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Development within the European Union of medical devices incorporating ancillary medicinal substances

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ABSTRACT

In recent years, there has been a remarkable increase in the development and clinical use of Medical Devices (MDs). To date, about 500,000 different types of MDs are commercialised in the EU, with a global turnover of about 100 billion Euros. Increasingly frequently, manufacturers develop devices containing medicinal substances; i.e., a substance that used alone can be considered a Medicinal Product (MP) that help or integrate the main action of the MD (ancillary action). The correct regulatory classification of these MDs is often difficult and is a matter of discussion with the Competent Authorities (CAs). However, a correct classification is crucial for the development strategy and for the subsequent pre-clinical and clinical studies. In fact, the pre-clinical and clinical development plan, the size and number of studies, the reference guidelines and the competent authorities are different for MDs and Medicinal Products (MPs). In the present paper, we analyse and discuss the key phases of development of a MD incorporating an ancillary medicinal substance. Special attention is devoted to: i) the classification of the products according to the relevant European Guidelines; ii) the methodology for clinical evaluation; iii) the assessment procedure by the CA. Finally, we mention a possible approach to address the complexity of the procedure, through the implementation of development teams.

1. Introduction

The Medical Device (MD) sector is of paramount importance in the European Union (EU). In the EU, there are over 500,000 medical and in vitro diagnostic devices on the market; the sector employs over 500,000 people in about 25,000 companies, most of which are micro-, small- and medium-sized enterprises; there are also many independent/academic developers. The MD industry generates nearly €100 billion in annual sales in the European market. About 6–8% of annual sales of medical devices and 10% of annual sales of in vitro devices is reinvested in research every year [1,2]. The clinical research activity is also relevant; in the last five years, the Website ClinicalTrials.gov registered 1883 studies on MDs and medicinal substances. As MPs and MDs are governed by different sets of rules, it is critical that manufacturers or academic developers choose, from the very beginning, the correct development process. Some MDs include medicinal substances (i.e., a substance that, used alone, can be considered a MP) that help or integrate the action of the MD (ancillary action); such devices are of special interest because they are often developed to address major medical conditions. Independent manufacturers and developers, especially in academy, often do not have formal regulatory specialization; they find it difficult to design development plan of a MD containing an ancillary medicinal substance that comply with the complex EU regulatory framework. The aim of the present paper is to review the existing regulations in the EU, providing developers and manufacturers with an overview of the process and the key steps of the development of MDs containing an ancillary medicinal substance; detailed guidance and indication for specific cases can be provided by the regulations and their related guidelines.

2. Material and methods

We conducted a research of the scientific literature, clinical trials and regulations on MDs and MDs containing medicinal substances. MEDLINE and PubMed databases were explored for retrieval of scientific articles. We used medical subject headings (MeSH) to identify synonyms of keywords and studies relating to the relevant research. The terms of interest were combined in different ways using Boolean operators "Medical Devices" AND "Active Pharmaceutical Ingredients"; "Medicinal substances"; "Medicinal Product"; "Drug". Research on the Website ClinicalTrials.gov was performed using the advanced search strategy and the above-mentioned keywords with Boolean operators. We considered all studies except for those whose status was reported

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as "*unknown*". Additional searches were performed using the search engine Google Scholar and the above-mentioned keywords, to identify studies not found through systematic research. We considered the researches carried out from 2012 the year of publication of the latest version of ISO 14155 (Good Clinical Practice for MD) [3]. We selected fifty-two papers and reviews. For regulations and guidelines, we consulted the websites of European Commission (EC) (https://ec.europa.eu/growth/sectors/medical-devices_it) and Italian Health Ministry (http://www.salute.gov.it/portale/temi/p2_4.jsp?area=dispositivi-medici). For economic data on Medical Device industry we consulted the above-mentioned website of the EC and the reports of the Italian Health Ministry [4,5,6] and Italian Association of Medical Device Manufacturers (AMDM) *Assobiomedica* from 2012 to 2015 [7,8,9,10].

3. Results

The existing regulations set a complex framework for the development of any MD. In this paper, we will discuss three key phases in the sequence that derives from the structure of the regulation.

3.1. Regulatory classification

The first and crucial step for any manufacturer is the correct classification of the product in development with respect to the category of MPs or MDs. In the EU, a MP is defined as "[…] any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis" [11]. European Regulations define a MD as a product that "achieves its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;" [12]. In other terms, MDs act by physical means and MPs act by pharmacological, immunological and metabolic means. However, the situation becomes more complicated when we consider the possible interactions between a device and a MP. The regulations foresee three main cases: a) the device is developed to administer one or more MPs but does not form an integrated and inseparable product with the MP (e.g., void syringes that can be used to administer different MPs, devices to administer aerosols or pumps for infusions); such devices are regulated as MDs; b) the device is developed to deliver a specific MP; the device and the MP form an integrated, non-reusable product (syringes that are pre-filled with heparin or insulin, medicated plaster to administer anti-inflammatory drugs); such devices are regulated as MPs; c) the device contains a medicinal substance to help and assist the main function of the MD [13]. Devices of this latter group are the object or our study. For a device to be defined as a MD containing an ancillary medicinal substance, there are three characteristics to be met: i) the substance, if used alone, can be considered a MP; ii) the substance is liable to act on the human body; iii) the action of the substance is ancillary to the action of the device. One example is bone cement containing antibiotic for the prevention of peri-prosthetic infection following knee or hip replacement. Prosthetic infection is a medical condition with serious consequences for patients and it has a high economic cost [14]. Several studies investigated the use of antibiotic bone cement to reduce the incidence of prosthetic infections [15,16,17]. In this case, the main action of the device (bone cement) is to physically support the prosthesis; the added antibiotic is ancillary, because its (pharmacological) action helps the main (physical) action of the device. Drug-eluting stents in cardiovascular medicine represent another classical example of Medical Devices containing a medicinal substance. In this case, the main (physical) action of the stent is to keep the vessel pervious, while heparin has the ancillary (pharmacological) action to reduce the rate of re-occlusion of the stent [18,19,20]. Once the MD is positioned correctly from the regulatory point of view, the next critical step is the definition of an adequate pre-clinical and clinical development programme.

3.2. Pre-clinical and clinical studies

MDs containing ancillary medicinal substances are considered as "high-risk MDs", therefore, a complete assessment is required, including a comprehensive pre-clinical and clinical evaluation. It is noteworthy that the pre-clinical evaluation for MDs in the context of the EU follows a different path compared to the pre-clinical evaluation of MPs. The pre-clinical evaluation of MDs should follow the International Standards Organization (ISO) guidelines of the 10993 group, where much attention is paid to biocompatibility testing and detection of leachables and extractables. The preclinical evaluation of these aspects is really of pivotal importance. It is noteworthy that pre-clinical studies conducted according to ISO 10993 series cannot be used for the approval of a MP, and that studies conducted according to ICH guidelines that are needed for MPs cannot be used for the approval of a MD. It is therefore of paramount importance that the assessment discussed in the previous section of this article is well defined and complete. In other terms, the manufacturer should decide from the very beginning if the product to be developed is going to be a MP or a MD. This decision has consequences in terms of budget and time for the development. The situation is similar for what concerns the Clinical Evaluation. Clinical Evaluation of MDs is a structured process, specifically designed for MDs that includes the evaluation of available scientific literature, evaluation of data obtained from clinical investigations on the product, and a critical review of both sources. In June 2016, the European Commission issued the fourth revision of the guideline MEDDEV 2.7/1. The description of the guideline is beyond the aim of this paper, here we underline some of the changes implemented by the MEDDEV guideline: higher scientific qualifications of the assessors, documented by an adequate curriculum vitae, punctual correspondence of the characteristics of the MD with essential requisites set by the MD Directives; stricter criteria to define the equivalence with existing MDs, standard protocols for bibliographic research, formal process of weighing the scientific evidence of clinical data. A specific appendix has been issued for coronary stent [21,22]. Clinical investigations on MDs must comply with the Declaration of Helsinki (DoH), and in this they are regulated in the same manner as studies on MPs. As for other guidance, studies on MPs are to be conducted according to the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH), [23] while studies on MDs (clinical investigations) are to be conducted according to the ISO guidelines, namely, ISO 14155:2012 [3]. The detailed discussion of the differences between studies on medicinal products and studies on medical devices is beyond the aim of this article. Therefore, here we underline that clinical investigations on MDs should focus on the assessment of the performance of the MD that must be expected from the project of the device, and on safety of use [24,25]. At the same time, in planning clinical investigations on MDs it is to be taken into account that there are specific points that must be included in the clinical investigation plan (i.e., protocol), such as the assessment of possible deficiencies of the MDs; i.e., any non-conformity of the device, from its performance to its instruction sheet and packaging. The requirements for surveillance of MDs under investigations are different from those for MPs; for instance, a deficiency that could have caused a serious adverse event (SAE) is to be reported as a SAE [26]. It is, therefore, important that studies on MDs are designed and conducted by personnel with specific experience in the field.

3.3. Assessment procedure

The assessment procedure of a MD containing an ancillary medicinal substance (Fig. 1) is rather complex, hence we will discuss the main steps to be considered in the planning of the process. In the world of MDs, the interface of the Manufacturer (or academic developer) is the Notified Body (NB). NBs are public or private organizations that are

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