Combined Medicinal Products and Medical Devices: Advantages and Quality Requirements

Paolo Rocco[1*]; Umberto M Musazzi[1]; Sara Manellari[1]; Paola Minghetti[1]

[1] Università degli Studi di Milano, Department of Pharmaceutical Sciences, Via G. Colombo 71, 20133, Milan, *paolo.rocco@unimi.it

UNIVERSITÀ DEGLI STUDI DI MILANO

DRUG DELIVERY & REGULATORY AFFAIRS UNIMI GROUP

INTRODUCTION

Both medicinal products (MPs) and medical devices (MDs) can have (or have exclusively in the case of MPs) the intended purpose of treating, curing, or preventing disease in human beings. Their EU regulatory frameworks, though, differ considerably, in philosophy and implementation [1,2,3].

Products of varying complexity which combine a medical device and a medicinal product (e.g., pre-filled syringes, nebulizers pre-charged with a specific medicine or catheters coated with heparin) are increasingly prevalent on the market. Though now subject to mature guidelines [4,5], these products represent a challenge, as each component undergoes a different regulatory pathway, with consequences on all aspects of product development.

Nevertheless, they show undoubted advantages for the patient. According to the European Medicines Agency (EMA) guideline on quality documentation for medicinal products when used with a medical device [4], these products can be classified, based on the principal mode of action, as (Figure 1):

- MPs combined with MDs, where the action of the MP is primary and not ancillary to that of the MD, which are ultimately classified as medicinal products (MP-MD combination products);
- MDs with an ancillary medicinal substance, which are ultimately classified as medical devices (not defined as combination products).

The former category comprises both integral medicinal products, where MD and MP form an integral product where the MD is not reusable, and medicinal products with a co-packaged or referenced device [3,4].

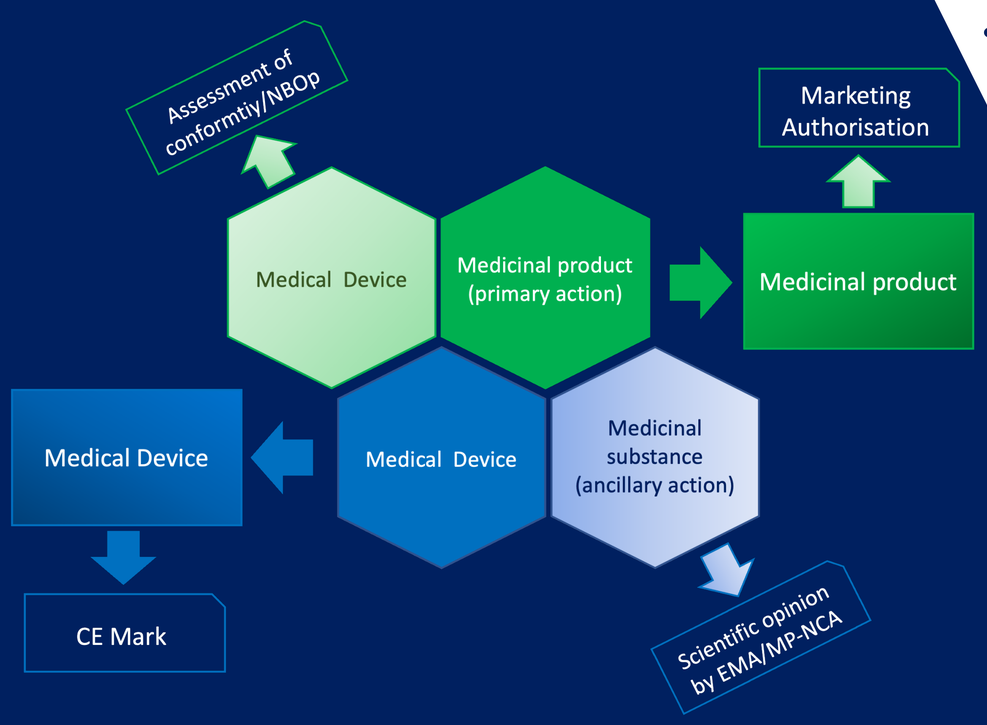

Figure 1. Classification and Regulatory pathways of MPs combined with MDs. MDR: Regulation (UE) 2012/745 MP-NCA: MP National Competent Authority. NBOp: Notified Body Opinion

Aim of the work is to review the additional quality requirements to be included in the dossier of MP-MD combination products and how their fulfilment demonstrate a direct improvement of the overall risk/benefit balance.

ADVANTAGES OF MP-MD COMBINATION PRODUCTS

The advantages of combination products, in terms of safety and efficacy, follow from the specific quality requirements that Applicants and Manufacturer must meet in addition to the requirements for the individual components.

As an example, demonstration of the ability of the MD to correctly deliver the MP in accordance with the stated posology assures correct dose and dose consistency throughout the product's life cycle, directly impacts efficacy (and safety) of the combination. In the case of integral medicinal products, such as prefilled syringes, quality is demonstrated for the finished combination and variables linked to partition and compounding are minimized.

In the case of integral medicinal products combined with a digital therapy, such as tablets containing a medicinal product with embedded sensor and relevant monitoring software adherence to treatment is improved or at least kept under control. Examples are the Digital Medicine System DM-Aripiprazole for the treatment of schizophrenia and bipolar I disorder (USA, withdrawn in 2020); or indacaterol/glycopyrronium bromide/mometasone inhalation powder (EU, authorized in 2020), where the dry-powder inhaler, may be supplemented by an electronic sensor meant to be used with a mobile/web-based application [3]. Cost effectiveness of quality assessment is also enhanced as, in all cases of combination products, only a specific medical device is intended to be used only for the administration and/or application of the integral, co-packaged or referencing medicinal product. This implies that compatibility, stability, usability are assessed only for a specific combination.

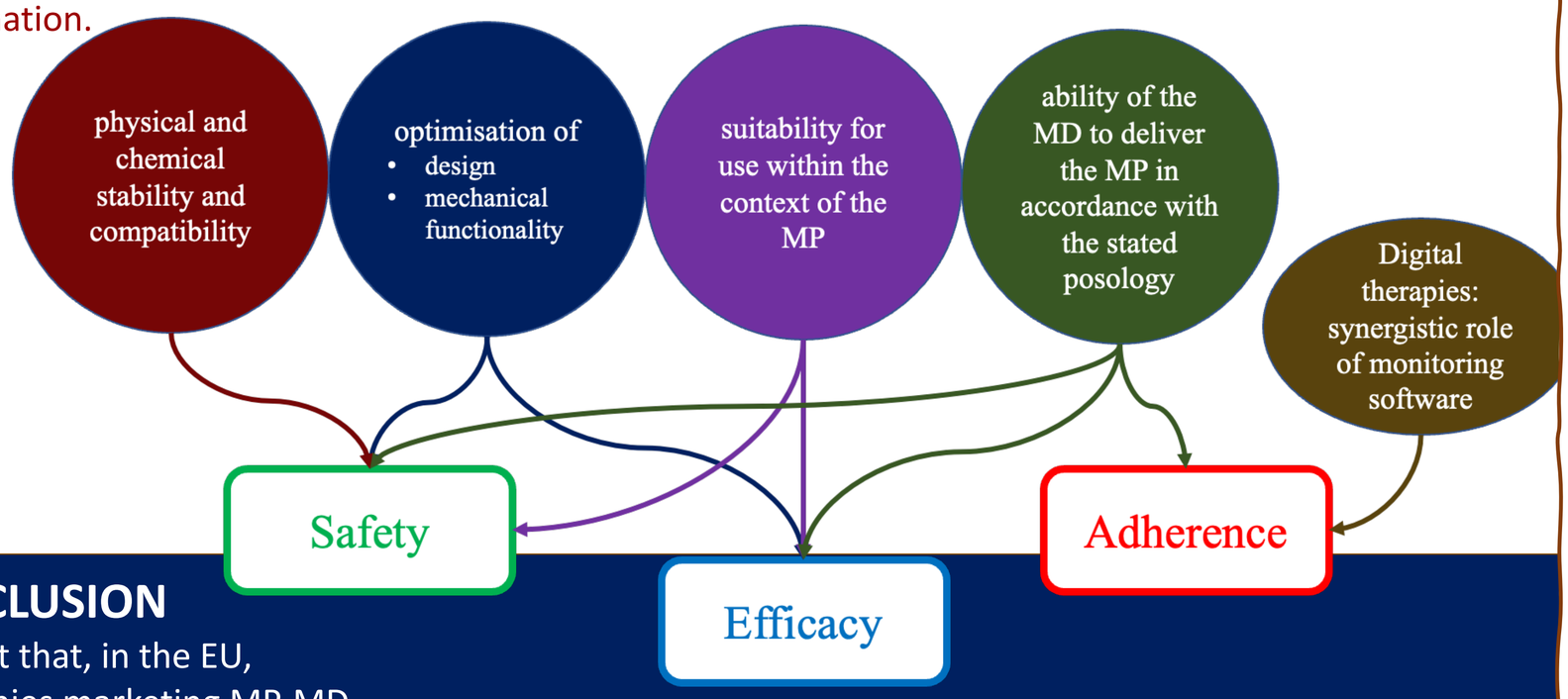

Figure 2: Impact of combination products additional quality requirements and features

QUALITY REQUIREMENTS

The dossier should include a full evaluation of the impact of the device on the product's quality profile. In particular, for integral MPs and MPs with co-packaged device: rationale for the choice of device, optimization of design and dose-delivery performance/mechanical functionality; suitability for use within the context of the MP (e.g. considering the rheological properties); the ability of the device to deliver/administer the MP in accordance with the stated posology (consistency of dosing); physical and chemical compatibility; stability; usability [3,4].

For placing on the market, the medicinal product Competent Authority is responsible in the assessment of the overall benefit-risk balance, while the manufacturer or Notified Body assesses the relevant General Safety and Performance Requirements (GSPRs) of the device [4].

CONCLUSION

The fact that, in the EU, companies marketing MP-MD combination products cannot benefit from the supervision or advice of a central authority may be an obstacle towards their development.

These obstacles should be removed as MP-MD combination products have undoubted advantages for the patient. Advances, in this sense, have been made, as demonstrated by the growing role of the European Medicines Agency into some aspects of the management of medical devices.

The quality requirements provided by the relevant guidelines for the MP-MD combination products, in addition to the requirements for the individual components, are suitable to demonstrate an improvement of the risk/benefit balance. Still, when a robust HTA assessment must be performed in support to reimbursement policy choices, more data of comparative nature may be needed to evaluate if these products really represent and advancement in healthcare.

REFERENCES

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