how an individual product is being interpreted for PMOA by the local authority.

As we see, even the definition of a combination product varies from country to country, thus adding to the challenge when trying to register a combination product in multiple countries outside of the United States. Therefore, it is recommended that manufacturers work closely with specific regulators to discuss regional requirements that are applicable to their product and also to determine the stability program needed for registration.

Stability testing for combination drug-device products

Stability studies are necessary to establish the expiration dating of the drug product, medical device, or combination product. The critical quality attributes that may change upon aging and impact patient safety, efficacy, and product quality should all be assessed and tested in the stability study. Stress Testing (Forced Degradation) should be conducted on the combination product's drug and device portions before commencing the formal stability study, as it helps determine the stability-indicating methods and the relevant factors contributing to the degradation kinetics. Stress tests can include factors such as oxidizers, temperature extremes, humidity extremes, sterilization extremes, acid/base exposures, and sometimes even transit extremes such as vibration. Exposure to as many possible degradation accelerators as possible is a highly cost-effective, data-driven approach to focus the formal stability study design on the most relevant quality attributes.

Drug-centric companies have a rigorous stability process because the global regulations are very prescriptive in all aspects, including, but not limited to, sample storage temperature and humidity conditions, sample pull period spacing, required physical and chemistry stability-indicating test methods, and bracketing/matrixing approaches. Medical devices have no equivalently prescriptive language about stability in the applicable regulations (21 CFR 820 and ISO 13485), which only describe that storage and expiry label claims must be data-driven.

Per 21 CFR 820.130 Subpart K, "Labeling and Packaging Control – Device packaging. Each manufacturer shall ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution."

Per 21 CFR 820.140,150 & 160, Subpart L states under Handling, Storage, Distribution, and Installation, "Each manufacturer shall establish and maintain procedures …to prevent …damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no … deteriorated product is used or distributed." When the quality of product deteriorates over time, it shall be stored in a manner to facilitate … and its condition shall be assessed as appropriate."

Finally, ISO 13485, 7.5.11 Preservation of Product. "The organization shall document procedures for preserving the conformity of product during processing, storage, handling, and distribution."

The language is flexible by design; it is important to note that some medical devices have no stability limitations and no label claim for expiry or storage and handling. This is especially true for intrinsically stable devices marketed in a "sterilize before use" condition.

There is one FDA Guidance for Industry: Shelf Life of Medical Devices (Clark 1991) from 1991, authored by Geoffrey S. Clark, a Microbiologist from the Division of Small Manufacturers Assistance. Despite its age, this document offers helpful thoughts on how to design the medical device stability portion of the program. The basic approach is the same as initially developed by Svante Arrhenius, the Swedish physicist, in 1889 and used in the pharmaceutical, medical device, and food industries. The differences between medical device and pharmaceutical stability are sample storage temperature and humidity conditions, sample pull period spacing, and physical and chemistry stability-indicating test methods. The use of bracketing/matrixing approaches is at the manufacturer's discretion based on the product's clinical performance criteria determined by the Medical Device Design Control Process.

Additionally, two consensus standards are necessary to consult before implementing any medical device study design:

ISO 11607–1:2019 (ISO 2019). The ISO 11607–1 document offers some of the most prescriptive stability information for medical device product packaging. It is purely sterile barrier packaging focused and includes the mandatory stability-indicating tests to conduct on the sterile barrier system (SBS) packaging. This standard defines the approach for worst-case testing. The worst-case consists of the product itself, sterilization (mode and exposure), size (large/small/heavy), fragility/sensitivity (breakable/oxygen or moisture), and shape (sharps). Medical device producers must determine how to bracket all the above into a science-driven, stochastic probability worst-case study design.

For example, a gamma-sterilized multi-polymer prefilled oxygen-sensitive drug delivery device in a foil lid with a Cyclic olefin copolymer (COC) resin tray Sterile Barrier System (SBS). Worst-case for stability would include:

a) Exposure to gamma dose higher than the allowable upper production specification limit (USL). It is important to remember that gamma exposure oper-

ates in a range. Every sample in the stability batch must be exposed to above the USL, not just the average from the dosimeters.

b) Largest and smallest sizes (dose and packages)
c) Exposure to the highest oxygen production specification limit (USL)
d) Minimally, the package test methods must include one of the ISO Package Tests for Seal Strength and one of the ISO Package Tests for SBS Integrity; in this example, microbial barrier by both closure integrity and oxygen ingress would be expected.
e) Additionally, medical device regulators are focused on the statistical validity of sample sizes. The minimal expectation for test methods is 95% confidence and 95% reliability. Package seal strength testing and oxygen barrier testing generate variable data. The sample sizes can be statistically estimated for the protocol and confirmed in the report using the mean and standard deviation relative to the applicable specification limits. Typically, closure integrity tests are attribute-based (i.e., Pass/Fail) and require an n=60 per pull period to meet the requirement for 95% reliability at a 95% confidence. Thus, zero failures are allowed.

ASTM F1980-21 (ASTM 2021). This standard provides guidance on accelerated aging to assess the sterile barrier system (packaging) and the medical device. "Information obtained using this guide may be regarded as sufficient evidence for expiration date claims for medical devices and sterile barrier systems until data from real-time aging studies are available."

Unlike accelerated aging studies for drug products, ASTM F1980 allows accelerated temperatures as high as 60 °C if there is no distortion of the sterile barrier system at this temperature or any thermal transitions occurring in any of the polymeric components of the device below 60 °C. Of course, the impact of the 60 °C temperature on the drug constituent will also need to be considered for a drug-device combination product.

When designing stability studies for such drug-device combination products, several important aspects need to be considered:

1. Packaging-For multiple device sizes, the bracketing concept can be used to consider worst-case scenarios. If the same size packaging is used for various device sizes (e.g., a urinary catheter), the largest size catheter may represent a worst-case, as there will likely be more stress on the packaging seals, potentially leading to seal creep. The device may also be more tightly pressed against the package and more likely to be damaged by external forces.
2. Strength-When the drug-device products consist of multiple strengths, the worst-case scenario may be justified and placed on stability. This may often consist of the lowest and highest dosage strengths.
3. Batch-When different batches are manufactured and limited samples are available for stability, matrixing can also be considered.
4. Sterility-For sterile drug-device products, the impact of the sterilization modality on the drug and the device needs to be considered. Typically, the worst case would involve the maximum dosage range. For a gamma-irradiated product with a nominal dosage of 25–40 kGy, all samples placed on stability should have received a minimum of 40 kGy of radiation.

Once determined that an attribute of the drug-device product is likely to be affected by time and storage conditions, whether the change presents a possible risk to the patient or product performance needs to be considered. This can be done using either a scientific or risk-based assessment (ASTM 2018).

The scientific assessment may include universal scientific or physical principles, in which case literature should be referenced. Lab data may also help when justifications are less obvious (ASTM 2018). Clinical history or the complaint history of a similar device used in a similar application may aid in the risk assessment. Table 4 lists some typical Drug ICH Guidelines that should be considered when designing stability studies to support a new combination product in addition to the device-related consensus standards discussed in the prior paragraphs. In this case, the consensus standards ASTM-F1980 and ISO-11607–1, as noted above, are explicitly applied to the device portion, and the ICH documents mentioned below are applied to the drug portion. Full compliance with both portions is required.

The relevant *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)* includes the following elements from Table 4.

The standards in Table 4 should be reviewed in detail before creating a combination product stability study. Specific testing approaches (Table 5) are mandatory for the drug portion of the combination product, while the device portion generally will focus more on stability-indicating physical property changes due to its PMOA. Often the device will include a force measurement analysis including but not limited to tensile, break, bend, burst, expression, or viscosity during stability. It is also recommended that both the device product and its sterile barrier package be visually compared to a control sample to detect any unforeseen aging-related changes. Chemical analysis is less common, although

Table 4 Relevant Globally Harmonized ICH Guidelines Applicable to Combination Products

Guideline Title	Guideline Content
Q1A(R2) – Stability Testing of New Drug Substances and Products	Prescriptive requirements for accelerated and long-term stability study design
Q1B – Stability Testing: Photostability Testing of New Drug Substances and Products	Prescriptive requirements for photostability study design
Q1D – Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	Prescriptive requirements for stability study representative product selection designs where every iteration of the product family is not planned to be evaluated
Q1E – Evaluation for Stability Data	Prescriptive requirements for presenting, analyzing, and drawing conclusions from stability data
Q2(R1) – Validation of Analytical Procedures: Text and Methodology	Prescriptive requirements for stability indicating procedures
Q3A – Q3E—Impurities	A series of prescriptive requirements for stability evaluation of degradants, impurities, and residual solvents, including requirements for extractables and leachables
Q4B – Q3E – Pharmacopoeias and Annexes	A series of the prescriptive test methods
Q6A – Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances	Defines the concepts of release testing versus stability testing specifications and parametric release versus sterility testing. Additionally, it prescriptively describes the tests and acceptance criteria generally applicable to all new drug products

sometimes it may be relevant and, if performed, would include methods such as oxidation index, water activity, pH, and FTIR. The package testing for sterile device portions is prescriptive; seal strength and sterile barrier system integrity must be performed.

Finally, one or more methods to test for the interactive properties of the combination product must be performed.

For a more specific example, let us consider an absorbable drug-eluting stent (DES), which is inserted into the coronary artery and used to support artery walls and prevent plaque from blocking blood flow (Healthline 2016). A DES typically consists of a bioabsorbable stent, a polymeric coating containing an anti-restenotic drug (used to prevent the artery from narrowing again after stenting or angioplasty) to be released over time. Table 6 shows possible stability-indicating tests to consider when designing a stability protocol for a DES:

Concept of Bracketing and Matrixing to be used for stability testing of combination products

Registration stability programs are expensive, and the cost increases exponentially for medical devices because there are often multiple sizes and iterations of packages. Therefore, reduced study designs are preferred as they reduce costs, laboratory burden, and stability chamber space. Although ICH embraces the concept, the study design must be statistically robust enough to confirm the uniformity (or lack thereof) of the degradation kinetics across the range of products to be produced in the product family. Alignment on the specific protocol design by the regulatory authorities is recommended.

Table 5 Typical Q6A parameters to Evaluate for a Drug-Based Stability Program

Testing Category	Tests to be Considered
Chemical testing	- Assay for Active Pharmaceutical Ingredient (API)- Impurity/Degradation Products- Photostability (if applicable)
Physical testing	- Appearance - Dissolution/Rate of release - Molecular Weight and Polydispersity of polymeric components in device and coating -Tensile strength of bonded device components
Microbiological testing	- Sterility - Particulate matter - Bacterial Endotoxin - Antimicrobial Effectiveness

Table 6 Stability-Indicating Tests to Consider for Drug-Eluting Stent (DES)

Stability-Indicating Test	Combination Product Portion	Technique(s)	Purpose
Appearance	Drug, Device & Sterile Barrier System (SBS)	Optical Inspection Microscopy Machine Vision Systems	Drug—Color change, foreign debris Device – Cracks, color change SBS- Voids, tears color change
Assay (Total Drug Content)	Drug Only	HPLC	Changes in concentration
Impurities or Degradation Products	Drug Only	HPLC GC–MS ICP-MS (elemental impurities)	Formation of inactive or toxic byproducts over time. May be completed as part of the Assay method
In Vitro Drug Release (Drug Elution)	Drug Only	Dissolution (USP apparatus 4)	Confirmation that API is released from the device in a controlled, consistent, and reproducible manner
Particulates	Drug & Device	USP < 788 >	Detect shedding from drug coating/surface or device delivery system
Packaging Integrity	SBS Only	Bubble Leak Dye Penetration Vacuum Decay	Confirmation that sterility will be maintained
Package Seal Strength	SBS Only	Peel Strength Burst Strength	Confirmation that contents and sterile barrier will be maintained
Polymer Molecular Weight	Drug & Device	Size Exclusion Chromatography (SEC)	Evidence for the polymeric coating on the device degrading over time. Molecular Weight (M_n, M_w) and Polydispersity Index (PDI) measurements at time points can be compared to T_0
Antioxidant/Drug Stabilizer	Drug Only	HPLC GC–MS	Determine low-level additives to stabilize drug substance. May be challenging to analyze due to the low concentration and interference from excipients in the product matrix
Tensile Strength	Device Only	Instron	Confirmation of linear elongation and break strength
Compression Strength	Device Only	Instron	Confirmation of resistance to externally applied forces
Burst Strength	Device Only	Instron	Confirmation of resistance to internally exerted forces
In-Vitro Strength (Tensile, Compression, and/or Burst)	Device Only	Instron	Confirmation of resistance to forces in the clinically relevant modality after exposure to physiological buffered solution for a clinically relevant period of time

Table modified from (Liu et al. 2018)

Bracketing

Bracketing and matrixing are tools that can be applied to stability protocols to reduce the number of samples tested for stability. ICH Q1D provides guidance on using these "reduced design" options to test new drug substances and products. These same concepts can be applied to the stability testing of combination products, particularly drug-device combination products. Bracketing is the most widely utilized.

Bracketing is a design of a stability schedule such that only samples on the extremes of certain factors, such as strength, container size, or fill volume, are tested at all time points. The assumption is that the stability of the extremes will represent any intermediate levels. If more than one factor is bracketed (i.e., Fill volume and size), it can't be assumed that the largest and smallest fill and size represent the extreme. Development data can be used to minimize the risk as needed. Essential factors such as container wall material or thickness, surface contact, surface area to volume ratio, and device size extremes should be considered. Sometimes an intermediate-range product is added to supplement the extremes.

For example, let us consider our drug-eluting stent (DES), which can be manufactured in multiple lengths and diameters. Diameters range from 2.25 mm to 3.50 mm, and lengths range from 8 to 33 mm. Figure 6 below shows the bracketing of the extreme lengths and diameters, thereby providing coverage for the intermediate sizes. Different packaging configurations would multiply the four corners by each package configuration. Additionally, combination drug product stability requires three independent batches as opposed to device-only stability. This further multiplies the volume of work—Using the Fig. 6 example, 4 Sizes X 2 Package X 3 Batches per each configuration would leave us 24 total batches just for market introduction. Additionally, an annual (ongoing) stability will need to be initiated each year using the brackets identified for the entire marketing life of the

product family. Globally, medical device "only" regulated products have no such requirement.

Matrixing

Matrixing is the design of a stability schedule, such that a selected subset of the total number of possible samples for all factor combinations is tested at specific time points. At a subsequent time point, another subset of samples will be tested. The design assumes that the stability of each subset tested represents the stability of all the configurations at a given time point. Matrixing can be applied to different batches, strengths, container sizes, and even container closure systems (ICH 2002). Generally, combination products that are device PMOA will not utilize matrixing because there are far too many product sizes and package configurations to support a statistically robust design.

Figure 7 illustrates a simple matrix for a pre-filled syringe where one-third of the tests were reduced based on ICH Q1D. The use of matrixing designs can reduce analytical effort by not testing every sample at every time point. When using this design, all configurations are placed on stability. However, selected samples across all batches are pulled as per the protocol. The design of schedules and how they are used must ensure that testing is evenly balanced across all batches in a randomized fashion.

From ICH Q1D, more advanced matrixing and bracketing designs can be used based on this concept. To effectively apply the reduced testing concept, the drug product and its intended use must be well understood. It is highly recommended that a risk assessment be conducted to determine if the device and the drug should be studied together or independently. The impact of the device on the drug product and how it affects the shelf life must be assessed if the device and drug are studied together.

Additional testing should also be considered for the physical stability of the drug products. As noted above, the packaging also needs to be considered, especially for sterile combination products where the maintenance of the sterile barrier must be ensured through the product's expiry.

Bracketing designs can be applied to all storage conditions; however, only batches of the extremes are placed in the chambers and tested. Matrixing should only be applied to samples stored at real-time conditions. It is possible to combine the two reduced designs; however, it

Diameter (mm)	Length (mm)					
	8	13	18	23	28	33
2.25	T	--	--	--	--	T
2.50	--	--	--	--	--	--
2.75	--	--	--	--	--	--
3.00	--	--	--	--	--	--
3.50	T	--	--	--	--	T

T: Configurations are tested

Fig. 6 Example of a Bracketing Design for a Single Package Configuration Drug-Eluting Stent (DES)

	Timepoints	0	3	6	9	12	18	24	36
1mL	**Batch A1**	T	T	--	T	T	--	T	T
	Batch A2	T	T	T	--	T	T	--	T
	Batch A3	T	--	T	T	T	T	T	T
10mL	**Batch B1**	T	--	T	T	T	T	T	T
	Batch B2	T	T	--	T	T	--	T	T
	Batch B3	T	T	T	--	T	T	--	T

T: Configurations are tested

Fig. 7 Example of a Matrixing Design for Pre-Filled Syringes, 1 mL and 10 mL

should be done with careful consideration and scientific justification required by ICH. The acceptance by the regulatory agencies of these reduced designs is diverse, and some agencies will not always accept data from matrixing stability studies. Bracketing and matrixing may reduce the power of the study design, and therefore the predicted shelf-life confidence is inherently decreased by a statistical factor. When considering the risk presented by the reduced confidence, the following information should be considered: data variability, quantity and quality of the existing data, number of factors, clinical impact, and anticipated shelf life.

Bracketed studies generally deliver more significant savings and carry lower risks as the main risk is different degradation kinetics shown by the extremes, which can be cost-effectively mitigated using data from well-designed forced degradation (stress testing) studies. On the other hand, matrixing studies on factors other than time points may compromise the shelf-life estimation as it may affect the poolability of data as described in Q1E. If the data are not poolable, estimating a shelf life for a missing factor combination may not be possible. Matrixing provides more modest savings and better flexibility as different matrixes can be used for different testing. All samples are placed on stability to allow reverting to full testing if needed. However, risks may be higher with the uncertainties of acceptance by some regulatory agencies. It is recommended that protocols or the stability plan of reduced design are discussed with relevant agencies before the studies are initiated.

Conclusion

Combination products offer therapeutic benefits that an individual drug product, medical device, or biologic cannot. However, the regulatory landscape for marketing combination devices has been challenging as most drug manufacturers lack an understanding of medical device CGMPs. In contrast, most device manufacturers lack an understanding of drug CGMPs. 21 CFR Part 4 has provided guidance and allows a streamlined approach for regulatory submissions for combination products based on determining which constituent part provides the Primary Mode of Action (PMOA). If the device is determined to provide the PMOA, then the entirety of the device CGMP must be satisfied, while only a limited number of sub-parts of the drug CGMP need to be satisfied. Conversely, if the drug constituent provides the PMOA, only compliance with a limited number of sub-parts of the device CGMP is required along with the entirety of the drug CGMP.

Bringing a legacy combination product into compliance with 21 CFR Part 4 generally requires a better understanding of the medical device CGMPs, especially since a design history file may need to be established. Performing a gap assessment and remediation are essential steps for bringing legacy combination products into 21 CFR Part 4 compliance. Designing a stability program for a combination drug-device can be particularly complex. The clinically relevant stability-indicating attributes of the drug, device, the interactions between the drug and device, and finally, the packaging must be considered. Reduced study designs, such as bracketing and matrixing, can be effectively utilized for combination products, reducing the number of samples required, the associated costs, and stability testing resources.

Abbreviations

ANVISA	Brazil National Health Surveillance Agency
API	Active Pharmaceutical Ingredient
ASTM	American Society for Testing and Materials
CAPA	Corrective and Preventive Action
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
COC	Cyclic Olefin Copolymer
CQA	Critical Quality Attributes
DDP	Design and Development Plan
DES	Drug-eluting Stent
DHF	Design History File
FDA	Food and Drug Administration
GSPR	General Safety and Performance Requirements
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO	International Organization for Standardization
MDR	Medical Device Regulations
MOA	Mode of Action
OTC	Over-the-Counter
PMOA	Primary Mode of Action
QbD	Quality by Design
QTPP	Quality Target Product Profile
SBS	Sterile Barrier System
SOP	Standard Operating Procedure
USL	Upper Specification Limit

Acknowledgements

The authors express their gratitude to the following colleagues for their time and effort in providing technical reviews: Jennifer Bromm-Dewar, M.S., DEKRA Certification; Tage Carlson, Ph.D., Hollister Incorporated; James Lorkowski, Ph.D., Takeda Pharmaceutical Company Limited; and John O'Neill, M.S., Stabilityhub.com.

Authors' contributions

These authors contributed equally. All authors have approved the final version of this manuscript.

Funding

No funding was granted for the preparation or authorship of this article

Availability of data and materials

Not applicable.

Declarations

Competing interests

The authors declare that they have no competing interests

Received: 4 March 2023 Accepted: 6 April 2023
Published online: 01 May 2023

References

Amor, David. Understanding Medical Device QMS Requirements for Combo Products: Pharma Company Edition, Med Device Online, March 14, 2016. https://www.meddeviceonline.com/doc/understanding-medical-device-qms-requirements-for-combo-products-pharma-company-edition-0001

Announcement of the State Food and Drug Administration on matters related to the registration of drug-device combination products (2021 No. 52). https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20210727154135199.html?type=pc&%3Bm=. Accessed 4 Apr 2023

ASTM F1980–21, Standard Guide for Accelerated Aging of Sterile Barrier Systems and Medical Devices, 21 December 2021. https://www.astm.org/f1980-21.

ASTM F2914–12(2018), Standard Guide for Identification of Shelf-Life Test Attributes for Endovascular Devices, updated Nov 20, 2018. Available at https://www.astm.org/f2914-12r18.html

Bosenberg, SG and Benevides I., Combined Products in Brazil-Brief Comments on ANVISA's (Brazilian National Health Surveillance Agency) Current Understanding, issued on September 23, 2022. https://www.kasznarleonardos.com/en/combined-products-in-brazil-brief-comments-on-anvisas-brazilian-national-health-surveillance-agency-current-understanding/

Chinese regulators revise drug-device combination product registration requirements. In: Emergo by UL. https://www.emergobyul.com/news/chinese-regulators-revise-drug-device-combination-product-registration-requirements. Accessed 4 Apr 2023

Clark, Geoffrey S., Shelf Life of Medical Devices, April 1991. Rockville, MD: Food and Drug Administration. https://www.fda.gov/media/72487/download

Cognidox, The Complete Guide to Medical Device Development. https://www.cognidox.com/medical-device-development-guide

CFR Part 4, https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-4 (Accessed 27 Dec 2022).

Drug-Eluting Stents: How do they work, Healthline, last reviewed on Jun 27, 2016. https://www.healthline.com/health/heart-disease/drug-eluting-stent

Food and Drug Administration (2015). Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products. Rockville, MD: Food and Drug Administration. https://www.fda.gov/media/90425/download (Accessed 27 Dec 2022).

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Tripartite Guideline: Stability Testing for New Dosage Forms Q1D. 7 February 2002. https://database.ich.org/sites/default/files/Q1D%20Guideline.pdf

ISO 11607–1:2019, Packaging for terminally sterilized medical devices— Part 1: Requirements for materials, sterile barrier systems, and packaging systems. https://www.iso.org/standard/70799.html

Liu J (2018) Chiesl. Thomas, and Kamberi, Marika, Test Method Selection and Specification Setting in Stability Testing for Combination Medical Device Products, Journal of GXP Compliance, Nov 22:16

Nasto, B. and Sutch, J., An overview of drug-device combination products in the EU, June 02, 2021. https://compliancenavigator.bsigroup.com/en/medicaldeviceblog/an-overview-of-drug-device-combination-products-in-the-eu/

National Medical Products Administration NMPA Notice on Matters Concerning the Registration of Drug-device Combination Products. http://english.nmpa.gov.cn/2021-07/27/c_661024.htm. Published July 27, 2021. Accessed 4 Apr 2023.

Notification- PMDA. https://www.pmda.go.jp/files/000153158.pdf. Accessed 4 Apr 2023

Ribeiro, A and Vianna JL, Medicinal product regulation and product liability in Brazil: overview, Thomson Reuters Practical Law, 01-Dec-2020. https://uk.practicallaw.thomsonreuters.com/7-384-1830?transitionType=Default&contextData=(sc.Default)&firstPage=true

Publisher's Note