MEDTECH & PHARMA
PLATFORM

Survey Report

"Navigating Regulatory Complexities for Integral and Non-Integral Drug-Device Combined Products"

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Introduction

In the European Union (EU), the oversight of combined products[1] is ensured by multiple legislations. The Medicinal Products Directive (Directive 2001/83/EC) and Regulation (EC No 726/2004) apply to the medicinal product component while the Medical Devices Regulation (MDR, 2017/745) and the In Vitro Diagnostics Regulation (IVDR, 2017/746) apply to the medical device or *in vitro* diagnostic (IVD) part. The regulatory pathway under which an integral drug-device combined product is marketed, and thus the primary legal framework that should be applied, is determined by the primary mode of action of the product; it is regulated under the Medicinal Products legislation where the action of the medical device is ancillary to that to the medicinal product and, vice versa, under the medical device legislation when the medicinal product is ancillary to that of the medical device. In the case of integral drug-device combined products classified as medicinal product, the product is evaluated by the EMA (or national competent authority) and necessitates the involvement of a Notified Body for the device part. For non-integral combined products, each component is expected to comply with the relevant legislation; non-integral combined products, which include co-packaged or cross-labelled products, are not physically integrated but the medicinal product and the medical device or IVD are used in a combined manner during the administration.

Given the interaction of several legislations, the regulatory process for the authorization of combined products, and for their life cycle once authorized, is characterized by challenges for manufacturers. This Medtech & Pharma Platform (MPP) Association report presents the results of a survey conducted by the MPP Association on existing challenges in the regulatory process for integral and non-integral combined products, highlighting practical steps to facilitate smooth regulatory processes, and proposing practical solutions to address hurdles currently faced by manufacturers.

Method

The methodology employed in this report aimed to gather insights into the challenges and compliance issues encountered by professionals involved in organizations dealing with combined products within the European Union. The survey specifically targeted pharmaceutical and medtech companies that are active in marketing and/or providing parts for combined products. Participating and responding organizations include the MPP Association's members as well as participants attending the association's annual conference in September 2023.

The survey questionnaire was structured into eight sections, commencing with the collection of optional participant information encompassing name, email, and company name. The subsequent sections (2-8) comprised multiple-choice questions designed to probe various facets of organization involvement, challenges faced, and compliance concerns associated with combined products within the EU market. These sections aimed to comprehensively explore the participants' experiences and perceptions in this specialized field.

The survey sample consists of 20 respondents representing 17 organizations. The largest group consists of large and medium size pharmaceutical, diagnostics or biotech companies followed by drug-delivery device manufacturers; the sample also includes an EU notified body. Feedback was also provided by

[1]The MPP Association defines a combined product as any combined use of a medicinal product, including biologics and advanced therapy medicinal products (ATMPs), with a device or diagnostic for medical purposes, without forming necessarily an integrated unit, covering also e-/m-health products. Combination products are considered a sub-group of combined products.

services providers and a trade media outlet. This sample provided a comprehensive perspective encompassing regulatory, industry, and compliance viewpoints within the research.

The primary objective of this survey was to gather valuable insights and perspectives from industry and other professionals directly involved in the landscape of combined products within the EU. The findings shed light on the challenges faced by organizations in this domain and contribute to a nuanced understanding of compliance issues. Moreover, this report identifies potential areas necessitating improvements or guidance within the regulatory framework governing combined products.

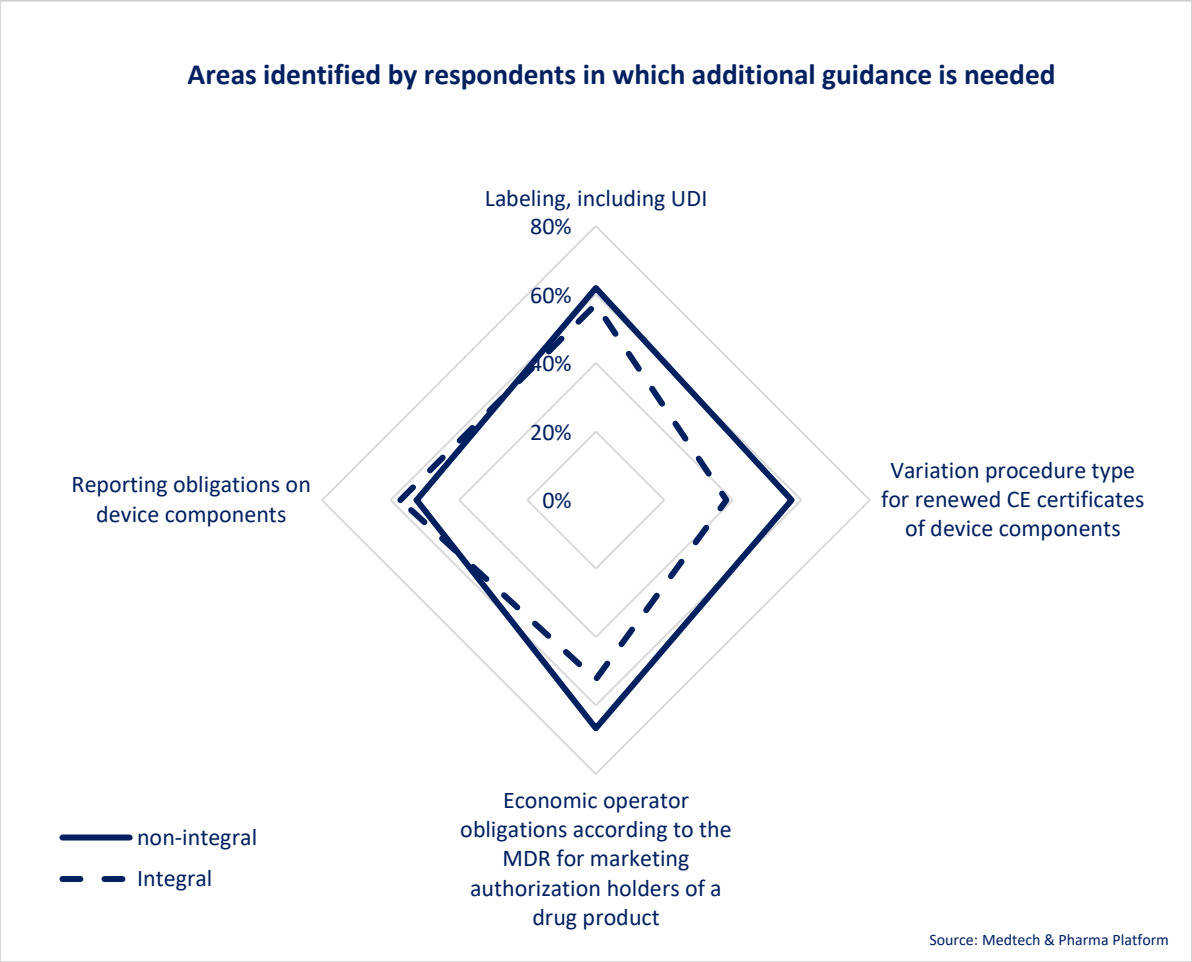
By employing this methodology, the survey seeks to offer a portrayal of the experiences and concerns of concerned stakeholders, thereby contributing to a more informed understanding of the regulatory landscape surrounding drug-device combinations in the European Union.

Survey results

This section presents the results of the survey in the different areas covered by the questions.

Clarity of EU legislation for combined products

The survey results show that 84% of respondents see non-compliance for integral drug-device combined products and 79% for non-integral combined products (co-packaged/referenced) as a risk to their business due to a lack of clarity in EU legislation on combined products.



There are several areas in which additional guidelines are needed to harmonize the wording of various EU legislations for integral and non-integral combined products. For non-integral combined products economic operator obligations in accordance with the MDR for marketing authorization holders of a medicinal product is the area where most respondents wish to receive more guidance, followed by labelling (including Unique Device Identifier (UDI)), the type of variation procedure to renew the CE certificates of device parts in case of changes to those parts, and reporting obligations on device parts. For integral combined products guidance on labelling (including UDI) and reporting obligations on device components were reported as the most salient issues followed by the type of variation procedure to renew the CE certificates of device parts.

Scientific advice

Scientific advice can facilitate the development of medicinal products by providing prospective feedback from regulators in the development of products. Following scientific advice increases the probability of obtaining marketing authorization[2]. It is therefore critical for combined products' applicants to acquire scientific advice to enhance the likelihood of regulatory approval and streamline the development process efficiently. However, the present survey highlights a quarter of respondents experienced difficulties in obtaining advice for their integral and non-integral combined products due to the absence of appropriate stakeholders in the scientific advice meeting, including Notified Bodies,

25% of survey respondents face hurdles obtaining advice for their integral and non-integral combined products due to the absence of appropriate stakeholders in the scientific advice meeting.

device manufacturers, or competent authorities. A major obstacle is the strict application of the MDR that prohibits Notified Bodies from providing "consultancy services", which have been considered thus far to cover scientific advice meetings. These respondents highlighted that this situation has adversely affected the registration timelines of their products.

Platform submissions

Many combined products rely on a similar medical device technology platform, especially in the cases such as pre-filled syringes, injection pens, autoinjectors, and inhalers. In such cases, the medicinal product varies across several combined products, but the drug-delivery device used in each product is similar. Applying a platform technology approach to the regulatory approval process of combined products, which could partially rely on utilizing existing data for the drug delivery device part, would help streamlining the submission process and avoid repetitive reviews.

45% of survey respondents encounter repetitive reviews and delays in the approval of marketing authorization applications for combined products that use previously used/existing delivery technology (i.e. platform technology).

[2] European Medicines Agency (EMA). Scientific advice and protocol assistance. Last accessed on 12 February 2024. https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance#:~:text=Scientific%20advice%20looks%20at%20how,of%20any%20advice%20previously%20given.

The survey results show the relevance of considering such an approach. 45% of respondents reported experiencing repetitive reviews and delays of marketing authorization applications when using previously used/existing delivery technology in multiple combined products. However, current regulations and guidance mandate repetitive reviews of identical platform information, yielding limited patient benefits.

Conflicting advice

The survey findings shed light on a need for greater alignment between the EMA and National Competent Authorities (NCAs) and Notified Bodies when assessing aspects like the summary of product characteristics (SmPC) and the Package Leaflet (PL) of co-packaged combined products. 55% of respondents reported having received conflicting requirements/advice from the EMA/NCA and Notified Bodies; of those 55%, 35% could find a compromise to address the conflicting feedback, while 20% reported that no compromise could be found and that they followed requirements formulated by the Notified Body.

55% of respondents received conflicting guidance from EMA/NCA and Notified Bodies. Among them, about two thirds reached compromises while one third followed Notified Body's requirements without any resolution.

Such issues originate from different expectations coming from the Notified Body and the EMA/NCAs on the medical device and medicinal product parts of a co-packaged combined products on aspects such as the information that is required to be included in the SmPC and PL. It is crucial to ensure an unified approach and eliminating discrepancies in the application of legislation.

Recommendations

The issues highlighted by this survey show the complexity and challenges faced by companies active in the field of combined products, especially for marketing authorization applicants seeking authorization for integral and non-integral combined products in the EU, and for the life cycle of authorized combined products. Based on those findings the MPP Association would recommend the following points:

- **EU legislation and guidance**: The MPP Association advocates for greater clarity and harmonization of the intersection of medicinal products and medical device and IVD legislations when applied to integral and non-integral combined products. In particular, clearer guidance in the following areas would be especially beneficial: labelling (including UDI), economic operator obligations in accordance with the MDR for marketing authorization holders of a medicinal product, reporting obligations on device parts, and the type of variation procedure to renew the CE certificates of device parts in case of changes to those parts.
- **Scientific advice for combined products**: To facilitate obtaining comprehensive scientific advice for combined products, the MPP Association would welcome a solution to involve Notified Bodies, device manufacturers, or national competent authorities, as needed, in the scientific advice process when relevant, at national or centralized level depending on the advice route chosen by the application.
- **Platform technology approach**: the MPP Association would recommend implementing a platform approach for the review of combined products utilizing same or similar drug-delivery devices. The MPP recommends incorporating measures in the medicinal products legislation

that would allow Notified Bodies to provide an opinion on medical device technology platforms which are part of drug-device combinations covered by the EU medicinal product legislation. This will prevent work duplication in the review of the information relating to the platform, as the notified body opinion on the platform would be considered when assessing specific combinations. Introducing in legislation the concept of platform technology master file would enable this objective.

- **Greater alignment between the EMA/NCAs and Notified Bodies**: Greater alignment is needed when assessing aspects like the summary of product characteristics and the package leaflet of co-packaged combined products. Issuance of common guidance, or input of Notified Bodies into pharmaceutical labelling guidance, would enable this.
- **Training and expertise**: The MPP Association would welcome creation of shared training between the EMA and the Notified Bodies with a view to foster staff expertise and experts knowledge on the specific aspects and implications of combined products, both from a medicinal product and a medical device perspective. This would contribute to the high quality and reliability of the scientific evaluation and technical documentation of combined products and foster a mutual understanding and interpretation of applicable rules and standards. The MPP Association would be glad to contribute, wherever appropriate, to such an initiative.

The MPP Association continuously seeks dialogue with relevant stakeholders to create an appropriate framework for combined products that fosters innovation, reduces time to market, and addresses patients' needs. We would be happy to discuss the proposed solutions in greater detail in order to find hands-on solution to current challenges in the area of combined products.

About MPP

The Medtech & Pharma Platform Association (MPP) brings together companies from the pharmaceutical, medtech, diagnostic and tech sectors and provides opportunities to exchange knowledge and to collaborate in technology and regulatory areas related to combined products.

The MPP's objectives are:

- To enhance synergies between the pharma, medtech, and tech industries,
- To establish new collaboration models to ensure and accelerate market access for safe and innovative treatment options,
- To work toward the development of a balanced and proportionate regulatory and policy framework for combined products including connected combined products.