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Short communication

Comparative analysis of the regulatory framework for post-marketing authorization changes in EU and USA

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Introduction

After obtaining marketing authorization (MA) for each medicine, the marketing authorisation holder is responsible to keep the submitted documentation for the medicine up to date with the technical and scientific progress, to change or improve the medicine or to introduce additional measures for improvement of the safety of medicine. These changes, referred as variations are essential in the lifecycle management of a medicinal product. The word "variation" is regulatory accepted in the European Union legislation, while terminology "post approval submissions" is used in the legislation of United States of America. In order to ensure the quality, efficiency and safety of medicines that reach patients, without compromising their health, the approval of these changes is subject to strict control by regulatory authorities and is conducted using specific procedures defined in the regulatory framework. The classification of these changes generally is based on the significance of the change and therefore the potential impact on quality, safety and efficacy of the medicinal product.

The aim of this study was to analyse the regulatory framework in European Union (EU) and in The United States of America (USA) covering variations /post-approval changes, classification of these changes and the procedures conducted by the competent authorities: European medicines Agency (EMA) and Food and Drug Administration (FDA).

Regulation of post-authorisation changes in EU

In accordance with Commission Regulation 1234/2008 and as amended by Regulation (EC) No. 712/2012, variations to Marketing Authorizations are classified as Type IA, Type IB, Type II and extension applications. Type IA variations, also known as "Do and tell "variations are minor variations which have minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product. Type IA_{IN} variations are minor variations that require immediate notification to the competent authority on implementation. Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder, but the holder must submit the variation simultaneously to all Member States concerned, to the national competent authority, or to the EMA, within 12 months from the date of the implementation. Type IB variations are minor variations which are not a Type IA variation nor a Type II variation nor an extension. These minor variations must be notified before implementation and they follow a 30 day assessment timetable: before implementing the change, the holder must wait 30 days to ensure that the notification is considered acceptable by the relevant authorities ('Tell, Wait and Do' procedure). Type II variations are major variations which may have a significant impact on the quality, safety or efficacy of the medicinal product. For these type of major variations a 60-day evaluation period applies. Urgent safety restriction are defined as an interim change to the product information due to new information having a bearing on the safe use of the medicinal product, concerning in particular one or more of the following items in the summary of product characteristics: therapeutic indications, posology, contra-indications, warnings, target species and withdrawal periods. Details of the classification of variations are provided in the Guidelines for variations 2013/C 223/01, where each change is

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numbered and subcategories depicted by letters and numbers. Where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the 'highest' variation type included in the group. Conditions necessary for a given change are outlined for each subcategory and listed below each change. Documentation to be submitted is identified including all parts of the dossier that are affected by the variation. National competent authority or the EMA are responsible to address any questions which holders may have regarding a particular upcoming variation. (Council of Europe, 2008; Council of Europe, 2012; European commission, 2013).

Regulation of post-approval changes in USA

Procedures and categorization of supplements and other changes to an approved medicine in the USA are defined in the section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and section 314.70 of the CFR - Code of Federal Regulations Title 21. Four reporting categories of post-approval changes are distinguished: major changes, moderate changes, supplement - changes being effected and minor change. The list of all changes contained in the supplement or annual report must be given in the supplement or annual report and each change should be described in details.

Major change refers to a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. This type of change is called *Prior Approval Supplement* and should be clearly labelled as such, and requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change.

Moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. There are two types of moderate changes. The first type is *Supplement - Changes Being Effected in 30 Days*, requiring submission of a supplement to FDA at least 30 days before the distribution of the medicinal product, produced after implementation of the change. The second type of moderate change is a *Supplement - Changes Being Effected* for which distribution of the medicinal product after implementation of the change can occur when FDA receives the supplement.

Minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. These changes are described by the applicant in the Annual Report.

Additionally, the applicant must notify FDA about each change in an approved application apart from the variations already provided in the application, except for editorial changes in previously submitted information (FDA, 2004).

Conclusion

Although the common share between the regulatory processes in the United States and Europe are their goals and also have many similarities, it doesn't exclude the fact that they have different categorizations of changes and general requirements.

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