Marletta M (2020) 01s: 13-15
https://doi.org/10.36118/pharmadvances.01.2020.03s

COMMENTARY Open Access

The new regulation 2017/745: an opportunity for innovation

M. Marletta

Medical Device and Pharmaceutical Service, Ministry of Health, Rome, Italy

As the Regulatory authority of Italy, the Member State which probably has been the most involved in the discussion regarding medical devices made of substances within Regulation 2017/745, I must highlight the importance that this regulation has for the development of new, innovative, highly needed, low risk therapeutic products that comply with the definition of medical devices. In fact, Regulation 2017/745 delineates the formerly called "borderline products" as "medical devices made of substances". These are products which comply with the definition of medical devices and that can well be developed within the medical device regulatory framework, which have brought great health innovation and Member State turnover in many Member States, in the last twenty years of Directive 93/42/EEC.

The Italian competent authority was involved with devotion during its presidency in writing the famous "white book" which has the task of incorporating all the switches from Directive 93/42 into the Regulation. Furthermore, it was involved from the very first proposed version of the Regulation, in September 2012, in the analysis of these "borderline products", to clarify all aspects which would allow their correct scientific and regulatory evaluation in order to allow them to gain access to the market as high quality, safe and efficacious products for the European population. As a regulatory authority participating in the development of the Regulation, we had to evaluate all aspects of these "products" made of substances. They present themselves as syrups, tablets, powders, fluids: it is well evident that macroscopically they resemble products which we are all used to consider "drugs".

For this reason, the tendency has always been to push them into the medicinal product Directive. This was, and still is, the standpoint of several Member States, which believe that the most logical path for natural complex substances is the Traditional Herbal Medicinal Products. This category of products completely waivers all the safety and efficacy requirements of Directive 2001/83 due to their claimed and documented long standing use in Europe and in the world. Logically, this approach has caused the complete stop of all research and innovation in this field. This is because on a microscopic level, complex substances, natural and synthetic, are not compliant with the definition of drugs and they cannot be developed according to the drug regulatory framework.

I have worked decades in both the medicinal product and the medical device departments and I can assuredly say that any product which is not developed according to the model of a single molecule (ie: new chemical entity, isolated chemical class from complex natural substances, biological drugs) cannot comply with the

requirements of the marketing authorization of Directive 2001/83. This is because the very framework of Directive 2001/83 requires the description of the behaviour of the specific active principle, having the pharmacological mechanism of action.
However, the difference between a medicinal product and a medical device made of substances is not intuitive, so discussion among all parties is crucial.
Terms such as "pharmacological mode of action" need to be correctly defined and interpreted, considering both the scientific and the regulatory aspects. In this sense, the interpretation of "pharmacological means" seems to be "a mode of action which can be described according to the Directive 2001/83 model".

In practice, Regulation 2017/745 allows products which cannot be described according to the model delineated by Directive 2001/83 (based on single pharmacologically acting molecules) to be developed with a robust development plan, thus allowing authorities to be confident of the certified products. This is because Regulation looks to many elements of Directive 2001/83 so as to ensure the quality, safety and efficacy aspects consolidated by pharma, but within the medical device risk-based framework.
This combination is the adequate approach for products as diverse and complex as medical devices made of substances wanted by many Member States and by the European Parliament within the Medical Regulation 2017/745, specifically classified with Rule 21 and controlled with General Requirement 12.2.
In particular, the first indent of Rule 21 was expressly included for complex substances, whether natural or synthetic. The European Parliament and several Member States were well conscious that these products, not possibly regulated as drugs, would be either lost to the market or marketed outside the health chain: ie outside the premarket assessment and post market follow up, and the adequate communication of the benefits would be lost. Right now, there is the occasion (and the need) to clarify the interpretation of some other crucial terms for the implementation of Regulation 2017/745, such as all aspects linked to classification Rule 21.
Rule 21 first indent refers to medical devices which need to be absorbed in order to achieve their intended purpose. The concept of absorption linked to efficacy needs to be discussed in case of complex substances, as well as the concept of absorption for safety purposes mentioned in Rule 21 second indent. Another delicate issue is the implementation of General Requirement 12.2, which makes reference to Directive 2001/83 for toxicological and ADME aspects not covered by the Regulation. It is quite logical that medical devices made of substances and complex substances have substantially different chemical characterizations, therefore the risk-based-case-by-case approach characteristic of the medical device framework should allow adequate discussion of each situation, also with Competent Authorities and/or Notified Bodies during product development.
As a Competent Authority of a Member State who is leader in the Medical Device field and specialized in medical devices made of substances, knowing also the intent of the European Parliament to promote innovation in health and health technology, my comment is that all reference to Directive 2001/83 should be seen as a check list to guarantee quality, safety and efficacy, but the practical approach must lie within the medical device risk-based approach.

During trilogue, we wisely created a box for medical devices made of substances. Now, as a Member State, I say that we need to wisely allow innovative products to fill this box. Regulation 2017/745 assures quality, safety and efficacy, we must not fear the regulatory innovation which is available today for the certification of medical devices made of substances, including complex substances, which have no other adequate regulatory framework available for them.
Rule 21 first indent allows to gain back the lost cranberry which concretely cannot be a medicinal product but which, under Regulation 2017/745, gives to the Competent Authority, the guarantee of a thorough development, including clinical evidence, and can be available for the European patient who would otherwise recur to repeated antibiotic treatment.

This is a concrete opportunity for an entire family of products based on complex natural and synthetic substances, which could help manage the new emergent illnesses of our time, such as syndromes, dysfunctional ailments and complex pathologies in general. We are at

a crucial point in the history of therapeutic products could be considered medicinal products, but do not actually fit the medicinal product model. We need to decide to let them have their path to market access within the medical device framework or to lose them as it has been done with cranberry and other subtances already. It must be clear that there the rigorous yet flexible medical device framework based on risk and on a case-by-case evaluation is the only regulatory framework concretely allowing their development.