Whitepaper

Combination Products:
Understanding and Appreciation of CMC Regulatory Considerations for Successful Submission Planning

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Introduction

Combination products have emerged as powerful technologies for delivering novel molecules and modernizing traditional therapies to make them more effective and safer. A combination product is comprised of one or more regulated different classes of medical products (ie, drug, device, or a biologic) that are intended for use together as a therapeutic or a diagnostic human medicine. The medical device and medicinal product constituents are regulated *per se* by regulatory authorities, like the US Food & Drug Agency (FDA) and the EU European Medicines Agency (EMA), within developed regulatory frameworks. Even so, regulatory challenges arise in product development strategies for manufacturers and review management policies for regulatory authorities when the individual elements are combined to form more complex and diverse drug device systems.

One of the main challenges lies within the demarcation between medical devices and medicines. It is for the manufacturer to initially determine the classification regarding with regards to the primary function of a combination product. FDA and EMA guidance documents include definitions and examples as well as laying out regulatory provisions for the manufacturer.

Secondly, depending on the regulatory pathway, various regulatory requirements need to be fulfilled for each component of the drug device combination with respect to preclinical testing, clinical investigation, manufacturing and quality control, adverse event reporting, promotion, advertising, and post approval changes.

Lastly, regional differences in regulatory requirements of combination products add another layer of complexity for product developers planning to launch combination products in multiple regions. These regional differences are yet unharmonized despite a few existing initiatives. As a whole, manufacturers in combination product space need good understanding and appreciation of regional regulatory considerations for successful submissions.

This white paper aims to provide baseline knowledge on comparative regulatory requirements by FDA and EMA with a primary focus on Chemistry, Manufacturing and Controls (CMC) and quality aspects of developing combination products. Starting off with basic definitions and examples of common drug device combinations, we navigate through regulatory pathways by providing key steps and tips on how to prepare content in electronic submissions. Strategic topics addressed in this paper aim to provide practical help to sponsors interested in the submission of combination product filings in the US and the EU.

Comparative US and EU Perspectives on Combination Products

With a rapidly growing combination product space and wider recognition that these products provide value in more effective, safer, and easier treatment solutions; much guidance published by regulatory agencies in recent years has focused on combination products to ensure complex yet advanced combination therapies are put on the right regulatory pathway. That said, sponsors still find their research and development efforts harder to gauge with the evolving guidance and regulatory information, while some areas remain uncovered.

Nonetheless, the available scientific guidelines for combination products are not nearly as harmonized internationally as drugs or biologics. Initiatives, such as the International Council for Harmonisation (ICH), World Health Organization (WHO), or other regional organizations (eg, the Association of Southeast Asian Nations [ASEAN] or Gulf Cooperation Council [GCC]) continuously harmonize drugs or biologics. However, FDA and EMA have different legislative and regulatory frameworks for medical devices resulting in different development trajectories.

A consolidated list of legislative and guidance documents available in the US and the EU for combination products are provided in Appendix 1 and Appendix 2.

Definitions and Different Types of Combination Products

Combination products are typically comprised of two or more single entity products that are drug, biologic, and medical device, any of which is otherwise regulated under available regulatory schemes. The manufacturer of a combination product will need to classify their product per the formal definition.

FDA defines multiple ways of combination explicitly in 21 CFR Part 3.2(e)[1]. These may be any combination of drug, biologic, or device that are combined physically, chemically, or otherwise; packaged together (co-packaged); or packaged separately but labeled for use together. Examples of combination products per definitions given by the FDA are included in Table 1.

[1]US CFR Title 21, Chapter I, Subchapter A, Part 3

In Europe, by contrast, a formal definition of combination products is not included in the legislation. Inconsistency starts with the lexicon: unlike the US, the term combination product is replaced by 'drug device combination (DDC)' in Europe. By the adoption in April 2017 of Regulation (EU) 2017/745 on Medical Devices[2] (MDR), EMA has defined two ways of drug device combinations: integral DDC and non integral DDC. An

Table 1. Combination Products as Defined by FDA

Definition	Examples
21 CFR Part 3.2(e)(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.	• A Monoclonal antibody combined with a therapeutic drug. • A device coated or impregnated with a drug or biologic. • Drug-eluting stent, pacing lead with steroid-coated tip, catheter with antimicrobial coating, condom with spermicide, transdermal patch. • Prefilled drug delivery systems (syringes, insulin injector pen, metered dose inhaler).
21 CFR Part 3.2(e)(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products.	• A drug or vaccine vial packaged with a delivery device. • A surgical tray with surgical instruments, drapes, and anesthetic or antimicrobial swabs. • First-aid kits containing devices (bandages, gauze), and drugs (antibiotic ointments, pain relievers).
21 CFR Part 3.2(e)(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, eg, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.	• A photosensitizing drug and activating laser/light source. • An ionotophoretic drug-delivery patch and controller.
21 CFR Part 3.2(e)(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.	

CFR = Code of Federal Regulations

integral DDC is comprised of a medicinal product and a medical device to form a single entity. Other types of drug device combinations, co packaged or separate but cross labeled are defined as non integral DDC. Table 2 presents examples of integral and non integral DDCs per definitions included in the regulation.

Primary Mode of Action as a Determination Method for Regulatory Pathways

In the US, combination products are reviewed and regulated by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), or the Center for Devices and Radiological Health (CDRFH) for the various regulatory pathways as outlined in Figure 1.

The Office of Combination Products (OCP) is responsible for the classification of combination products and assignment to a specific FDA center as primary jurisdiction for premarket review and post

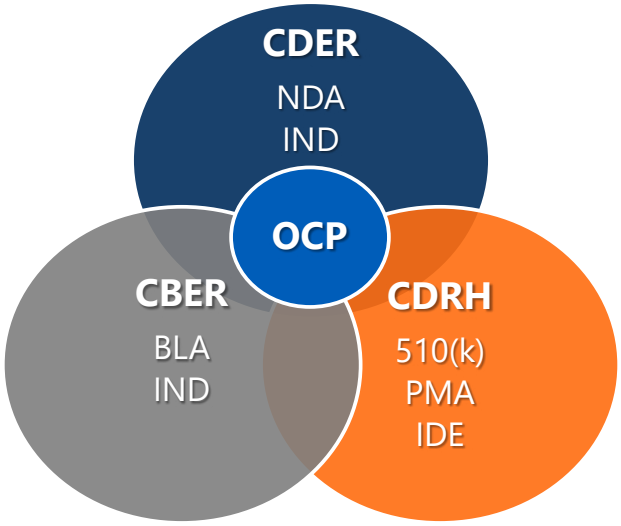
Table 2. Drug-Device Combinations as Defined by EMA

Definition	Examples
Integral Drug-Device Combinations *Article 1(8) MDR* Devices that when placed on the market or put into service incorporate, as an integral part, a substance that, if used separately, would be considered as a medicinal product [including biologics], provided that the action of the substance is principal. *Article 1(9) MDR* Devices intended to administer a medicinal product [including biologics], where they form a single integral product intended exclusively for use in the given combination and which is not reusable.	• Devices for delivery to site of action eg, the dropper on the top of the container with eye drops or the mouthpiece on the top of spray cans for throat sprays. • Single dose pre-filled syringes, pens and injectors. • Multi-dose pens and injectors containing a pre-filled cartridge where the cartridge cannot be replaced, and the pen is not designed for subsequent use with a new cartridge. • Drug-releasing intra-uterine devices; pre-assembled, non-reusable applicators for vaginal tablets. • Dry powder inhalers that are assembled with the medicinal component and ready for use with single or multiple doses but cannot be refilled when all doses are taken • Implants containing medicinal products whose primary purpose is to release the medicinal product. • Medicinal products with an embedded sensor.
Non-integral Drug-Device Combinations *Article 2(11) MDR* *Draft Guideline on the quality requirements for drug-device combinations*[#] The medicinal product(s) and device(s) are not physically integrated during manufacturing but are combined for administration and co packaged. The medicinal product(s) and device(s) are not physically integrated during manufacturing but are combined for administration, labelled for use together in the Product Information (Summary of Product Characteristics and Package Leaflet) of the medicinal product but supplied separately.	• Oral administration devices (eg, cups, spoons, syringes). • Injection needles and filter needles. • Refillable pens and injectors (eg, using cartridges). • Reusable dry powder inhalers; spacers for inhalation sprays. • Nebulizers, vaporizers. • Pumps for medicinal product delivery. • Electronic tablet dispensers.

[*]EMA/CHMP/QWP/BWP/259165/2019

MDR = REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

Figure 1. Potential Regulatory Pathways for a Combination Drug in FDA Centers



510(k) = premarket notification; BLA = Biologics Licensing Application; CBER = Center for Biologics Evaluation and Research; CDER = Center for Drug Evaluation and Research; CDRFH = Center for Devices and Radiological Health; IDE = Investigational Device Exemption; IND = Investigational New Drug Application; NDA = New Drug Application; OCP = Office of Combination Products; PMA = premarket approval.

market regulation. The status of a combination product is assigned by OCP based on the primary mode of action (PMOA) as defined in 21 CFR Part 3.2(m) below:

"Primary mode of action is 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."

A combination product with a drug led PMOA is assigned to CDER, a device led PMOA to CDRH, and a biologic PMOA to CBER by OCP (21 CFR Part 3.4). The assigned center becomes a lead center to perform the premarket review and collaborates with other centers as required.

When a sponsor cannot determine the status with certainty for reasons such as lack of subordinate PMOA or multiple PMOAs, they can initiate a Request for Designation (RFD) process as described in 21 CFR Part 3.7.

In Europe, EMA is responsible for evaluating the quality, safety, and efficacy of marketing applications assessed through the centralized procedure, including the safety and performance of the medical device in relation to its use in medicinal products. The same PMOA mechanism is used by EMA to determine the regulatory pathway for combination products (Article 1(8) and 1(9) of MDR).

Notified Bodies (NB) are organizations in the EU that are designated by Member States to assess medical devices for conformity with the defined standards. These organizations are not part of EMA, unlike CDRH in FDA. However, when it comes to the assessment of the medical device component of a combination product, NBs play an important role.

The medical device element of integral DDCs must meet the relevant requirements in Annex I of MDR as follows:

- Either a *declaration of conformity* or the *EU NB certificate* for the device component with a CE marking (administrative marking that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area);
- When there is no declaration of conformity or EU NB certificate, for sterile class I, measuring class I, class IIA, class IIb or class III medical devices, the sponsor should provide an *opinion from an NB on the conformity of the device*;
- For non-sterile, non-measuring, or non-reuable class I devices, a *declaration of conformity* should be provided.

Medical device components of non-integral DDCs that are co-packaged or obtained separately must be CE marked in accordance with the MDR.

In case of uncertainty about the PMOA, unlike in the

[2]REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Direc tive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

US, there is no single agency determination process in Europe. However, EMA recognizes the need for consultation related to complex products, also called borderline products, and EMA's Innovation Task provides advice to medical product developers on eligibility to EMA procedures as to the research and development of borderline products.

Product Development Considerations

Given all the diversity in regulatory frameworks, combination products are likely to create challenges to product development and management with respect to preclinical safety, CMC and cGMP, labeling, clinical study design, or post marketing safety requirements.

Manufacturing Quality of Combination Products: cGMP or QSR

In the US, the quality of manufacturing medicinal drug products is largely governed by drug quality regulations (current Good Manufacturing Practice [cGMP]: 21 CFR Part 201-11 for pharmaceuticals, 21 CFR Part 600-680 for biologics, and 21 CFR Part 1271 for blood and tissue based products) while medical devices are manufactured under quality systems regulation (QSR) (21 CFR Part 820). FDA conclusively published the final rule on cGMP requirements for combination products on January 22, 2013 (78 FR 4307). The final rule did not essentially introduce any new requirements but intended to clarify which cGMP requirements apply to combination products and set forth a transparent and streamlined regulatory framework for the industry to use when demonstrating compliance with applicable cGMP requirements.

The key aspects of the final rule on cGMP requirements for combinations products are discussed in two main groups per the type of combination products:

- *Cross-labeled combination products, when each constituent manufactured at separate facilities*: cGMP requirements for each constituent part are the same as those that would apply if these were not part of a combination product (eg, for a drug/device combination product, only 21 CFR Parts 210 and 211 apply to the manufacture of the drug constituent and only 21 CFR Part 820 applies to the device part);
- *Single entity combination products, co packaged combination products and cross labeled combination products when each constituent manufactured at the same facility:* streamlined cGMP operating system with two options as follows:
  - *Drug cGMP based streamlined approach*: drug cGMPs and 6 elements of the device QSR – management responsibility (21 CFR Part 820.20), design controls (21 CFR Part 820.30), purchasing controls (21 CFR Part 820.50), corrective and preventive action (21 CFR Part 820.100), installation (21 CFR Part 820.170), and servicing (21 CFR Part 820.200);
  - *Device QSR based streamlined approach*: device QSR and 8 elements of the drug cGMPs – testing of components (21 CFR Part 211.84), calculation of yield (21 CFR Part 211.103), tamper-evident packaging (21 CFR Part 211.132), expiration dating (21 CFR Part 211.137), testing and release (21 CFR Part 211.165), stability testing (21 CFR Part 211.166), special testing (21 CFR Part 211.167), and reserve samples (21 CFR Part 211.170).

In Europe, the quality of manufacturing medical devices is laid out in Article 10 of MDR and the quality of manufacturing medicinal products is governed by the principles and guidelines of GMP, which are included in the following legal instruments: Regulation 1252/2014, Directive 2003/94/EC, Directive 94/41/EC, and Directive 2001/82/EC. No guideline or Question & Answer document has been published by EMA yet for the clarification of the quality requirements or streamlining the quality systems of drugs and devices manufactured in the same facility to be used as integral or non integral DDCs.

Device Information in Electronic Submissions: CMC Requirements

As of today, no guidance for industry has been published by FDA on CMC specific format and content requirements for regulatory filings of combination products. FDA recommends a pre submission meeting with the lead Center to discuss how to organize the New Drug Application (NDA)/Biologics License Application (BLA) with respect to electronic Common Technical Document (eCTD) submission to locate the device related information.

In Europe, a Marketing Approval Application (MAA) for an integral DDC should include evidence of the conformity of the device component with the relevant General Safety and Performance Requirements (GPRSs) in the dossier structure in alignment with the eCTD format[3]. EMA's draft guideline[4] on quality requirements for medical devices in combination products gives detailed information on how CMC sections should be organized.

Based on the guideline by EMA and in-practice experience gained so far for both regions, Table 3 presents a recommended list of Module 3 sections on how to locate the specific content for single-entity combination products (ie, integral DDCs).

For non integral DDCs with co packed medical devices, EMA requests DDC information as described and applicable to the device would need to be included in the eCTD dossier for the following modules: 3.2.P.1, 3.2.P.2 (3.2.P.2.1, 3.2.P.2.2, 3.2.P.2.5 and 3.2.P.2.6), 3.2.P.7, 3.2.P.8, 3.2.A.2, and 3.2.R, respectively.

For non integral DDCs with separately provided devices, EMA states that the impact of the device on the drug (when used together) should be addressed with a risk based approach, with consideration as to the need for a usability study. The results of such studies should be provided in eCTD Module 3.2.P.2 Pharmaceutical Development. In this section, data on compatibility, dosing accuracy, handling, and manipulation, as

Table 3. Location of CMC Information and Data in eCTD Dossier Structure for Single Entity Combination Products

eCTD Module 3 Section	Information Related to the Combination Product
3.2.P.1 Description and Composition	Concise information related to description and function of the combination product.
3.2.P.2 Pharmaceutical Development	Summary of all information related to the device development including rationale for its selection, suitability of its intended use.
3.2.P.2.1 Components of the Drug Product	High-level description of the combination product.
3.2.P.2.2 Drug Product	Suitability of device within context of the combination product, its therapeutic indication and the target patient population, bridging information to devices used in clinical development.
3.2.P.2.3 Manufacturing Process Development	Concise description of manufacturing process of the combination product including sterilization process, if applicable, comparative process descriptions from pivotal or bridging clinical studies to the commercial combination product (analytical comparability), control strategy of the manufacturing process.
3.2.P.2.4 Container Closure System	Description and rationale of CCS including all components, functional performance, physical and chemical compatibility between the device and the drug product.
3.2.P.2.5 Microbiological Attributes	For sterile products, demonstration of in-use and shelf-life integrity of the combination product (container closure integrity testing of the assembled device).
3.2.P.3 Manufacture	
3.2.P.3.1 Manufacturer(s)	Manufacturer information for the combination product assembly, packaging, sterilization, labeling and testing sites. **For US**: FEI and DUNS number. **For EU**: EU batch release site
3.2.P.3.3 Description of Manufacturing Process and Process Controls	Description of manufacturing process for the combination product including subassembly steps, washing, coating, sterilization, depyrogenation, filling, or labelling, as applicable, with critical process parameters shown. **For US**: QMS of the combination product: demonstration of manufacturing facilities is operated in compliance with 21 CFR Part 4; post-marketing complaint handling reporting requirements in 21 CFR Part 211.180, Part 192, and Part 198 for drugs, and 21 CFR Part 600.80 for biologics are fulfilled.
3.2.P.3.4 Controls of Critical Steps and Intermediates	Justification of any combination product-related critical steps as described in Module 3.2.P.3.3 and description of device-specific intermediates along with relevant specifications, test methods and their validation, and as any holding times, as applicable.
3.2.P.3.5 Process Validation and/or Evaluation	Process validation for the manufacture of the combination product including assembly, sterilization, and filling.

3.2.P.5 Control of Drug Product	
3.2.P.5.1 Specification(s)	• Description of the combination product's appearance, performance tests such as extractable volume, delivered dose uniformity and functionality of device at both release and shelf-life. • Other critical test parameters related to critical quality attributes of the combination product, such as glide force, needle penetration force, seal integrity, delivery time, exposed needle length after activation of device, activation force, transdermal adhesion properties, lock-out system control to prevent over-dosing and signals to confirm dose deliver to the patient/user.
3.2.P.7 Container Closure System	• Description of the combination product including materials of construction and its specification, test procedures, technical drawings. • Information on sites and processes for sterilization and/or subassembly of the device(s). If a sterile CE-marked device is used, the NB certificate of conformity. **For US**: Device Description and Design Features; Device Development, Device Design Verification, Device Risk Management; Device Design Validation (includes HF studies) by providing information and with reference to supplier's DMF (also an LoA) as hyperlinked to the detailed information provided in Module 3.2.R (see below).
3.2.P.8 Stability	Stability studies for the combination product to include functionality tests, in-use stability, microbial quality, sterility, content/potency, purity for the entire shelf-life and in-use period, and simulated transport studies encompassing chemical and physical stability. **For US**: reference to device accelerated aging data to simulate 2 to 3 years storage of the device components in Device Design Verification.
3.2.A.2 Adventitious Agents Safety Evaluation	**For EU:** For all materials of human and animal origin used in the manufacturing process of the combination product, a statement on Transmissible Spongiform Encephalopathies confirming compliance to European Standard "Medical devices utilizing animal tissues and their derivatives – part 3 (EN ISO 22442-3:2007)" and Ph. Eur. 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products", viral risk assessment in accordance with European Standard "Medical devices utilizing animal tissues and their derivatives – part 3 (EN ISO 22442-1:2015)" and Ph. Eur. 5.1.7 "Viral Safety", as well as detailed information regarding other adventitious agents such as bacteria, mycoplasma, and fungi.
3.2.R Regional Information, Medical Device	**For US**: Demonstration of device design verification testing (environmental tests, functional tests, performance tests, including accelerated aging studies to applicable standards and FDA guidance); reference to reports in Supplier's Master Access File by hyperlinks; compliance of device, packaging and labeling to 21 CFR Part 820.30; device design verification, device design validation, device design development history; summary of device subsystem design changes across verification, human factors formative and summative results (summary of root-cause analysis on any device deficiencies and anomalies), Usability Engineering File Summary and human factors reports; clinical studies, and the commercial configuration; references to IFU (in Module 1) and Clinical Overview (in Module 2.5) for risk/benefit; user risk assessment report, as applicable. **For EU**: Demonstration of compliance of the device(s) with MDR Annex 1 (ie, the applicable GSPRs) per classification of device, NB opinion and usability (human factor engineering) studies.

CCS = container closure system; CE marking = administrative marking that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area; CFR = Code of Federal Regulations; DMF = drug master file; DUNS = data universal numbering system; EN ISO = European Standard; FDA = US Food and Drug Administration; GSPR = general safety and performance requirements; HF = human factor; IFU = instructions for use; LoA = Letter of Authorization; MDR = medical device regulation of April 2017 in the EU; NB = notified body; Ph. Eur. = European Pharmacopeia; QMS = quality management system.

[3]Volume 2B Notice to Applicants Medicinal Products for Human Use – Presentation and Format of the Dossier
[4]EMA/CHMP/QWP/BWP/259165/2019

applicable, should also be provided. In-use stability data is expected to be presented in eCTD Module 3.2.P.8 Stability. Information on device stability and human factors studies should be presented in Module 3.2.R Regional Information, as applicable.

Importance of Usability/Human Factors Engineering Studies

Human Factors Engineering is a multi-discipline scientific approach to understand people, their characteristics, environments, and the tools they need to use in these environments. Poor medical device design, instructions, and/or package design can lead user actions to error and result in potentially harmful consequences.

In the US, usability assessment of devices and instructions for use are required per the FDA Guidance for medical devices[5] (February 2016). This assessment aims to maximize the likelihood that new devices will be safe and effective for the intended users, uses, and user environments. FDA gives guidance[6] to clarify how human factors (HF) concepts apply to the development of a combination product when one of the constituent parts is a device.

The description, aim and usage areas of three types of HF studies are presented in Table 4. The main reasons why these studies are critical to combination product development can be summarized under three headings:

1. Demonstrating the intended users can safely and effectively operate the device per its intended use, in its intended environment.
2. Optimizing the combination product prototype user interface by formative studies at following aspects:
    - Device (eg, sounds, lights, buttons, orientation, shape, functionality),
    - Labels (eg, Instructions for Use [IFU], device labels),
    - Packaging (eg, cartons, trays)
3. Validating the final finished combination product user interface by summative studies.

Submission of Human Factor Studies in Regulatory Filings with Examples

In the US, FDA guidance advises the submission of HF data for the following two groups of combination products:

1. Products for use outside the health care environment or by laypersons (eg, home use products, products for self administration by patients or lay caregivers);
2. Combination products that have a device constituent part for which HF data should be submitted.

For combination products that do not fall within these two categories, a use risk analysis for the combination product should be completed. If the use risk analysis identifies the need for HF studies, then an HF validation study should be conducted, and the results should be submitted in the regulatory filing.

Interestingly, for a prefilled syringe (PFS) with a staked needle, HF data for a health care professional use may not be required provided that the syringe, needle, and needle guard design are commonly used and well understood. On the other hand, if the PFS has a novelty in its syringe, needle, or needle guard, and there is a potential concern about use related risk, then HF data may be required. It is also likely that HF data for PFS would be required in case PFS is for use by a unique patient profile (eg, blind users) if there is potential concern about the product differentiation or PFS is used in complex and high risk setting, or in an unconventional way.

Continued with the case in the US, for combination products in vials, ampoules, or oral tablet device combinations, HF data typically are not required. However, if the preparation and administration process of a combination product involves more than a simple 'draw medicine and inject' step, or if the process requires user to make a decision based on the labeling (eg, selecting the correct number of vials to use), then additional risk evaluation and HF data may be required.

The assessment of use risk associated with the device starts by including the use risk analysis data in the Investigational New Drug application (IND) submission. Depending on the use-risk analysis results, further HF studies along with the HF study protocol should be submitted and approved by FDA. The HF study results

are typically included in NDA/BLA filings to support device design validation. As mentioned in Table 3, HF data is included in Module 3.2.P.7 Container Closure System as part of the Device Design Validation package, along with other information on device design. Supporting HF information including HF validation study protocol, study report, use risk analysis, and usability summary report are included in section Module 3.2.R Regional Information. HF information should also be cross referenced from Module 5.3.5.4 Other Study Reports with links to Module 3 documents, as applicable.

In Europe, according to draft guideline on the quality requirements for drug device combinations[7], a summary of HF data should be provided in Module 3.2.R Regional Information, and could be cross-referenced from Module 5.3.5.4 Other Study Reports, to demonstrate usability requirements are met per GSPR of MDR.

Demonstration of Comparability

Combination products might undergo changes in terms of design and dosage form during their lifecycle. One example scenario might be the case that clinical devices and formulations used during pivotal Phase 3 studies may undergo different final formulations before commercialization. Another likely scenario might be that a novel delivery system may be developed for an approved drug or biologic post approval. Likewise, design improvements are frequently introduced to an approved combination product (eg, a new manual needle guard to a marketed product with a classic PFS) as well as new intended users could be added to the label (eg, switch from a health care professional use only product to a self administration use). Equally important, a biosimilar product with an interchangeability claim necessitates the demonstration of comparability.

Changes, either in the formulation, excipient, or device design, as in exemplified scenarios, may affect the drug product delivery characteristics and clinical performance of the combination product. Therefore, all requires a comparability exercise. The extent of clinical and/or quality data required to support such changes depends on the nature of the change and the development stage.

[5]Guidance for Industry and FDA Staff, Applying Human Factors and Usability Engineering to Optimize Medical Device Design, February 2016

[6]Draft Guidance for Industry and FDA Staff on Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, February 2016

[7]EMA/CHMP/QWP/BWP/259165/2019

Table 4. Human Factor (HF) Study Types by Design

Type of HF Study	Brief Description, Aim and Use
Use-related Risk Analysis	Foundation of an HF study, with purpose to identify use-related high-risk hazards associated with the combination product. Identified critical user tasks and associated risks are evaluated in HF studies. Common methods used are Failure Mode and Effects Analysis and Fault Tree Analysis.
HF Formative Studies	Designed to evaluate early combination product prototypes based on the identified use-related hazards as a result of a prior use-related risk analysis. Iterative HF formative studies optimize the design of the combination product user interface for safety.
HF Summative Studies	Demonstrate that the final finished combination product user interface maximizes the likelihood that the product will be safely and effectively used by the intended users, for the intended uses, and in the intended use environments. Two types of validation studies are available for use: HF simulated-use validation study focusing on confirming the design via simulation methods; HF actual-use validation study focusing on confirmation of device design within a real environment of use.

The process of establishing the scientific relevance of information developed in an earlier phase of the development program or another development program to support the combination product for which an applicant seeks approval is termed *'bridging'*. FDA recognizes the need to help applicants consider the type and scope of information that may be leveraged for a combination product as detailed in their guidance.

In general, the aim of a bridging exercise is to ensure the quality, safety, and efficacy of the next generation combination product in comparison to the earlier version of the product. A list of potential data packages to obtain from bridging activities and their aims are explained in Table 5. Not all bridging studies are necessarily required in all filings. Rather, a stepwise approach should be adopted based on the results obtained and the necessity of further studies. The studies are listed from top to down to reflect the stepwise approach.

When embarking on a next generation combination product to make it easier to use, safer, and more effective, a holistic approach should be adopted during the development program with a stepwise progression of bridging studies to information gaps.

[8]Draft Guidance for Industry and FDA Staff on Bridging for Drug Device and Biologic Device Combination Products, December 2019

[9]Towns, J.K. A Science and Risk-Based Approach to Bridging Drug-Device Combination Products. In Jameel F, et al.eds. Development of Biopharmaceutical Drug-Device Products, Vol 5, AAPS Advances in Pharmaceutical Sciences Series, 2020

Table 5. Potential Data Packages to Bridge Information Gaps (in order of stepwise approach)[9]

Bridging Studies	Description/Aspects Covered	When Required
Device Tolerability	Delivery attributed to the device (eg, leakage, pain in injection site)	When implementing new device platform technologies
Drug Product Comparability	Analytical testing of interactions between the molecule, formulation, and device components of the drug product formulation to assure no adverse impact to (1) biopharmaceutical molecule or (2) increase in leachable/extractables from CCS (eg, shearing of mAb from AI)	When the drug product is delivered through the device
Device Verification/Validation	Ensures technical robustness/reliability of the device design for the intended purpose	Changes in device design within platform
Human Factors	Usability assessments of device and IFU to ensure safe and effective use of the combination product	Changes in intended user and environments (eg from clinical to home use) or changes in device designs, novel device platforms
Bioequivalence	PK comparability or relative bioavailability study	Different device constituent part (eg from a PFS to AI) for drug products that exhibits high PK variability or nonlinear PK
Clinical Home Use (CHU) for Real-life Patient Handling (RLPH) Experience	Clinical investigation to assess the ability of the device to deliver a full dose of drug or biologic when used by the intended user as a home use device	Home-use claim
Pivotal Phase 3 Studies	Efficacy and safety data per the label claim	Introduction of a novel device platform

AI = auto-injector; mAb = monoclonal antibody; PFS = prefilled syringe; PK = pharmacokinetics.

A Case Analysis: Bridging a Lyophilizate Formulation for Clinical Use to an Auto injector for Patient Self-administration from a Quality Perspective

Background:

The sponsor conducted pivotal Phase 3 clinical studies for a therapeutic antibody product, indicated for use in multiple myeloma patients, with dosage forms of 100 mg lyophilized powder in vial (LYO) and 200 mg lyophilized powder in vial (LYO). Commercial dose has been defined as 100 mg/mL solution for injection in prefilled syringe (PFS) or 100 mg/mL solution for injection in auto injector (AI). The highest dose to be marketed will be 200 mg delivered as 2 x 1 mL injections.

Additionally, the following information about the product is available:

- PFS: Prefilled syringe included staked needle, rigid needle shield, and rubber stopper
- AI: auto injector with a detachable cap included in the package
- Secondary packaging of all LYO, PFS, and AI forms have patient information leaflet and label in the outer package
- Drug product formulation (excipients, drug concentration) in AI is identical to PFS
- PFS and AI have the same product container and same injection depth

Case:

To demonstrate a good clinical response and ensure safe and well tolerated use of the commercial PFS and AI dosage forms of the product, what bridging studies from a quality perspective does the sponsor need to plan to support CMC sections of the regulatory filing?

Table 6. Potential Bridging Studies to Support the Case

Bridging Studies	Comparability between LYO to PFS	Comparability between PFS to AI
Device Tolerability	Perform to demonstrate comparability for the changes related to the delivery attributed to the device (eg, leakage, pain in injection site).	Perform to demonstrate comparability for the changes related to the delivery attributed to the device (eg, leakage, pain in injection site).
Drug Product Comparability	Release and characterization tests (eg, potency, purity, aggregation, impurity profiles, glycosylation, deamidation, etc.) Long term stability of DP in PFS. Compatibility with the PFS. Leachable/extractables testing. Shipping studies. Process validation of PFS.	Long term stability of DP in AI. Dose accuracy and functional stability. Microbial integrity of the CCS for assembly of the PFS into AI cartridge. Process validation of PFS-AI cartridge.
Device Verification/Validation	Dose, injection time, reliability, injection depth, activation, and overriding forces, and cap removal torque. Accelerated aging studies for the durability of components, subassemblies and assembled PFS. Biocompatibility testing (ISO 10993).	Dose, injection time, reliability, injection depth, activation, and overriding forces, and cap removal torque. Accelerated aging studies for the durability of components, subassemblies and assembled AI.
Human Factors	Usability assessments of device and IFU to ensure safe and effective use of the combination product in clinical home use.	Usability assessments of device and IFU to ensure safe and effective use of the combination product in clinical home use.

AI = auto-injector; CCS = container closure system; DP = drug product; IFU = instructions for use; ISO = The International Organization for Standardization; LYO = lyophilizate; PFS = pre-filled syringe.

Solution:

A potential list of bridging studies to support the quality aspect of PFS and AI dosage forms in the regulatory filing is presented in Table 6. It needs to be emphasized that each case depends on many different factors and more than way of bridging the information gap is possible.

In Place of Conclusion: Key Steps and Tips to Successful Applications

The Importance of Regulatory Writing

- Single-entity, co-packed, or separately provided, complex or simple; well-written description of a combination product is essential.
- Regulatory documents must be written to reflect overall information and knowledge on combination product.
- Authoring should support regulatory strategic plan.
- Regulatory writers should be technically skilled to enhance the regulatory strategic plan with a good authoring strategy accompanied by a source document gap assessment.

Product Development Plan

- Identify and plan for any potential product changes, steps to those changes and their impact to product quality, efficacy, and safety.
- Conduct labeling and HF studies as appropriate.
- Plan for potential post-approval changes.
- Discuss and plan for any proprietary issues (eg, Master Files).
- Platform devices may need testing for modifications.
- Consider testing final-finished combination product as a whole.

Tips for submission to US Authorities

- Determine classification and lead center (initiate communication with FDA via RFD).
- Early interactions with FDA via pre-IND/IDE meetings with pertinent centers and OCP.
- 510(k) cleared device may go under review again at the time of NDA/BLA review.

Tips for Submission to European Authorities

- Engage with EMA's Innovation Task for confirmation on regulatory strategy.
- Prepare for MDR implementation dates and new requirements.
- NB assessment is on critical path for submission.
- Choice of NB having good relations with the agency.
- Essential Requirements (ER) for medical devices is replaced by General Safety and Performance Requirements (GSPR).

Appendix 1. List[1] of Legislative and Guidance Documents Related to Combination Products in the US

US	Legislation
Combination Products	**Statutory Provisions** • 21st Century Cures Act, Section 3038. Combination Product Innovation, Dec. 13, 2016 • 21 U.S.C. 353 (g) – Combination Product – section 503 (g) of the Federal Food, Drug, and Cosmetic Act **Regulations** • 21 CFR Part 3 • 21 CFR Part 4

Guidance	• Guidance for Industry and FDA Stuff on Submission and Resolution of Formal Disputes Regarding the Timelines of Premarket Review of a Combination Product (May 2004) • Guidance for Industry and FDA Staff on Application User Fees for Combination Products (April 2005) • Guidance for Industry and FDA Staff on Early Development Considerations for Innovative Combination Products (September 2006) • Guidance for Industry and FDA Staff on Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (July 2007) • Guidance for Industry on New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products (January 2010) • Guidance for Industry on How to Write a Request for Designation (RFD) (April 2011) • Draft Guidance for Industry and FDA Staff on Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA (January 2013) • Draft Guidance for Industry and FDA Staff on Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4 (April 2013) • Guidance for Industry and FDA Staff on Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (June 2013) • Draft Guidance for Industry and FDA Staff on Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (February 2016) • Guidance for Industry and FDA Staff on Current Good Manufacturing Practice Requirements for Combination Products: (January 2017) • Guidance for Industry and FDA Staff on Classification of Products as Drugs and Devices and Additional Product Classification Issues (September 2017) • Guidance for Industry on How to Pre-Request for Designation (Pre-RFD) (February 2018) • Draft Guidance for Industry and FDA Staff on Principles of Premarket Pathways for Combination Products (February 2019)

	• Guidance for Industry and FDA Staff on Post-marketing Safety Reporting for Combination Products (July 2019) • Draft Guidance for Industry and FDA Staff on Bridging for Drug-Device and Biologic-Device Combination Products (December 2019) • Draft Guidance for Industry and FDA Staff on Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA (April 2020) Guidance for Industry and FDA Staff on Requesting FDA Feedback on Combination Products (December 2020)
Medical Device	**Regulations** • 21 CFR Part 800 **Guidance** • Guidance for Industry and FDA Staff on Applying Human Factors and Usability Engineering to Medical Devices (February 2016) • Guidance for Industry on Design Control for Medical Device Manufacturers (March 1997) • Draft Guidance for Industry on Coronary Drug-Eluting Stents (March 2008) Guidance for Industry and FDA Staff on Heparin-Containing Medica Devices and Combination Products: Recommendations for Labeling and Safety Testing (September 2018)
Drug or Biologic	**Regulations** • 21 CFR Part 312 (Investigational New Drug Application) • 21 CFR Part 314 (New Drug Application) • 21 CFR Part 600 (Biologic License Application) **Guidance** • Guidance: for Industry Container Closure Systems for Packaging Human Drugs and Biologics (July 1999) • Guidance for Industry on Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient Use Containers for Human Use (October 2018) • Guidance for Industry on Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (February 2019)

[1] The list of legislative and guidance by FDA for combination products is exhaustive as of the date of this white paper. The list of legislation and guidance for medical devices and drug/biologic products is not exhaustive, only major ones relevant to combination products are included for reference.

Appendix 2. List[1] of Legislative and Guidance Documents Related to Combination Products in the EU

EU	Legislation
Combination Products	**Regulations** • Regulation (EU) 2017/745 on Medical Devices (MDR), Article 117 **Guidance** • Draft Guideline on the Quality Requirements for Drug-Device Combinations (EMA/CHMP/QWP/BWP/259165/2019)
Medical Device	**Regulations** • Regulation (EU) 2017/745 on Medical Devices (MDR) • Regulation (EU) 2017/746 on In Vitro Diagnostic Medical Devices (IVDR) **Guidance** • Question &Answer on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ([EU] 2017/745 and [EU] 2017/746) EMA/37991/2019
Drug and/or Biologic	**Directives and Regulations** • Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use • Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

About the Author

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