An Approach of developing a strategy for regulatory approval for a Drug-Patch Combination Product according to the Current European Regulations

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ABSTRACT

The increasing relevance of combination products (CPs) in modern therapy is driven by the expanding range of technological and pharmaceutical possibilities. However, the current European regulatory framework, particularly under the Medical Device Regulation (MDR), poses challenges when classifying and approving combination products that do not clearly fit established categories. This paper analyses the regulatory landscape for CPs, identifies key issues in qualification, approval pathway selection, standard application, and proposes strategies to address these gaps. Using a case study involving a hybrid drug-device system for oncology therapy, the study illustrates how clinical needs may necessitate regulatory solutions that extend beyond conventional classifications. Key findings highlight the lack of regulatory clarity for products with dual modes of action and the need for coordinated evaluation between authorities. Strategic recommendations include enhanced guidance on Notified Body Opinion (NBOp) applicability, acceptance of integrated testing, and the establishment of a joint consultation mechanism.

Keywords: Approval strategy; Regulatory framework; Combination product; Drug-device combination; Mode of action

1. Introduction

The introduction of the European Medical Device Regulation (MDR) has brought major challenges for the medical device and pharmaceutical industries. The new legal requirements and associated guidelines, such as MDCG 2022-5, have led to adjustments in the interpretation of combination products (CPs) and influence how they are qualified and approved (Medical Device Coordination Group, 2024; EUR-Lex, 2024). At the same time, the importance of CPs is growing as technologies and pharmaceuticals evolve, the range of possible combinations is expanding, offering new opportunities to address clinical problems more effectively or to solve them at all. However, the requirement to fit all conceivable combinations into a limited set of

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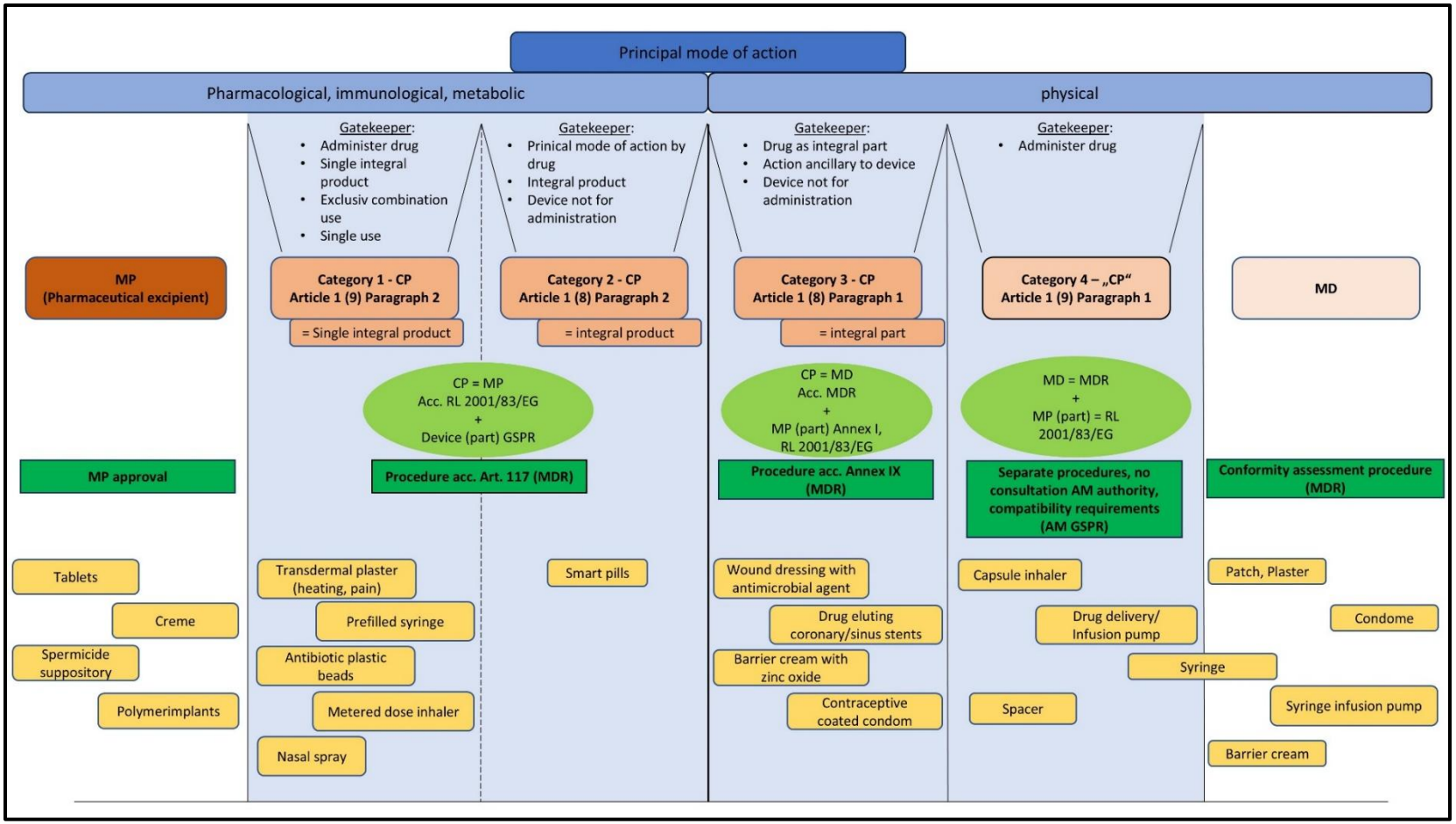

Figure 1: Overview of the legal categories of medicinal products, medical devices and combination products with product examples (CP = Combination Product, MP= Medicinal Product, MD = Medical Device)

regulatory categories can hinder innovation. In some cases, especially where regulatory precedent is lacking, promising solutions are not pursued due to uncertainty. Small businesses in particular are suffering from the growing and increasingly complex regulation (DIHK et al., 2023). Early considerations regarding approval strategies can help to reduce the time-and-costs-to-market. The study objective is to analyse the current regulatory environment for CPs, associated gaps in regulation as well as issues in gaining approval. Furthermore, a case study illustrates how an approval strategy can be developed for a hybrid drug-device combination for oncology therapy, which may later serve as a platform technology.

2. Overview Regulatory Framework

In the European Union (EU), a regulatory distinction is made between medical devices (MD) and medicinal products (MP). Both have their own legal regulations. Placing on the market of MDs is governed by the MDR (EU), instead MPs are governed by Directive 2001/83/EG and Regulation 536/2014 (EU) (EUR-Lex, 2024; EUR-Lex, 2022a; EUR-Lex, 2022b).

The main differentiation criterion is the mode of action. Products that achieve their medical purpose physically fall under the category of MDs and products with an immunological, metabolic or pharmacological mode of action fall under the regulation of MPs.

Examples of MDs are plasters, creams or condoms, which achieve their purpose by forming a mechanical barrier (physically). They are solely subject to the conformity assessment procedure (MDR).

Examples of MPs are active substances in various dosage forms, such as Active Pharmaceutical Ingredients (APIs) in tablet/capsule form, suppositories, salves or injections. Dosage forms according to the European Pharmacopoeia (Ph. Eur.) can also be implants or transdermal patches. These products are subject to MP regulation and authorisation (Medical Device Coordination Group, 2024; Europäisches Arzneibuch, 2023).

Products that combine a MP and a MD are referred to as Combinations products. Combination products are not regulated in any independent legislation. They usually must fulfil requirements from both areas but are subject to only one authorisation pathway. While pharmaceutical legislation does not make any statements about CPs, the MDR contains regulations for this in Article 1 (8) and (9). Figure 1 shows an overview of the categorisations.

According to this, a distinction can be made between four types of CPs, which are essentially determined by the factors of its purpose, its principal mode of action and if a drug is integral part of it.

Category-1-CPs are subject to the provisions of Article 1 (9) paragraph 2 (MDR). These are single integral products that are intended for the administration of MPs, are not reusable and are exclusive in this combination (Medical Device Coordination Group, 2024; EUR-Lex, 2024). The products are fully subject to Directive 2001/83/EG, whereby the MD part must fulfil the General safety and performance requirements (GSPR) according MDR. The certification is regulated in Article 117 (MDR). Example products are transdermal patches or prefilled syrings.

Category-2-CPs are subject to Article 1 (8) paragraph 2 (MDR). These are integral products, not intended for drug administration, but where the principal mode of action is pharmacology origin. An example are so-called smart pills, in which a sensor is built into the pill, which monitors the correct intake (Sideri, 2022). Category-2-CPs have the same regulatory status as Category-1-CPs.

Category-3-CPs are subject to Article 1 (8) paragraph 1 (MDR). They are MDs that contain a MP as an integral part. However, MP does not act primarily but supports the MD in its physical, principal mode of action. Category-3-CPs are not intended for the administration of drugs. These CPs are subject to the conformity assessment procedure in accordance with the MDR. Supplementary requirements apply to the MP part (e.g. Directive 2001, Annex I). The procedure according to MDR Annex IX applies, which requires the consultation and scientific evaluation by MP authority (Medical Device Coordination Group, 2024; EUR-Lex, 2024; European Commission, 2019b). Product examples are drug-eluting stents or API-coated wound-dressings.

Category-4-CP is subject to the regulation according to Article 1 (9) paragraph 1 (MDR). This category is not directly categorised as a CP, according to recital 10 of MDR or as a drug-device combination (Medical Device Coordination Group, 2024). These are devices intended to administer MPs but do not have an integral MP component. To fulfil the medical purpose, the non-exclusive combination with a MP is required. However, the components can be placed on the market separately, packaged together (Co-packaged) or referred to in the respective package leaflet (cross-labelled). Generally, these are reusable products. For placing on the market, the MDR applies to the MD and the MP regulation for separate MP. Consultation with the MP authority is not required for the MD, but the compatibility requirements of the GSPR apply to the MP (Medical Device Coordination Group, 2024; EUR-Lex, 2024). Product examples are drug-delivery pumps or capsule inhalers.

Issues involved in gaining approval for Drug-Device Combination Products

Due to the complexity of regulation and the technical possibilities there are a lot of challenges gaining the approval for drug-device combinations. First, there is an issue by identifying the relevant regulatory documents like applicable legislations, standards and guidelines for the product. This process is called regulatory landscaping.

Issue 1 – Regulatory Landscaping

Only by identifying and applying the right regulations on this base a valid qualification of the regulatory status of the product can be done. Beside the MDR and Directive 2001, there could be depending on product design, different other regulations which can influence the strategy of gaining the approval. For software-based device components, additional regulations may become relevant depending on the specific application, such as the EU Artificial Intelligence Regulation (AI Act) or data protection regulations. If products contain animal components or donor material, specific provisions such as the Animal By-Products Regulation (Regulation (EC) No 1069/2009) or rules on the use of human

tissues and cells (e.g., Directive 2004/23/EC) may also apply. These legal acts then apply in addition to the requirements of medical device law (MDR) and must therefore be considered. It is crucial to carry out the landscaping analysis early in the development process to know all these criteria or rules for correct qualification.

Issue 2 – Regulatory Qualification

The main criterion for determining the regulatory status of a combination product is the primary mode of action. There are several challenges associated with this step. First, in the early stages of development, the precise modes of action are frequently not fully understood and may only become evident once the product is finalised and tested in clinical studies. In some cases, it may not be possible to determine them definitively at all. If initial hypotheses regarding the product's mechanisms prove incorrect, a re-qualification process becomes necessary, which can entail substantial additional effort.

Second, following the identification of all potential modes of action, the subsequent step is to determine the primary (dominant) mechanism. This process can be particularly challenging in cases involving multiple mechanisms, as it demands the evaluation and weighting of each component's contribution to the overall clinical outcome. The question that arises subsequently is that of how these products should be regulated when they exhibit two equally dominant modes of action – one physical and one pharmacological – both of which serve the same medical purpose. It is evident that no mode of action can be deemed merely ancillary, and as a result there is no obvious primary mechanism, creating a significant regulatory challenge.

The third challenge pertains to combination products that serve two distinct medical purposes simultaneously, relying on both a physical and a pharmacological mode of action. Such hybrid combination products, as examined in the case study, fall outside the conventional regulatory framework, which typically assumes a single, clearly dominant medical purpose. This limitation becomes evident during the product registration process, where a unique product code aligned with a single intended purpose must be assigned.

A further challenge regarding regulatory qualification is an undefined legal intersection between components where it is not clear if they are MD-parts or pharmaceutical excipient. An example are biopolymers as formulations in the pharmaceutical sector. Biopolymers are used in many products as pharmaceutical excipients (Eu.Phr.) and in implants (like Gliadel® (Arbor Pharmaceutical) or Ozurdex® polymer pen (Allergan Pharmaceuticals Ireland)) (Ashby et al., 2016; European Medicines Agency, 2024a). The GSPR has not necessarily been proven for the polymer matrix used. On the other hand, the polymer composite, e.g. in Antibiotic plastic beads, is classified as a device-part according to category 1 by the MDCG (Medical Device Coordination Group, 2024).

Another example of the difficulty in distinguishing between device parts and excipients/drugs is cellulose. The device part of a transdermal heat patch is a cellulose fiber composite. Conformity with the GSPR must be demonstrated for this (Medical

Device Coordination Group, 2024; Beiersdorf AG, 2023). Cellulose is often chosen instead of gelatine for medicines in capsule form. This is generally recognized as a dosage form and excipient. No GSPR evidence applies to this cellulose composite, although it is a vehicle for the drug substance as well (Mašková, 2020).

In general, it is difficult to classify what exactly qualifies a component as an MD part. It is frequently argued that this is the case as soon as the component itself could be qualified as MD. In the example of transdermal patches (cellulose fiber compounds or matrix patches), these components have no clinical benefit without an active ingredient and therefore cannot be considered a MD. For example, the silicone-polyacrylate composite of a pain patch is "useless" without an active ingredient. The same applies to the cellulose fiber composite of heat plasters. Individually, they would therefore not be "certifiable".

Issue 3 – Choice of regulatory pathway

Depending on the regulatory status, various authorization pathways or combinations thereof are available. Each pathway has specific advantages and disadvantages and may impact future product modifications as well as efforts in additional approval processes.

The implementation of the procedure according to Article 117 (MDR) places manufacturers before the decision to demonstrate conformity for the MD-part either with the conformity assessment procedure or the NBOp procedure.

In this decision-making process, the evidence to be provided should be evaluated to ensure a strategically reasonable approach. Products with multiple modes of action pose a particular regulatory challenge. For instance, the primary focus of the NBOp for an applicator device is on the evaluation of correct drug delivery functionality. The review of additional functionalities originating from the applicator are not intended in NBOp procedure and additional effort is required.

The conformity assessment procedure for medical devices and the approval of medicinal products can follow different routes as well. The conformity assessment may be conducted via self-certification (Annex IV), the quality management system and technical documentation assessment (Annex IX), type examination (Annex X) combined with production quality assurance (Annex XI, Part A), or product verification (Annex XI, Part B). Similarly, medicinal product approvals can follow various regulatory pathways, including national/ decentralized and centralized procedures. Additionally, special routes such as orphan drug designation or the PRIME program are available to accelerate and simplify the procedure for special therapies.

The selection of an optimal regulatory strategy includes considerations about future indication extensions and design changes at an early stage. This is particularly relevant for CPs, where the involvement of two regulatory bodies has a major impact on the approval effort. Moreover, MD-parts intended to function as platform technologies should be designed during the initial approval phase in a manner that mitigates regulatory complexity for subsequent line extensions.

Issue 4 – Application of different standards

The choice of the approval pathway determines which manufacturer has the

primary responsibility of the authorisation procedure.

In the case of a marketing authorization application (MAA), the manufacturer of the MP is primarily responsible for demonstrating conformity with MD requirements. Conversely, for other CP pathways, the MD manufacturer is responsible for providing evidence of the ancillary efficacy and safety of the MP part.

Regardless of the regulatory approach, the legal manufacturer of the CP must be the legal manufacturer of both parts and, as such, must comply with all the relevant standards of both sectors. This is often the case with larger pharmaceutical companies. Alternatively, the legal manufacturer must consolidate and align all the requirements of the missing sector for approval. These requirements can be categorised into four key areas: quality, documentation, proof of efficacy, and safety.

In terms of quality, compliance with ISO 13485 for medical devices and Good Manufacturing Practice (GMP) guidelines for medicinal products is essential. The documentation requirements differ significantly, as medical device data must be provided in Technical Documentation format (Annex II, MDR), whereas medicinal product data must be submitted in a dossier following the Common Technical Document (CTD) format.

Preclinical safety evidence is also assessed differently. For medicinal products, non-clinical safety testing follows ICH M3(R2) guidelines, whereas for medical devices, safety is primarily demonstrated through risk management (ISO 14971), usability studies (ISO 62366), and biocompatibility testing (ISO 10993). Clinical efficacy studies also adhere to different regulatory frameworks. While medicinal products must comply with Good Clinical Practice (GCP) guidelines, medical devices are regulated under ISO 14155 for clinical investigations.

Other areas such as sterilization, packaging, and stability testing show significant overlaps between medicinal products and medical devices, yet distinct regulatory requirements apply. Despite these differences, each authorization body independently assesses its respective part of the combination product. In a combined approval process, most tests must be repeated to ensure the validity of results when both components interact.

A complex challenge arises with single integral products, where the medicinal product is incorporated into the medical device during manufacturing. As a result, the MD component cannot be tested separately for aspects such as biocompatibility, making an integrated study design necessary to simultaneously fulfill both regulatory requirements.

3. Description of the case study

Clinical problem

This case study discusses a product approach initially designed for pleural mesothelioma. However, the underlying concept may also be applicable to other tumor entities in the future.

At tumor therapy we are confronted with two main clinical problems: the inadequate wound care of internal tissue defects after tumour resection and insufficient oncology treatment. Problems after tumour resection include intra- and postoperative bleeding, scarring with surrounding tissue, air or liquid leakage development or

uncompensated tissue loss (Vayvada, 2020; Aigner et al., 2021). Intraoperative wound management is usually carried out provisionally with tamponades or collagen-containing products or haemostatic agents (e.g. TachoSil™ (Corza Medical GmbH)) (European Medicines Agency, 2024b; D'Amico et al., 2018). The products do not cover the full range of clinical requirements.

Furthermore, a fundamental problem in oncological therapy is that not all tumor cells can be completely removed (R0 resection), particularly in the case of high-risk structures. Adjuvant therapies such as systemic or local chemotherapy and radiotherapy are limited in their use to one or a few applications. The residual tumour cells proliferate. In addition, the above-mentioned therapeutic measures are all associated with severe side effects (Aigner et al., 2021; Watzka, 2019).

One approach to solve these problems is the continuous and local release of an anti-cancer drug with simultaneous wound healing-promoting effects due to an Active Pharmaceutical Ingredient (API) applicator.

Product approach

This approach is implemented in the following hybrid combination product (Figure 2). The basis is a sponge-like structure, which consists of a novel, recombinant collagen material and contains an API depot-capable layer. This depot-layer consists of a polymer-collagen combination, which can carry and later release an API.

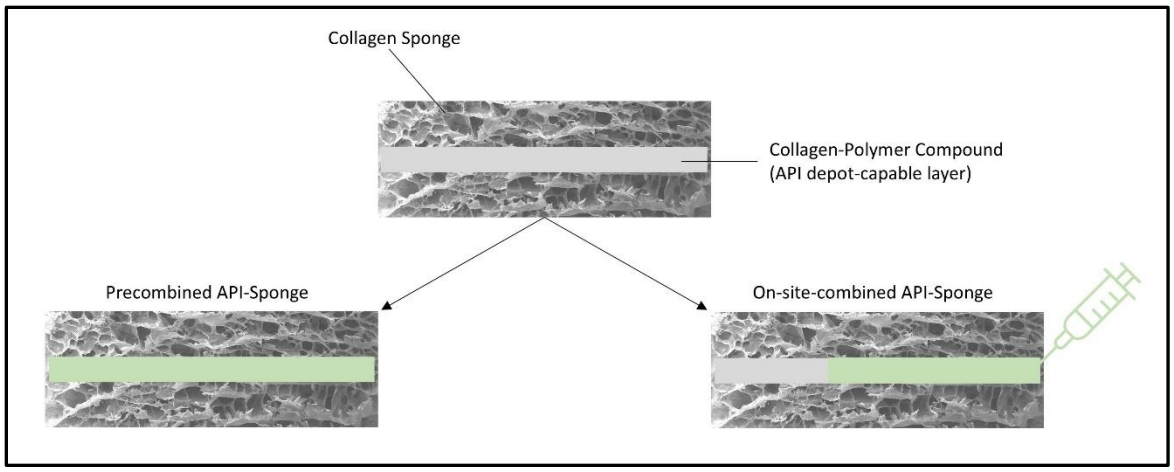

Figure 1: Schematic structure of the product and its different versions (precombined and on-site-combined patch)

The product may be used as a precombined product, meaning that the API is incorporated into the patch during the manufacturing process. Alternatively, the empty patch can be combined with the API immediately prior to application, either by directly applying the API onto the depot layer or by allowing the patch to become fully saturated with the API.

The structure enables a long-lasting, local release of the enclosed active ingredient and thus acts as an applicator. In addition, the collagen and polymer structure could also show positive effects without the drug component. The assumptions about the

mode of actions of the single components are summarized in Table 1. For the legal classification the modes of action were classified in physical effects, like building a mechanical barrier or the haemostatic effect of collagen and pharmacological effects such as caused by the API itself.

Table 1: Hypotheses on the mode of actions of the components and their classification

Mode of action	Description	Classification
Collagen-Sponge	Mechanical barrier • Mechanical barrier on a tissue defect by the collagen structure • Protection of injured tissue from external influences (mechanical stressors, microorganisms, dehydration) • Sealing of tissue defects (after resection)	Physical
	Haemostatic agent • haemostatic effect of the collagen carrier structure (natural blood coagulation) • Adhesion of platelets due to the surface properties of the collagen sponge activates platelet aggregation and a haemostatic effect sets in (Wang, 2022)	Physical
Collagen-Polymer compound	API-administration • release mechanism of the potential active ingredients from potential particle-system by hydration and subsequent diffusion (Fredenberg, 2011) • absorption and release mechanism from collagen sponge by the capillary effect	Physical
API	Pharmacological effect e.g. cytostatic effect due to cisplatin	Pharmacological

4. Issue-solving in the case study

Issue 1 – Regulatory Landscaping

Based on the available product assumptions and the determination of the European market as the target for initial approval, a regulatory landscaping was conducted.

The objective was to identify all potentially applicable regulations relevant to the development project, as these form the basis for the legal qualification and the subsequent approval strategy. Sources included EU databases such as EUR-Lex (EUR-Lex, n.d.) and EudraLex (EudraLex, n.d.), as well as documents from the EU Commission (European Commission, n.d.-a; European Commission, 2019a), the European Medicines Agency (EMA) (European Medicines Agency, n.d.-b) and International Council for Harmonisation (ICH) (International Council for Harmonisation, n.d.). Additionally, national databases from Germany (Bundesministerium der Justiz (Germany), n.d.; DIN Media GmbH, n.d.) were consulted. The identified regulations were reviewed regarding their scope, subject matter, and current validity. Consolidated versions of relevant regulations were also

considered. This process requires continuous updating throughout the course of the project. An overview of results is shown in Table 2

Table 2: Overview of the regulatory landscaping

	Type of regulatory documents	Number of identified documents
Medical device	Total number:	77
	Regulations/directives	7
	Standards	34 (14 harmonised)
	MDCG guidelines	36
Medicinal product	Total number:	194
	Pharmaceutical legislations (Vol. 1)	16
	Notices to Applicants (Vol. 2)	13
	GMP (Vol. 4)	23
	Pharmacovigilance (Vol. 9)	1
	Clinical trials (Vol. 10)	71
	ICH guidelines	70

Thus, the regulatory foundation for the project has been established. The two primary legal frameworks governing the approval procedures - the Medical Device Regulation (MDR) and Directive 2001/83/EC - remain applicable. Broader regulations such as Regulation (EC) No 1069/2009 or Directive 2004/23/EC could be excluded based on the material characteristics and design of the product. Nevertheless, numerous additional regulatory documents were identified - for example, those governing testing requirements and clinical studies - which are essential for gaining approval.

Issue 2 – Regulatory Qualification

As shown in Figure 2, a product with an identical technical design can be manufactured in various ways. It may be produced with or without the active substance, and either as a pre-combined or as an on-site combined patch. The regulatory qualification essentially depends on the product's integrality, its principal mode of action, and its intended purpose. Table 3 and Figure 3 summarize and evaluate the different variants accordingly.

The precombined oncology patch is a single-integral, ready-to-use combination of all three components. It can be subdivided into variants A, B, and C, which differ in terms of their assumed principal mode of action and intended purpose, although all mechanisms of action listed in Table 1 are present in each case.

Table 3: Qualification of the design variants

Design	No.	Integrality	Intended purpose	Principal MoA	Regulatory status
Pre-combined oncology patch	A	Yes	Administration	Pharmacological	MP
	B	Yes	Administration	Pharmacological	MP (CP-Cat 1)
	C	Yes	Administration + Dressing	Hybride	legally not intended
On-site-combined oncology patch	D	No	Administration + Dressing	Hybride	legally not intended
	E	No	Administration	Physical	MD (CP-Cat 4)
Woundpatch	F	No	Dressing	Physical	MD

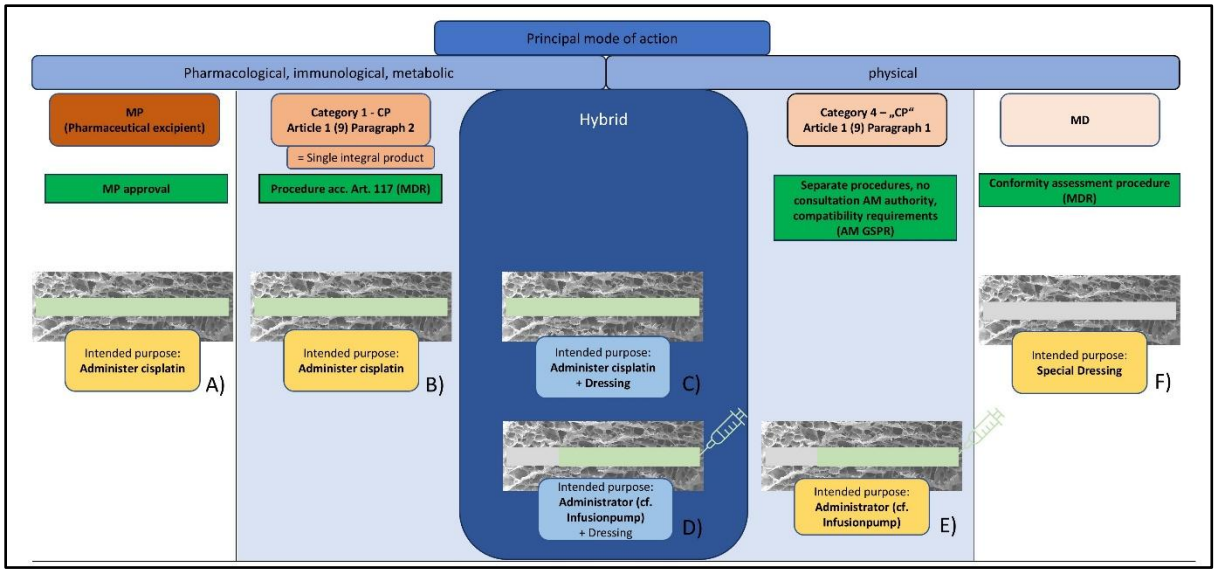

Figure 2: Overview of the classification of product variants in the applicable legal categories and in the new form of hybrid products.

In **Variant A**, the product may be qualified as a conventional medicinal product. The intended purpose is the administration of cisplatin for oncology therapy, with a pharmacological principal mode of action. Within the MAA, a new dosage form (implant) is approved for the API cisplatin, in addition to the conventional dosage forms powder/solution for systemic therapy. The patch component is legally considered an excipient and is not further examined for any independent clinical benefit. Its actual and additional modes of action (e.g. mechanical barrier) are not addressed during the MAA process. A comparable regulatory status can be found in the case of TachoSil™ (Corza Medical GmbH).

In **Variant B**, the same product may be legally classified differently. In this case, the collagen sponge is no longer considered an excipient (as in Variant A) but rather a distinct medical device component. According to MDR criteria, the combination would then be regarded as a single-integral product intended for the administration of an active substance. The medical device component fulfills an ancillary function relative to the intended purpose (administration of cisplatin for oncology therapy), qualifying the product as a Combination Product – Type 1 (CP-1). A comparable case can be seen in transdermal patches, although in those cases the carrier material (e.g., cellulose fiber compound) has no independent therapeutic purpose or mode of action (Beiersdorf AG, 2023).

However, all described modes of action are equally present and relevant in this product. From a clinical perspective, the concurrent oncological and wound-healing effects are both meaningful and necessary. Consequently, it would be logically consistent to offer a product with dual intended purposes. In such a case, the medicinal product would simultaneously fulfill the criteria for a wound dressing (EMDN: M04). This **hybrid form (Variant C)**, however, is not provided for in legislation and therefore cannot be classified in a clear regulatory status.

In contrast to the precombined patch, the on-site-combined patch does not constitute a ready-to-use, single-integral product. Instead, the patch is marketed separately as an API-depot-capable device and combined with the active substance briefly before application. In **Variant E**, the patch would be marketed as a drug delivery applicator (EMDN: A99, cf. infusion pump). The principal mode of action is the physical mechanism of drug release, qualifying the product as a CP-4.

However, as previously discussed, mechanisms supporting wound healing are simultaneously present and could also be claimed. This suggests that, in addition to the intended purpose of a drug administrator (EMDN: A99), a second intended purpose of dressing (EMDN: M04) should be recognized to fully reflect the product's therapeutic capabilities. This scenario is represented in **Variant D**, which, similar to Variant C, constitutes a hybrid form not explicitly foreseen in current regulatory frameworks.

The simplest product configuration is represented by **Variant F**, in which only the modes of action related to the dressing properties are claimed, thus determining the intended purpose (EMDN: M04). Nevertheless, the theoretical potential for drug uptake and release remains inherent to the product's design. Comparable products

include certain creams that claim only physical device-related functions (e.g. mechanical barrier), but also a potential by design for drug uptake (European Commission, 2019b).

Issue 3 – Option analysis and Choice of regulatory pathway

The qualification outlined above determines the options for approval pathways.

As previously outlined, in **Variant A**, the product would be approved as a conventional medicinal product. In this case, the active substance (cisplatin) would be authorized with a new excipient (a collagen-polymer structure), a new therapeutic indication (pleural mesothelioma), and a new dosage form (implant). The carrier system would be classified as a pharmaceutical excipient during the approval process. This pathway would represent the most time-efficient regulatory pathway, provided that the sole therapeutic objective is the oncological effect.

However, a major limitation of this approach lies in the fact that the actual physical modes of action - those essential for wound management - are not claimed and therefore omitted from the regulatory assessment. As a result, the full therapeutic potential of the product is not acknowledged within the marketing authorization framework

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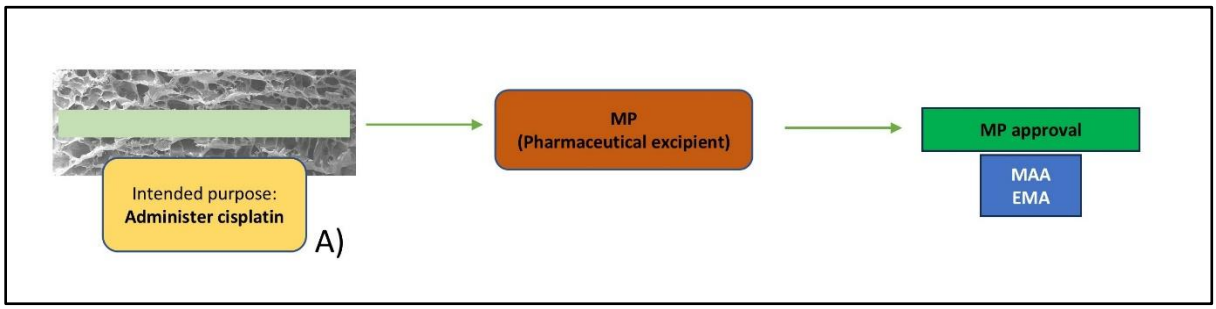

Figure 3: Approval pathway scenario 1 – Medicinal product approval. (MAA= Marketing Authorisation Application)

In **Variant B**, the product is classified as a Combination Product Type 1 (CP-1) in accordance with Article 1(9), paragraph 2 of Directive 2001/83/EC, whereby the MD part must demonstrate conformity with GSPR. In this case, the Article 117 MDR procedure must be followed as part of the MAA.

The Article 117 procedure provides two options: Firstly, the conformity of the MD part can be demonstrated via an existing CE mark of the component in the MAA for the MP. Secondly, conformity with the GSPR can be obtained from the notified body via the new NBOp as part of the MP authorization (c.f. Figure 5).

Hereby, the notified body would assess safety aspects such as whether the carrier material causes undesirable side effects (e.g., irritation), or whether any chemical interaction with the active substance might lead to the formation of toxic or carcinogenic, mutagenic, or reprotoxic (CMR) compounds. Additionally, performance characteristics would be evaluated - such as the adhesive behavior of the patch at the application site and the

reproducibility of the drug release rate. However, it is important to note that the notified body does not provide any efficacy assessment in this process.

In contrast, the alternative scenario under Article 117 involves a CE-marked device, where the safety and performance aspects mentioned above have already been evaluated during its conformity assessment procedure. Therefore, no further involvement of the notified body is required later at MAA. This approach would correspond to **Variant E**.

From a regulatory perspective, the pathway described for Variant B does not offer a significant superiority compared to the approach of Variant A. Since the physical modes of action relevant to wound management remain unclaimed and thus disregarded in both cases, Variant A might even be more appropriate due to its simplicity. Consequently, a prior CE certification of Variant E would not provide any advantage in this context.

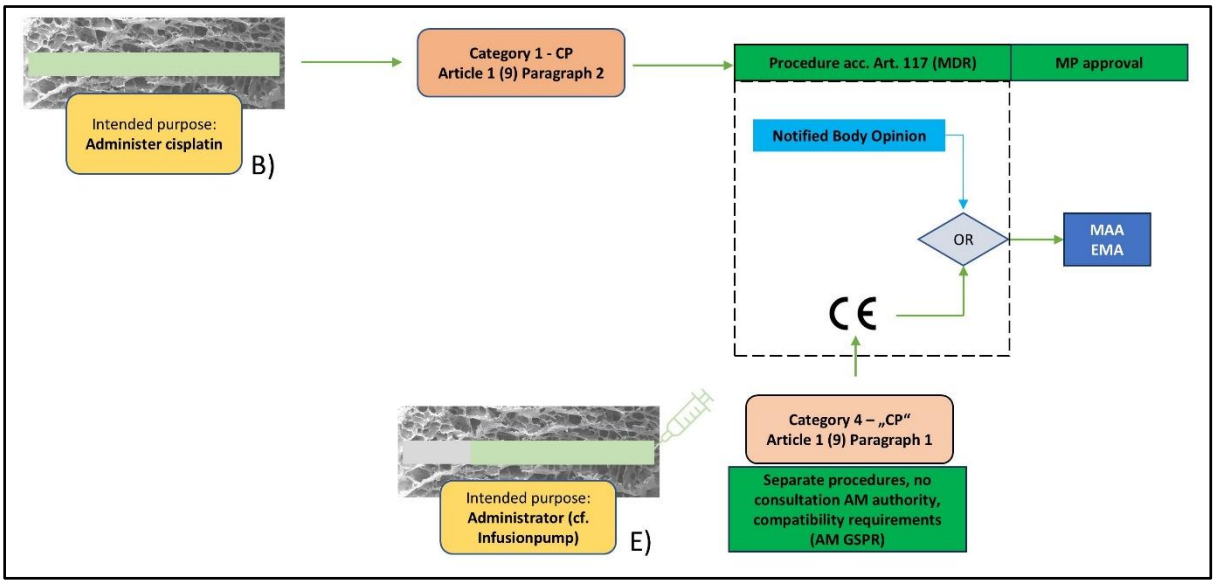

Figure 4: Approval pathway scenario 2 – Medicinal product approval and Procedure article 117 MDR with previous CE-marking of Administrator device. (MAA= Marketing Authorisation Application)

The only variant that claims all clinically necessary modes of action is **Variant C**. As previously discussed, Variant C constitutes a hybrid form for which no clear regulatory classification currently exists. Its regulatory status is most closely that of a Combination Product Type 1 (CP-1). Therefore, the Article 117 MDR procedure is again applicable (c.f. Figure 6).

In this case, however, the involvement of the notified body becomes significantly more complex. Whereas in Variant B the notified body only verifies the conformity of the ancillary functionalities with the GSPR, in Variant C the expansion of the intended purpose to include a dressing function considerably broadens the scope of the conformity assessment. The clinical benefit

associated with the dressing component is not evaluated by the EMA during the marketing authorization process. Likewise, the format of the Notified Body Opinion (NBOp) is not designed to replace a full conformity assessment for a dressing; it is only intended to show conformity for an ancillary component. Theoretically, it is conceivable that the NBOp process could be adapted, with the notified body also assessing the clinical benefit of the dressing component and transmitting the findings to the medicinal product authority. However, from a marketing perspective, this approach is strategically unfavorable: without a separate CE certification, it would not be possible to market the dressing independently without the active substance.

A potential solution would be to first complete a full conformity assessment procedure for the drug-free patch (**Variant F**), thereby obtaining CE certification, and subsequently pursue a hybrid NBOp process. This hybrid form of the NBOp would require the notified body not only to verify the ancillary performance aspects (e.g., drug release rate) but also to reassess the conformity of the dressing in the combined state, as the combination with the active substance may introduce new material interactions.

In this hybrid NBOp, the notified body would review studies conducted with the combined product and, through a gap analysis, assess whether the safety aspects (e.g., biocompatibility) and efficacy/performance aspects (e.g., mechanical barrier function) of the previously CE-certified dressing have been affected by the integration with the active substance. Importantly, the demonstration of safety and efficacy related to the oncological therapy would remain within the responsibility of the EMA.

At this point, significant efficiency gains become apparent. In particular, during the preclinical development phase, multiple tests and studies for Variants C and F could be conducted in parallel, allowing the necessary data for the subsequent hybrid NBOp procedure to be generated and reviewed more efficiently.

The superiority of this approach (scenario 3) in terms of approval strategy will be seen in the future in the expansion of oncological indications and active substances, as the CE-certified carrier structure (Variant F) takes on the role of a platform technology.

The first area of application was strategically chosen for drug approval. For the indication of malignant pleural mesothelioma, various special programs of the European pharmaceutical regulation are available. The use of such programmes requires the centralized procedure of the EU. For example, the orphan drugs regulation according to Regulation 141/2000 is intended to promote the development and approval of MPs for rare diseases, by providing financial relief. This includes support in the approval process, e.g. through the elimination of fees, and preferential treatment through market exclusivity. The regulation defines several criteria for such MPs, which are all fulfilled for the present case (EUR-Lex, 2019).

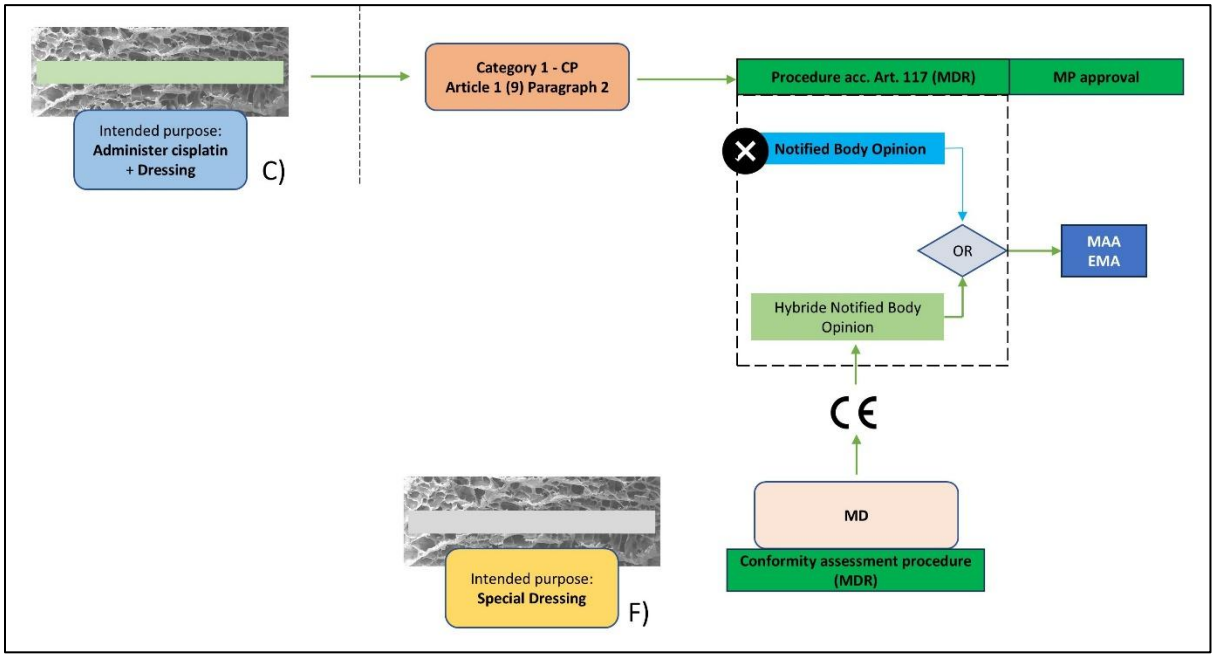

Figure 5: Approval pathway scenario 3 – Medicinal product approval and Procedure article 117 MDR with previous CE-marking of medical device for dressing purposes. (MAA= Marketing Authorisation Application)

The PRIME procedure was identified as the second potential procedure. The focus here is not on direct financial relief, but on an actual acceleration of the approval process and early advice from the EMA during development. The program is aimed specifically at SMEs and micro-enterprises. To obtain "priority medicines" status from the EMA, patients must not have a treatment option available or a major therapeutic benefit over existing forms of treatment must be expected. In addition, the potential benefit of the MP with unmet medical need must be demonstrated based on previous clinical data. Applicability in the case study is conceivable (European Medicines Agency, n.d.-a).

Issue 4 – Application of different standards

As illustrated in Figure 6 (Scenario 3), the preferred regulatory strategy is a two-stage approval process. In this approach, regulatory efforts can be significantly reduced by integrating key aspects of the hybrid combination product already during the development and conformity assessment phase of the medical device component. In order to identify gaps and opportunities, a comparison of the applicable standards in the key areas must be undertaken. Consequently, it is then possible to derive which regulatory requirements have already been combined and can be brought forward in the process. Table 4 provides an overview of the most relevant standards from both the medicinal product and medical device domains.

Table 4: Comparison of applicable standards for medical devices and medicinal products by category

Standard	Medical Device	Medicinal Product
Documentation/Dossier	Technical Documentation/GSPR (MDR)	CTD (Common Technical Document)
Quality management	ISO 13485	GMP ICH Q10
(Preclinical) Safety	ISO 10993 ISO 14971 ISO 62366	ICH M3 (R2) ICH Q9
Clinical Safety	Clinical Evaluation (MDCGs) ISO 14155	GCP
Packaging	ISO 11607	CPMP/QWP/4359/03 (plastic primary packaging materials) ISO 15378 GMP
Sterility/ Microbiology	ISO 11137 (Radiation) ISO 11737 (Microbiology) ISO 11138	Ph.Eur./GMP

This strategy is illustrated using an example from the domain of preclinical safety, specifically regarding genotoxicity testing. Before clinical application, both components of the combination product must be assessed for genotoxic potential during the preclinical phase. In the case of medical devices, genotoxicity testing is conducted as part of the biocompatibility assessment in accordance with ISO 10993-3. In the context of medicinal product development, ICH M3(R2) provides the applicable standard for genotoxicity testing. Notably, both frameworks describe a comparable battery of tests, including the Ames test and in vitro micronucleus or chromosomal aberration assays. The proposed regulatory strategy involves conducting a single, integrated genotoxicity study on the API-free patch during conformity assessment procedure that satisfies both ISO and ICH requirements. This approach combines the testing requirements from both standards into one protocol. The results are documented in an integrated study report, which serves requirements of both standards. Subsequently, additional testing and a gap analysis are required to assess whether the combination of cisplatin with the patch introduces new genotoxic substances. These data, while not mandatory for the CE marking of the patch itself can be retained together with separate genotoxicity data of cisplatin. This dataset can then be submitted directly to the EMA as part of the final assessment of the hybrid combination product. By relocating these evaluations into the medical device development phase, the need for an additional iteration involving the Notified Body Opinion (NBOp) process

may potentially be eliminated and thus streamlining the overall regulatory pathway.

5. Suggestions for improving the regulatory process

The preceding analysis has demonstrated a significant regulatory gap concerning hybrid combination products. Due to this gap in legal framework it is challenging for manufacturers to assess the regulatory landscape with confidence. As a result, product development is often adapted to regulatory constraints rather than being primarily guided by real clinical needs or technological possibilities.

Considering this, we propose several strategic measures to improve regulatory clarity and alignment. First, a formal statement from the competent regulatory authorities is needed to clarify how hybrid products - particularly those combining pharmacological and physical effects with differing intended purposes - are to be assessed. This includes defining how the efficacy assessment of physical effects (e.g., dressing functions) should be addressed within the framework of the Notified Body Opinion (NBOp) process. As discussed previously, there exists a conflict of responsibilities: the EMA has overall authority over the combination product but does not evaluate the physical benefit of the device component, while the NBOp is not designed for full benefit assessment of device functionality. This regulatory ambiguity impairs transparent product planning.

Secondly, the acceptance of data bridging strategies and integrated testing approaches needs clarification. If a manufacturer has already generated data on biocompatibility or usability within a CE-marking process, it should be specified under what conditions these data may be reused in an NBOp context, and to what supplementary data in the combined state can be reserved for submission to the EMA.

It is essential that these clarifications take the form of non-binding, recommendatory guidance rather than new legal obligations, to avoid increasing bureaucratic complexity or creating additional regulatory barriers.

In the long term, the establishment of a joint coordination mechanism between competent authorities would be highly beneficial. Such a mechanism could serve not only to clarify internal responsibility sharing, but also to provide joint advice to manufacturers, which is currently fragmented. While the EMA is authorized to provide formal guidance, notified bodies are not. Furthermore, a shared digital platform could be envisioned to manage data bridging across both regulatory domains more transparently and effectively. An extension of EUDAMED to include modules for combination product platforms could be a meaningful step.

6. Conclusion

This work outlined the current regulatory framework and main issues associated with the approval of combination products. Using a case study, a clinically relevant problem was presented that can only be effectively addressed through a hybrid combination product - one that currently lacks a clear regulatory status. For the main issues - regulatory landscaping, qualification, regulatory pathway, and applicable standards - practical approaches were proposed for the case study. Despite the difficult legal situation, a coherent line of argument was established, and a preferred

strategy identified. The project will proceed in defined stages, with early engagement of regulatory authorities and notified bodies as a central element. Additionally, suggestions to improve these circumstances in the future were made.

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8. Conflict of Interest statement

The author was employed by the Otto-von-Guericke University Magdeburg and the MD2B LifeScience GmbH (Germany) during the research project. MD2B LifeScience owns a patent application on the product combination described in this report.

9. References

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