

White Paper

Unlocking regulatory complexities

The key to combination product success



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Introduction

Technological advances and scientific discoveries have significantly enhanced our ability to develop new ways to diagnose and treat patients' illnesses and maintain their health. One of the most exciting and diverse developments is the convergence of drugs and devices into combination products.

These products consist of two regulated components, a drug and a medical device, which are combined to develop a single product. But such novel combination products pose numerous regulatory hurdles for sponsors, even when comprised of previously cleared components. Drug-device combination products are notably complex, particularly when it comes to designing clinical trials and preparing for regulatory review. Partnering with a contract research organization (CRO) with experience in planning and executing both medical device and drug trials can help sponsors navigate these hurdles.

This paper explores medical device combination product strategies IQVIA™ recommends to improve the regulatory journey from classification to market clearance for sponsors.

A growing market

The commercial market for drug-device combination products is expected to grow at a compound annual growth rate of more than 11 percent by 2019.¹ There are a number of drivers behind this growth, primarily an emergent patient population with chronic diseases such as cardiovascular disease, diabetes, prostate cancer and others. Demand for minimally invasive surgeries and portable devices, such as inhalers and insulin injectors, is also fueling growth.

For regulatory purposes, the U.S. Food and Drug Administration (FDA) defines combination products as therapeutic and diagnostic products that combine drugs, devices or biological products.² Many other regulatory

authorities ranging from Japan's Pharmaceuticals and Medical Device Agency (PMDA) and China's State Food and Drug Administration (SFDA) to Canada's Health Authority (Health Canada) and the European Medicines Agency (EMA) review and approve combination products via processes that differ from the FDA and from each other, even within EU member countries. While this paper focuses on the FDA requirements for combination products, IQVIA can provide counsel regarding the requirements crucial to clinical evaluations and timely market clearance globally.

Regulatory complexities: Understanding the regulatory perspective

Combination products tend to be governed by different regulations based on their components and primary mode of action. This can lead to challenges for regulatory authorities to agree on product jurisdiction for review. Moreover, across the globe, such classifications are subject to different interpretations.

Therefore, it is not surprising that, as the FDA readily states, combination products raise complex regulatory, policy and review management issues.³ This complicated environment holds true not only in the U.S., but globally as well.

The FDA enacted a system to review and regulate combination products in 2002 when it established the Office of Combination Products (OCP). This office

is charged with improving the transparency and predictability of the review process, clearance and ensuring the post-market regulation of combination products. Because of the OCP, the FDA accepted 350 original premarket applications and performed 932 inter-Center consulting reviews for combination products in FY 2015.³

By its charter, the OCP is a facilitator both between industry and the FDA and among the Agency’s human medical product centers: the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH). The journey of a combined product through the FDA begins with classification to one of these centers, which then conducts a risk review to evaluate safety and efficacy (effectiveness or performance) of the proposed product.

As OCP notes, each component of a combination product can have a different regulatory pathway, which in turn can impact the product’s overarching regulatory journey, ranging from its “preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, user fees and post-approval modifications.”³

Where should a combined product sponsor begin?

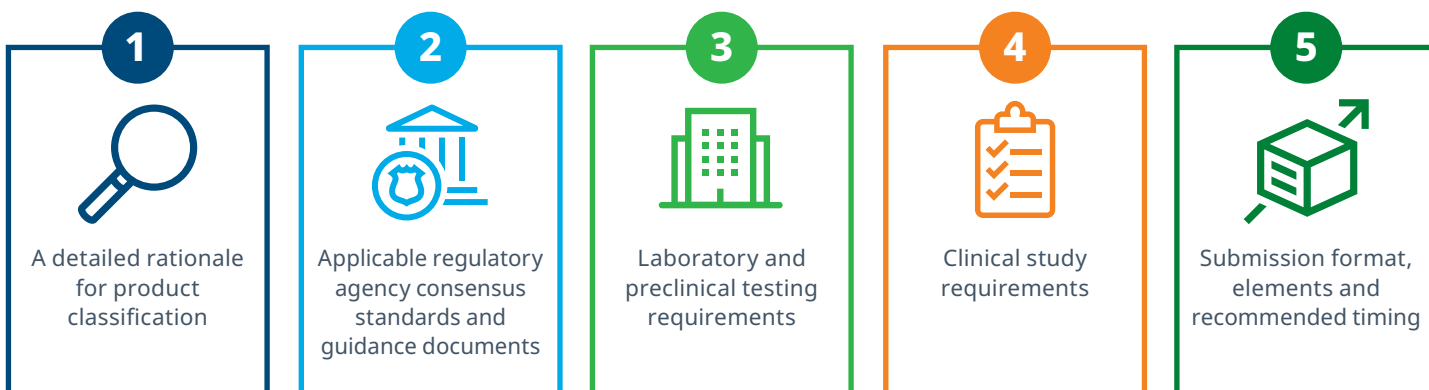
Using a CRO to navigate the process

A sponsor’s first step for combination products is identifying the information a regulatory agency requires to determine the product’s identity and assignment for review and clearance. Because global harmonization is still an unrealized goal, a combination product sponsor must have an excellent understanding of how the potential market is regulated and how obtaining a first market clearance might influence subsequent markets. A sponsor, therefore, might be well advised to seek the counsel of a qualified CRO early in the development process to obtain a detailed strategy for the proposed combination product’s regulatory process, tailored by an assessment of the product and each applicable regulatory agency.

PRODUCT CLASSIFICATION VIA THE RFD

As part of the product classification rationale, IQVIA encourages sponsors to explore a stepped, or staged, entrance into the regulatory pathway, beginning with defining the product’s simplest and clearest indication.

Sponsors should expect a CRO to provide at least five aspects to a combination product regulatory strategy:



This indication must consider the product’s proposed primary mode of action (PMOA) and intended use. PMOA is the foundation of a combination product’s regulatory strategy, and the FDA uses the PMOA to assign the product’s lead review center.

Helpful in selecting a PMOA is understanding how the FDA classifies combination products into four groups: a drug and a device; a biologic and a device; a drug and a biologic; a drug, a device and a biologic. The Agency refines these types by noting the combination can be physical, chemical or otherwise mixed to produce a single entity or to be packaged together as a unit. Alternatively, the proposed labeling may indicate that a separately packaged investigational drug, device or biologic can only be used with another individually specified investigational component to achieve the intended use, indication or effect.⁴

To assign a lead Center, especially when the PMOA is unclear, the OCP suggests but does not require sponsors to submit a Request for Designation (RFD), also known as an applicant’s letter of request. In an applicant’s letter of request a sponsor can recommend how the combination product should be regulated, as a drug, device or biologic, and, therefore, the Center to which it should be assigned for review. The RFD decision is binding and the lead Center will review all subsequent submissions required for investigational testing or market clearance of the combined product, including risk classification.

As part of the RFD, sponsors must provide each component’s mode of action, the product’s PMOA and the basis for this PMOA, such as a literature review or proprietary data. These supporting factors help the FDA consider questions such as the relative contribution and its duration of effect or action for each part or how the overall intended therapeutic effect of the product is achieved.

A wrinkle in the PMOA determination can occur if the product has two distinct therapeutic effects resulting from two different modes of action that are not related

WHAT IS A PRIMARY MODE OF ACTION?

Combination products may have a drug, biologic, or device mode of action (MOA), even though each of its regulated components contributes a different MOA. The FDA definition of MOA is “the means by which a product achieves an intended therapeutic effect or action,” which might be to “diagnose, cure, mitigate, treat, or prevent disease or affect the structure or any function of the body.”⁵ The FDA defines the PMOA as the single MOA “that provides the most important therapeutic action of the combination product.”⁵ When looking at the parts of a combination product, the FDA determines each part’s MOA as:⁶

- Biologic if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product;
- Device if it acts only through mechanical means; or
- Drug if it acts through chemical, metabolic, pharmacological, or immunological means.

to each other. For example, as the FDA explains, vision-correcting contact lenses impregnated with a drug for treating glaucoma.⁵ In such situations the Agency advises sponsors to use an assignment algorithm and to provide information about related products. If a predicate combination product exists, the algorithm determines that the Agency selects the Center that regulated the earlier product. But for truly first-of-its-kind combination products, the Agency makes the assignment to the Center with the most expertise related to the safety or efficacy questions regarding the

AN EXAMPLE OF INTENDED USE

Traditionally, medical devices intended solely for one use, such as a controlled drug delivery device, fall in the purview of the FDA's CDRH. However, if a drug delivery device is intended for use with a particular drug product, then it is a device-drug combination product. The PMOA for such a device and its submission must, therefore, go to CDER, with a submission for each specific pharmaceutical that is combined with the device. To acquire submission data, each such device-drug combination requires testing to help ensure drug stability and potency with the device use, as well as new pharmacology/toxicology studies and human clinical trials to prove the device-drug combination is equivalent or superior to any previously approved comparable combination products. However, before human clinical trials can begin, each combination product requires an accepted Investigational New Drug (IND) submission from CDER. The size, length of follow-up, and complexity of clinical trials for such a combination product will be very similar to those typically required for a New Drug Application (NDA) and would be necessary for each intended use. A similar regulatory path for a delivery device–biologic combination product usually would involve CBER and require a Biologic License Application (BLA) instead of an NDA.

new product. Questions might include the schedule and duration of use, dose and route of administration or which component has the greatest risks.

Intended use is another critical factor in the classification rationale. Only after a sponsor understands the product and the subtleties of its PMOA can a clear definition of its intended use and indications be realized.

The recommended stepped approach to product designation asks a sponsor to consider the simplest intended use — even if the sponsor has no intention of marketing that use — because the time saved in the regulatory submission process could be well worth it. For example, after a sponsor achieves successful clearance of its first combination product and the Agency is more comfortable with the technology and quality of product design and development, the sponsor can pursue another submission for a new indication using the original device as the predicate. Clearance for these new indications generally will likely be much faster.

TO USE THE RFD OR NOT?

The FDA recommends RFDs when a combination product's classification or the potential Center assignment is unclear or in dispute. But, the RFD is not the only way to pursue a designation. Sponsors can choose an informal determination process if the FDA has experience with similar products. If a sponsor is unsure about submitting a RFD for a binding determination and would prefer a preliminary assessment to gain insight into the PMOA the FDA would select, a sponsor may submit a pre-RFD (a pre-submission, or Q-sub). A pre-RFD is non-binding and is not subject to the RFD 15-page submission limit. For companies early in their product development, having this feedback may shape the manner in which the sponsor positions their business with respect to quality systems, testing, financial obligations and marketing strategies. This alternative pathway allows the sponsor and the FDA to

review the relevant scientific background and rationale for the designation as well as provide a venue for future discussions for preclinical and clinical studies and gain consensus with the reviewing division.

Sponsors are well advised not to ask a regulatory agency for a product designation, either via RFD or informally, too early in the development process. Thoughtful documentation and evaluation of the PMOA and intended use that considers safety and effectiveness of each part alone and when acting together in the combined product must be done before regulatory submission.

For example, if an antimicrobial coating on a device is solely to reduce device contamination, a sponsor needs the data to not only prove that the agent is effective but also that it is not eluted from the device under conditions of use. If such safety and risk data are not provided, regulatory reviewers are very likely to err on the side of caution and designate a higher risk class for the product than might otherwise be warranted. The consequences could then start with the primary review jurisdiction being assigned to the incorrect Center, which is then long and difficult to change and may result in a more limiting label and market.

THE RFD RESPONSE

The FDA responds within five days to let sponsors know if the RFD is deemed complete or if additional information is needed.

Once submitted, a complete RFD may raise questions, which the FDA may send to a sponsor. Responses should be made via email as soon as possible to expedite the process, but IQVIA recommends sponsors also send a formal letter response copying the Agency's question number and text followed by the sponsor's response to each question.

The FDA then makes the lead Center assignment based on the sponsor's request, predicate devices (if applicable), and a complex algorithm of potential safety and

effectiveness issues. The FDA will generally provide a sponsor with a written response making the assignment within 60 days of a sponsor's original submission. The Agency's response to the RFD is binding, although the sponsor is allowed to counter-respond.

And the designation is...

If the Agency response is favorable, a sponsor may proceed as planned with product development and submission.

If, however, the Agency determination is one with which a sponsor does not agree, a sponsor may respond in writing within 15 days, but the correspondence cannot include new information.

If a sponsor has new information **not included in the original request** that is pertinent to the Agency's decision, a new RFD should be submitted. Of note, one of the requirements of the cover letter for any type of submission to the FDA is a listing of all previous correspondence with the Agency regarding the product.

Designations are binding and will permanently attach to the product for a particular intended use. If a sponsor is not successful in getting the Agency to change the designation, it may be possible to change or limit the intended use for the product such that a new designation a sponsor deems more favorable might be made.

The development three-step: Considerations for clinical trials

With a successful group and lead Center designation, combination products can begin their clinical trial journey. Sponsors must undertake such trials to yield the data necessary for the safety and efficacy evaluations that could lead to approval. But just as combination products are more complex than a single component, so too are their clinical trials. For example, the new product will "own" the adverse events for each of the separate components.

Because, in many cases, the particular combinations have never before been tested in humans, IQVIA has found it best for sponsors to undertake a three-step approach to trials. This stepped approach is particularly successful for investigational products that combine a drug or biologic with a delivery device because of the likely major differences in human bioavailability (BA) and bioequivalence (BE) for the added agent that result from the new delivery method. The FDA will want BA/BE studies done first, before a pilot trial can commence. IQVIA recommends starting with small feasibility trials, usually about 20 patients, to establish safety, begin to define the expected adverse effects, and validate the performance of the product in the field before advancing to the second step of a pilot study and then a third step to larger pivotal trials. Of note, pivotal trial size typically will be based on the rates achieved in the BA/BE studies compared with the standard of care.

STEP 1: BEGINNING WITH BA/BE

Studies BA/BE studies typically must be randomized, placebo-controlled and parallel in design and require comparative clinical endpoints in patients with a clinical diagnosis for the condition of interest. In such trials, investigators randomize patients to receive the proposed combination product, reference product alone (standard of care) or the device alone. Typically, the randomization is 2:2:1, with equal numbers randomized to each active treatment arm and half as many to the device alone arm. If ethical issues are a concern for use of the device alone, the FDA may allow a crossover design for the study, so that patients who received the device alone but did not resolve their condition within a specified time could be later randomized to one of the two treatment groups.

While these BA/BE studies typically are double-blinded, this design may not always be possible. The FDA will usually accept an unblinded design if a single, blinded core laboratory can be used for all of the trial evaluations. To demonstrate BE, both active treatments should also be superior to device alone, which also shows the study design is adequately sensitive to document a difference between products.

The FDA does not specify the size of the required BA/BE studies, but does specify that it is the sponsor's responsibility to enroll sufficient patients for the study to demonstrate bioequivalence between the products. Study requirements for combination products can be defined only from the pre-investigational new drug discussions with CDER or the pre-biologics license application discussions with CBER.

IQVIA recommends a staged process, in which a smaller, pilot-controlled trial, generally involving around 50 subjects, verifies safety and confirms patient inclusion and exclusion criteria before moving to the larger pivotal trial.

STEP 2: MOVE TO A SMALLER, PILOT-CONTROLLED TRIAL

Changing established clinical practice is difficult. Typically pivotal trials require a prospective, two-arm, controlled study that is at least partially blinded to directly compare both the safety and efficacy of the combination product with a previously cleared product or standard of care.

Again, IQVIA recommends a staged process, in which a smaller, pilot-controlled trial, generally involving around 50 subjects, verifies safety and confirms patient inclusion and exclusion criteria before moving to the larger pivotal trial.

STEP 3: PROVE WITH LARGER PIVOTAL STUDIES

The size of the full pivotal trial depends on the PMOA, intended use and claims for the combination product, the adverse event types and rates observed in previous studies, and the product efficacy compared with standard of care. Generally, patient numbers are smaller for trials to establish equivalence, as trials powered to show superiority of the new combination product to standard care will be much larger.

For example, a randomized, double-blind two-arm study of a new drug- or biologic-coated device against a non-coated device would be used to show non-inferiority in efficacy with an increase in safety, such as fewer adverse events, or decreased infection rates. Such a trial would require a smaller sample size than a superiority study. In contrast, a two- or three-arm superiority trial against the competitor “predicate” product increases trial size significantly, while also increasing trial complexity, number of sites required and trial duration.

The FDA generally only requires combination products trials to show “substantial equivalence” to a predicate device or standard of care, so the patient numbers are generally smaller in these trials. In contrast, Centers for Medicare & Medicaid Services (CMS) may require a new combination product be superior in terms of safety, efficacy or both, with a decrease in the overall cost of care, before a new reimbursement code can be issued. As a result, such superiority trials are much more expensive to undertake because of the larger number of required patients, the additional data required for healthcare cost comparison and the longer timelines required to show differentials between the new treatment and current standard of care. Many sponsors opt to obtain market clearance from the EU, FDA or both, and then perform long-term registry studies to obtain the data required for CMS. While not explored in this paper, it should be noted obtaining coordinated CMS and FDA approval in the designation is essential in the R&D process for sponsors.

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One additional note of caution: Many companies decide to begin extensive clinical studies outside the U.S. (OUS), which may have a number of advantages, but requires careful evaluation. A sponsor must ensure the rigor of these studies and the subsequent data are of the caliber required by the FDA as well as other regulatory agencies. In fact, in most cases, data from European trials would be acceptable for partial completion of human clinical study requirements. However, the FDA will not accept results from OUS studies as part of the clinical validation unless the Agency is convinced that clinical practice for the specific treatment indication in these countries is nearly identical to that of the U.S. For this reason, a sponsor must understand the details and differences of country-specific, and regionally specific, clinical practices and choose trial sites accordingly.

Planning and executing combination product trials present a unique set of challenges but following this three-step process can help improve the regulatory journey from classification to market clearance. Additionally, a CRO with medical device and pharmaceutical experience can assist in providing accurate and current direction and best practices to companies that will have immediate and long-term impact on the success and use of the pivotal trial and the subsequent data.

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