TECHNICAL BULLETIN

Extractable and leachable challenges in drug-device combination products

Health Inspired, Quality Driven.

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Introduction

A medical device is any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings and to have a primarily physical effect. The main effect of medical devices in or on the human body is not achieved through pharmacological, immunological or metabolic means, unlike medicinal products.

In addition to the categories of medicinal products and medical devices, combination products are common therapeutic and diagnostic products that combine drugs, devices and/or biological products and thus lead to the desired effects on and in the body through careful dosing. Per the definition from the US FDA, a combination product is a product composed of any combination of a drug and a device, a biological product and a device or a drug and a biological product, or a combination of all three.

Companies that want to market combination products must be compliant with many regulations when preparing for approval.

Three important aspects are the biocompatibility, chemical characterization of materials and toxicological risk evaluation of potentially leachable substances for the safety assessment of the design components from which the final combination product is constructed. A strong understanding of the risks that leachables may pose during the use of a combination product first requires thoughtful and informed design of extractable and leachable studies as part of chemical characterization of both the solid device/ medical formulation (solution, emulsion or semi-liquid) and the container closure system that protects the finished product from environment impact, with the appropriate application of industry guidance.

Different regulatory expectations and definitions depending on the authority for understanding the term "combination products"

Due to the increasing integration of drugs and devices that can be observed in the latest generation of combination products, the regulatory authorities have developed specific competencies and regulations in recent years. Depending on the authority, some products have been recorded and classified using terms such as "combination product", "systems for combined use" or "drug-device combinations". In this context, it must be emphasized that the official terminology and definitions of what constitutes a combination product in the legal sense can vary by authority. For example, in the United States, a combination product is a legally distinct type of product composed of two or more different types of medical products, i.e. any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product [21 CFR §3.2(e)][iii].

As an innovator, the critical first step is to determine if a product falls under the combination product category. For example, the US FDA regulates all combination products, and one or two of its three review centers (Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), or Center for Devices and Radiological Health (CDRH)) are designated as the lead review center(s) for the combination product. The US FDA assigns a lead regulatory review center based on the product's primary mode of action (PMOA), defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product". The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. Both the lead regulatory review center and the regulatory pathway depend on the combination product construction constituents and its mode of action in its clinical application. Note that an in vitro device that is a companion diagnostic to an associated therapeutic product would not generally be considered as a combination product.

In Europe, the Medical Device Regulation (MDR) has already come into force. Medical devices must successfully complete a conformity procedure to receive a CE mark and be allowed on the market. With the "new" MDR, some products are classified in higher risk categories, which increases the requirements within the framework of the conformity procedure.

In the regulations of the European Union, the term "combination product" is not as clearly defined as in the 21 CFR §3.2(e) but is more circumscribed. This type of device includes "devices incorporating a medicinal substance as an integral part which has an action ancillary to that of the device" and "devices intended to administer a medicinal product, placed on the market as a non-integral product". Devices that incorporate a medicinal substance either as ancillary or primary purpose, such as drug-eluting stents (endowed with drug active with only local action) or metered-dose inhalers (which deliver a formulated drug active ingredient to the lungs via a medical device component). For example, a drug-eluting stent is a tube made of a mesh-like material used to treat narrowed arteries in medical procedures both mechanically (by providing a supporting scaffold inside the artery) and pharmacologically (by slowly releasing a pharmaceutical compound). The special feature of the drug-stent combination is that it has a coating that releases the drug directly into the blood vessel wall. Thus, the stent slowly releases a drug to prevent the growth of scar tissue and new obstructive plaque material that caused the original blood vessel stenosis. With a local effect of the drug and release in small doses, the primary effect of this combination product is in the support and dilation of the blood vessel and not in the systemic pharmacological effect. In contrast, a metered-dose inhaler is a device that delivers a specific amount of medication to the lungs in the form of a short burst of aerosolized medicine that is usually self-administered by the patient via inhalation. The primary function of this device is to ensure the correct dosage of the pharmacologically active drug to treat respiratory diseases.

In China, under the National Medical Products Administration (NMPA, 2021-07-27), the understanding of "combination products" is similar to that in Europe. Drug-device combination products refer to medical products composed of drugs and medical devices and produced as a single entity. Drug-led drug-device combination products must be registered in accordance with the relevant requirements for drugs and device-led drug-device combination products must follow medical device regulations. Nevertheless, there are still certain details to consider, particularly in the EU, where the PMOA plays an important role in classification.

Other aspects that must be considered

Generally, a container closure system protects the product from environmental conditions, safeguarding its purity, strength, safety and efficacy. The integrity of a container closure system is crucial, particularly for pharmaceuticals, biologics and biotechnologies, as well as for combination products used in patient treatments. The regulatory agencies provide specific guidance on packaging requirements for container closure integrity and general integrity testing. For example, ISO 11607-1 details the elemental attributes demanded of materials and pre-formed systems intended for use in packaging systems for sterilized medical devices.

It takes into consideration the vast array of potential materials, medical devices, packaging system designs and sterilization methods. In addition, as before, the suitability of the medical device component for the specific medicinal product in the combination in question must be demonstrated. Among other factors not discussed here, compatibility testing involves a series of analytical techniques designed to detect and quantify any interactions (compatibility) between the drug/device and its packaging or immediate surrounding materials.

Medicinal products used in combination with a medical device, the European view

Extractables and leachables studies are carried out according to different guidelines and standards. The leading standard applicable to combination products depends on which primary mode of action (PMOA) best describes the final product, which legal classification is to be made, and which approval path must be followed. In the European Union, the applicable scenario is determined according to Figure 1, as described above. The US FDA has defined the basic requirements for combination products to be expected in its January 2017 Guidance for Industry "Current Good Manufacturing Practice Requirements for Combination Products" . A more recent guidance "Principles of Premarket Pathways for Combination Products" was published in January 2022 for both industry and FDA staff.

In the EU, regulations governing combination products are highly complex. Pharmaceutical legal requirements regarding marketing authorization and GMP must be complied with and the legal requirements for medical devices must also be considered. This means orientation towards the Medical Device Regulation (MDR) and compliance with harmonized standards. A notified body may also be involved. According to the current medical devices' legislative framework, the EMA mainly provides scientific opinions to notified bodies through consultation procedures. EMA's regulatory role is limited to the assessment of certain categories of medical devices and in vitro diagnostics, and in the context of medicinal products used in combination with a medical device. EMA can only address questions under its remit.

If the principal intended action is achieved by the medicine, it is considered as a medicinal product that includes a medical device. The device part of the combination may require a conformity assessment.

The relevant requirements can be found in the EMA guideline on combination products. For the practical implementation of Art. 117 MDR, these are in particular:

- Guideline on the quality requirements for drug-device combinations (EMA/CHMP/QWP/BWP/259165/2019) (adopted, legal effective date 01/01/2022)[vii]
- Questions & answers on implementation of the medical devices and in vitro diagnostic medical devices regulations ((EU) 2017/745 and (EU) 2017/746) (EMA/37991/2019) , last updated: May 21, 2024
- MDCG 2022 – 5 Rev. 1 Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices – October 2024[iii]

A substance is considered a medicinal product if it meets the definition provided in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of the same article. The MDR sets out four regulatory scenarios for medical devices intended for use with a medicinal product in Article 1(8) and Article 1(9), see flow chart of Figure 1:

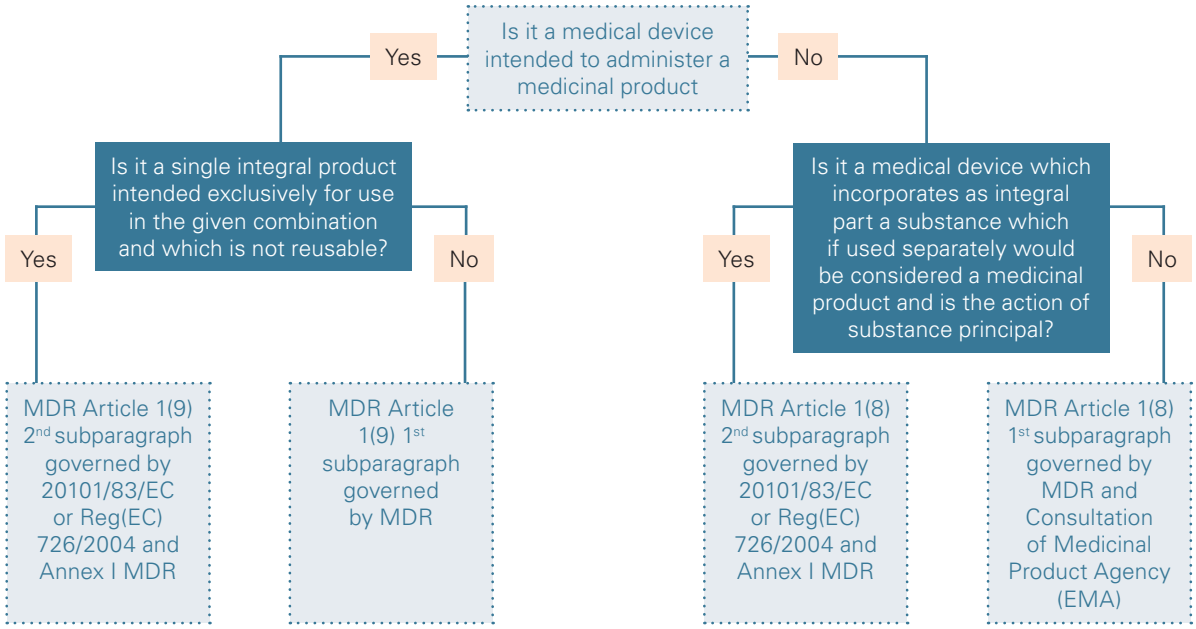

Figure 1: Medical device and medical product integral combinations regulated as medicinal products.

Assigning the correct sections of the regulations requires an understanding of the term "integral".

A medical device incorporates one or more active substances which, if used separately, would be considered a medicinal product. This includes medicinal products derived from human blood or plasma, non-viable tissues or cells of human origin or their derivatives as an integral part, within the meaning of Article 1(8) of the MDR. This is the case only if the device and the substance form an integral product when placed on the market or put into service. The MDCG 2022 – 5 Rev. 1 provides guidance on products that are not considered "integral".

The terms "integral" in the context of Article 1 (9) second paragraph, is as follows: A device intended to administer a medicinal product and the respective medicinal product form a single integral product, within the meaning of Article 1 (9) of MDR, if and only if the device and the medicinal product form an integral entity when placed on the market and, furthermore, the product is intended exclusively for use in the given combination and which is not reusable. Devices for administration of medicinal products where the medicinal product is supplied separately (Article 1(9) first paragraph) are not integral products.

A single integral product consists of at least two constituent parts, one of which is a device, and the other is a medicinal product. They are combined in such a manner that they are not intended to be separated prior to administration.

Medical devices that are co-packaged with medicinal products or referenced in the medicinal product information leaflet but are not 'integral' or 'single integral' products, are not considered as combination products (as defined in Recital (10) of the MDR) or drug-device combinations. These products are regulated independently.

Contrast this US definition with Europe, where there is currently no formal legal definition given to the term "combination product".

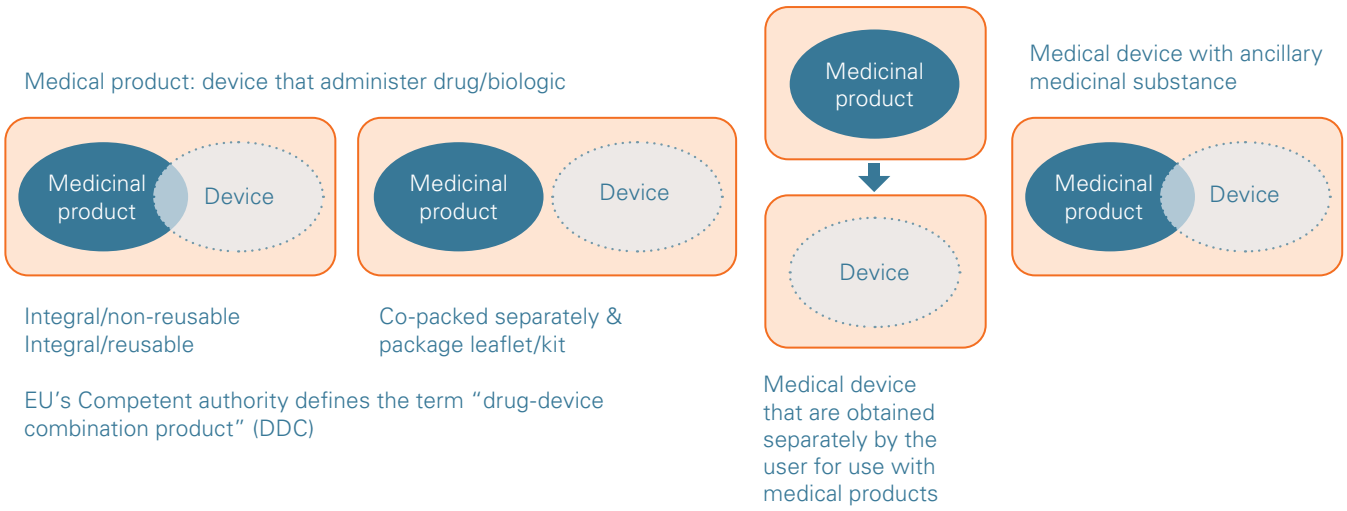

Figure 2: Different medical device – medicinal product configurations (EU).

How to decide the regulatory status?

When deciding on the regulatory status of a combination product, the first step is establishing whether the product under consideration is an integral product according to the explanations provided above. As a second step, it should be determined if the action of the medicinal product incorporated in the device is principal or ancillary to that of the device part of the integral product.

To be considered as a device-drug and fall under the EU MDR, the primary mode of action (PMOA) should be achieved by the device part, with the substance having an ancillary action. A medical device that contains an ancillary medicinal substance to support the proper functioning of the device falls under medical device legislation and must be CE marked. Examples of medical devices with an ancillary medicinal substance include:

- Drug-eluting stents
- Bone cement containing an antibiotic
- Catheters coated with heparin or an antibiotic agent
- Condoms coated with spermicides

Before issuing a CE certificate, the notified body must seek a scientific opinion from the EMA on the quality and safety of the ancillary substance if it is derived from human blood or plasma, or if it falls within the scope of the centralized procedure for the authorization of medicines. For other substances, the notified body can seek an opinion from a national competent authority or from EMA, e.g. in cases where the EMA has already evaluated a medicine containing the same medicinal substance.

If the principal intended action of the integral product is achieved by the substance, the entire product is regulated as a medicinal product under Directive 2001/83/EC or Regulation (EC) No 726/2004.

Examples of medicinal products and devices from a single integrated product are typically:

- Pre-filled syringes and pens
- Patches for transdermal drug delivery
- Pre-filled inhalers

A marketing authorization application should include a CE certificate for the device, or if not CE marked but would need to be certified if marketed separately, the applicant must include an opinion from a notified body on the device's conformity. Not all eventualities are discussed here. As shown in Figure 2, there is also the configuration of a medicinal product and device as separate items contained in same pack (co-packed) or obtained separately. Examples include:

- Reusable pen for insulin cartridges
- Tablet delivery system with controller for pain management

The device part must be CE marked in accordance with EU medical device legislation. Diagnostic products are not discussed in this white paper.

Good explanations of combination products can be found in Susan Neadle's handbook. Obtaining a global regulatory overview requires a considerable amount of time, which can be significantly reduced by using good, concise and clearly laid out specialist literature.

Some medical devices are made of substances or mixtures absorbed by the human body to achieve their intended purpose. These devices are normally introduced into the human body via an orifice or applied to the skin. A typical example of such a drug-device combination would be a prefilled syringe system containing a dermal filler. This filler is injected under the skin to create a smoother and/or fuller appearance.

These formulations could contain a mild painkiller to make the procedure more pleasant for the patient. In this example, before issuing a CE certificate, the notified body must seek a scientific opinion from the EMA or a national competent authority on the compliance of the substance with the requirements laid down in Annex I to Directive 2001/83/EC.

Applicants who are unsure of the correct classification of their product should consult a national competent authority and provide information on the product's composition and constituents, along with a scientific explanation of the mode of action and its intended purpose.

Designing extractables and leachables studies for combination products

In recent decades, various standards, guidelines and recommendations on extractables and leachables (E&L) studies have been published by American and European expert panels, supported by US and/or EU authorities. Some key references are shown in Table 1.

Table 1: Some key guidelines or references for the study organization of E&L studies, biocompatibility and toxicological evaluation.

Topic[§]	Medicinal Product	Key Reference	Medical Device	Key Reference
BIOCOMPATIBILITY	Endpoints	USP <87>, <88> USP <1031>	Endpoints	ISO 10993-1 (EU) Use of ISO 10993-1, US FDA guidance for industry, Sept. 2023
EXTRACTION STUDY	Packaging	USP <1663>, general Compendium Chapters USP, Ph. Eur, JP	Chemical characterization of MD	ISO 10993-12/18
	Single use systems in biopharmaceutical manufacturing	USP <1665>, <665>	Breathing gas pathways	ISO 18562 parts 1 - 4
SUPPORTING	Guideline for Extractables and Leachables	ICH Q3E (draft expected in 2025)	Chemical analysis for biocompatibility assessment of medical devices	US FDA Draft guidance for Industry Sept. 20, 2024
	Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular), PQRI[&] October 2021 and cited literature therein		Different topics, see ISO 10993 series	ISO 10993 parts 2-11, 13-16, 19-23 and 33
LEACHABLES	Container closures	USP <1664>, <1664.1> EMEA/CVMP/205/04, CPMP/QWP/4359/03 (Guideline on plastic immediate packaging materials), EMA/CHMP/20607/2024 (Draft guideline on the pharmaceuti-cal quality of inhalation and nasal medicinal product) EMA/CHMP/QWP/BWP/259165/2019 (Draft: Guideline on the quality requirements for drug-device Combinations)	General references	EN ISO 11607 ISO/TS 16775 ASTM F2475-20
TOXICOLOGICAL ASSESSMENTS	Toxicological concern thresholds, used as reference	ICH M7 PQRI[&] publications	Toxicological risk assessment, Toxicological concern thresholds	ISO 10993-17, ISO/TS 21726
	Elemental impurities	ICH Q3D, USP <232>, <233>	---	---

[§]The table does not include all regulations or specific standards to be observed [xii].

[&]PQRI: Product Quality Research Institute

These key documents govern study designs on E&L or biocompatibility for either pharmaceutical drug applications and medical devices or used as a reference for both regulated areas. Combination prod-ucts are often located between these regulated worlds and there are many so-called "gray areas" that require both a regulatory and scientifically adapted study approach with measures that must be well-founded to achieve approval of the finished product.

From the regulatory perspective discussion above, the correct classification of the finished product first must be made before any analytical testing is carried out.

A comparative discussion of the leading key guidelines on E&L

USP <1663> "Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Sys-tems", USP <1664> "Assessment of Leachables Associated with Pharmaceutical", <1664.1> "Orally Inhaled and Nasal Drug Products" and the upcoming chapters <1664.2> "Leachable Chapter for Parenteral Drug Products", <1664.3> Leachable Chapter for Ophthalmic Drug Products, <1664.4> Leachable Chapter for Topical and Transdermal Drug Products, <1664.5> Leachable Chapter for Oral Dosage forms are currently the leading monograph standard to set up an extractable and leachable safety assessment for pharmaceutical applications. It remains to be seen to what extent ICH will harmonize these principles within USP <1663> and <1664> in the upcoming ICH Q3E Guideline for Extractables and Leachables (E&L). In this context, a helpful summary of the use of USP <1663> and <1664> and other compendium monographs, as well as expectations of the American, European and Canadian regulatory authorities can be found in a publication by Abhishek Chakraborty[xiii].

For extraction studies using solvents on a laboratory scale, the first monograph to be mentioned is USP <1663> "Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Sys-tems", which is applicable for container closure systems for pharmaceuticals and US marketed drug-led combination products. An example is a drug dosage form where the dosing unit simultaneously functions as a storage container (packaging/delivering systems) such as a pre-filled syringe system. The extraction strategy is carried out in a laboratory process and is based on the risk of interaction between the formulated drug and the contact material of the packaging/delivery system. The extrac-tions are mainly carried out under accelerated temperature conditions, with the extraction times of-ten being between 24 hours to 72 hours. The extraction conditions are chosen so that the basic struc-tural integrity of the material is not damaged, meaning no dissolution of the material polymers, de-lamination or even excessive swelling. What constitutes a violation of the structural integrity of mate-rials is not precisely defined in the monographs.

Many drug products are compositionally intermediate between the polar and non-polar liquid or semi-solid and solid forms. Examples of such products include "aqueous" drug products that contain stabilizers, solubilizing agents, chelating agents and buffers, lipids-containing products, and biotechnology products containing proteins, peptides and blood-derived products.

Such products have a char-acteristic polarity which establishes their "extracting power" or interaction risks with contact materi-als. Thus, an appropriate simulating or extraction solvent will have a polarity that matches or mimics that of the formulated drug product but maximizes the extraction studies outcome. Binary mixtures of miscible solvents (such as alcohol/water) or buffer systems have been utilized as simulating solvents for these types of drug products. The overall study concept must make it possible to predict the leach-ables arising under clinical application conditions or over the course of the shelf life of the finished drug product, ensuring a quantitative and qualitative correlation between the extractables and leachables.

In contrast, for medical device products or device-lead combination products that are classified as prolonged or long-term medical devices under the ISO 10993 series, extractions are often carried out as exhaustive extractions using solvents of various polarities in order to fully chemically characterize long-term contacting medical devices (e.g. implantable medical devices). The extraction procedure is then carried out in accordance with ISO 10993-18 and ISO 10993-12, whereby certain regulatory ex-pectations must be considered in the study concept. The toxicological assessment of the exhaustive chemical profile is then carried out in accordance with ISO 10993-17 and ISO/TS 21726. Exhaustive extractions under harsh temperature conditions of organic polymer contact materials in chemical characterization studies with strongly interacting solvents can often lead to high amounts of extracta-ble substances. This can result in overestimated worst-case release amounts of potential leachables, leading to unfavorable toxicological assessments. Leachable studies under clinical use conditions for the release of migratory substances from an implant over very long periods of time in a living organ-ism are often not justifiable, practicable or implementable for ethical reasons. In addition, a supple-mental study that simulates clinical use of the device can sometimes be used, when justified, such as to refine the exposure estimate to enable a more accurate toxicological risk as-assessment. Simulation studies are designed to mimic clinical use conditions and filter out harsher characterization profiles to focus on what is relevant. It is often helpful to discuss with the regulatory authority about the planned approach for such studies prior to study initiation.

ISO 10993-18 provides information on recommendations on how to design simulation studies, but the selection of solvents or release reagents must be justified, as well as the extraction conditions. For example, ISO 10993-18 recommends surrogate extraction vehicles to correlate chemical analyses with biological tests. However, the ISO standard recommends using surrogate vehicles with caution, as they are not recognized by all authorities. The US FDA recently drafted guidance "Chemical Analysis for Biocompatibility Assessment of Medical Devices" which does not provide in detail with how leachable or simulation studies should be designed. This requires scientific evidence, either through publicly available literature or own studies, which make the study design of the simulation plausible.

In contrast, leachables studies under controlled climatic storage conditions in pharmaceutical packag-ing can very well be carried out over years considering USP <1664> & <1664.1> and ICH Q1 A-F recommended conditions to stability studies.

Therefore, extraction studies for pharmaceutical packaging applications usually do not need to be conducted under conditions as harsh or exhaustive as those studies under ISO 10993-18. From the discussion so far, it is clear, that combination products must meet the requirements of both medicinal products and medical devices, or only in partial aspects. Therefore, extractables and leachables studies must be designed within a risk management process in such a way that medicinal product and medical device legal requirements can be met.

Some combination products might need to proceed through regulatory submission to both the Center for Biologics Evaluation and Research (CBER)/Center for Drug Evaluation and Research (CDER) and Center of Devices and Radiological Health (CDRH) within the US FDA. For those combination products, it is recommended that all the aspects of USP <1663> & <1664> and ISO 10993-18 should be considered.

Additional information on packaging materials used in medical devices technology

The process of developing and constructing a packaging system for terminally sterilized medical de-vices and combination products is a convoluted endeavor. Stress conditions acting on the material, such as autoclaving or high-energy irradiation, can change safety profiles (leachables) as well as barri-er properties. The definitive nature of the medical device, the intended sterilization methods, the in-tended use, expiration date, transport and storage all influence the packaging system design and choice of materials. The combination of the medical device and the packaging system should perform efficiently, safely and adequately in the end-user's hands. In addition to testing barrier properties, physical characteristics and sterility, it is also essential to ensure that no interacting chemicals, either through the packaging process itself or over the product storage period, contaminate the packaged product and put the patient at risk. Particularly for medical devices and combination products with the PMOA focuses on functionality as a medical device, these interaction studies can often be carried out alongside ISO 11607 and ASTM-F1980 shelf-life/stability testing studies. In addition, ICH Q1 A-F prin-ciples may be considered in the shelf-life study design. Real-time aging and accelerated aging tests are often performed together to determine shelf life and the effects of aging on materials. Aging can re-sult in chemical changes to the packaging, potentially altering leachables over the shelf-life of the packaged product. Accelerated aging data is recognized by regulatory agencies as an acceptable means of rapidly generating data, however this data is only accepted until these tests can be repeated on real-time product/packaging samples.

Analytical techniques used in E&L studies

Due to the diverse chemical properties of extractables (volatile, semi-volatile and non-volatile organic compounds as well as element impurities), a combination of analytical techniques is often required for extractables and leachables testing. These techniques typically include gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS) and inductively coupled plasma-mass spectrometry (ICP-MS). The analytical study design must make sure that multiple or-thogonal analytical techniques fully enable the detection (coverage rate), quantification and chemical-structural identity of the potential leachables.

It is possible that authentic reference standards are not commercially available for all chemical compounds, therefore the extracted substances are often quantitatively estimated against a surrogate reference standard, resulting in analytical uncertainty in quantitative results. All substances that exceed a dose-related analytical evaluation threshold (AET) must be reported and evaluated for toxicological risk assessment (TRA). To prevent underreporting of the chemical profile, the AETs are corrected downwards using a detector response uncertainty factor.

Summary

When designing an extractable and leachable study for combination products, there are a lot of regulatory and analytical factors to be considered. Depending on the primary mode of action (PMOA) of the combination product, the study design will follow different regulatory and industry guidance.
It is recommended to discuss with E&L industry experts to design the studies properly and minimize regulatory approval delays.

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[iii] See www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types , Current content as of 02/15/2018

[iv] See www.ema.europa.eu/en/human-regulatory-overview/medical-devices/consultation-procedure-ancillary-medicinal-substances-medical-devices, accessed 01/05/2025

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[v] Regulatory agencies, such as the FDA and EMA, require comprehensive compatibility testing as part of the drug approval process. These studies are essential to demonstrate that the packaging or device materials do not adversely affect the drug product's safety, efficacy, or quality.

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