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Pharmacovigilance Legal Requirements for Marketing Authorization Holders in Spain

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Background

This review is based on the Royal Decree 577/2013 from 26 July 2013, which regulates the Pharmacovigilance of Medicinal Products for human use in Spain.

Review

Up to 26 July 2013, the Royal Decree 1344/2007 of 11 October, on the pharmacovigilance of medicinal products for human use, was regulating pharmacovigilance in Spain, building on the National Law 29/2006 of 26 July, on guarantees and rational use of medicines and health products.

This Royal Decree, based on European Directives recently modified, has been derogated. So as of today, the new Royal Decree 577/2013 from 26 July 2013 is regulating pharmacovigilance in Spain.

In this royal decree the responsibilities of the Spanish Agency for Medicines and Health Products, regional centers, health professionals and citizens and the obligations of the Marketing Authorization Holders (MAHs) are determined. All of them are designed to provide continuously the best information about drug safety, allowing the adoption of appropriate measures and ensure that the drugs available on the market present a favorable benefit-risk ratio for the population in the approved conditions of use. The responsibilities of the MAHs are covered in articles 8 through 14. In this review we are going to focus on these responsibilities.

The new features included in the Royal Decree are highly relevant. Among them, we can highlight the new definition of adverse reaction, so it becomes: "Any noxious and unintended response to a drug", such also includes adverse reactions arising from any use outside the terms of the authorization of the commercialization, abuse and medication errors.

There is an increased focus on transparency and communication on drug safety, serving the right of information to patients and health professionals, and increasing its participation in the healthcare system, including the possibility of reporting suspected adverse drug reactions by patients. In fact, the Spanish Agency has created a web portal (www.notificaRAM.es) in order to facilitate patients the reporting of adverse reaction to drugs directly.

At the European level, it is also important to highlight the creation of the European Pharmacovigilance Risk Assessment Committee (PRAC), which aims to streamline and harmonize decision making after the evaluation of risks associated with drugs and implement equitable, comprehensive and simultaneous decisions in all Member States. The publication of all the recommendations of the PRAC, and a summary of the risk management plans to be performed by MAHs is collected. The option to hold public hearings in the process of assessing security issues of special relevance is also contemplated.

Pharmacovigilance activities in the countries of the European Union will be reviewed by the European Commission on a biennial basis in order to ensure that all responsibilities are met. This review includes both the functions in this area of the Spanish Agency for Medicines and Health Products and regional centers. Moreover, the Spanish Agency for Medicines and Health Products shall meet the minimum quality requirements set out in the implementing measures of the European Commission.

Finally, it should be noted that the Directive 2010/84/CE of the European Parliament and of the Council of 15 December 2010, incorporates Article 105, which imposes permanent control of the authorities on the management of funds intended for the conduct of pharmacovigilance, the use of communication networks and market surveillance operations as a fundamental guarantee to preserve their independence. While this is already in place in Spain, should also be applied to the field of pharmacoepidemiology, so that, with the necessary independence, studies of particular interest to protect public health are performed from the public sector.

Besides, administrative consequences are indicated in case of the conditions for the marketing authorization of medicinal products for human use are affected for safety or security reasons, incorporating a new urgent procedure for the evaluation of security problems in Europe. Finally, post-authorization studies with drugs are regulated.

Moreover, it will be necessary to adapt the content of some of the committees assigned to the Spanish Agency for Medicines and Health Products, namely, the Committee on Safety of Medicines for Human Use and the Committee for the Coordination of post-authorization studies.

Regarding the responsibilities for MAHs covered in articles 8 through 14: Art. 8 cope with the pharmacovigilance system. The MAH should have a Pharmacovigilance Master File, which can be requested by the Spanish Agency at any time and should be provided within 7 days' notice. The Pharmacovigilance Master File should also be present at any inspection. Besides, the MAH should make regular pharmacovigilance audits, should have an European Responsible Person for Pharmacovigilance (as well as a local Contact Person for Pharmacovigilance in Spain, regulated in Art.14), should make scientific evaluations of their data and should follow the Good Pharmacovigilance Practices published by the Spanish Agency at their homepage.

The MAHs should collect adverse reactions from health care professional, patients and post-authorisation studies happening in Spain, any country of the EU or a third country. The reporting point

for these cases will be EudraVigilance, there will be a deadline of 15 days for serious and 90 for non-serious cases and the information will be transmitted electronically according to the E2B standard. For the Spanish cases, the MAH should include the necessary information in order to identify the region or province in order to facilitate the evaluation by the regional pharmacovigilance centers, all information on these cases should be provided in Spanish together with a summary in English (Art.9).

Existing administrative procedures are simplified and the online submission of periodic safety update reports (PSURs) prepared by the Marketing Authorization Holder is made possible; these reports will have the same format and will be accessible to all agencies responsible for drug regulation in the Member States, who will carry out the evaluation according to new procedures in order improve system efficiency; thus the cooperation of the authorities of the Member States in assessing the risks of drugs and decision narrows and the coordinating role of the European Medicines Agency is clarified. The frequency and the dates of submission of these PSURs will be made public at the Spanish Agency and the EMA websites (Art.10).

The obligation of the MAHs to identify potential safety issues proactively is enhanced. The risk management plan will become part of the marketing authorization (with a summary in Spanish if submitted to the Spanish Agency) (Art.11), and the MAHs have the obligation to collect and communicate to the Spanish Agency all data generated and that may affect the risk-benefit balance of their medicines. In this respect, this Royal Decree establishes the possibility of imposing the MAHs the obligations to carry out post-authorization studies on the safety or efficacy of medicines in routine medical practice as a condition of the marketing authorization, making possible for the health authorities to suspend the marketing authorization if there is any breach of these obligations. These obligations will be reflected in the risk management plan.

In line with the continuous revision of the risk-benefit ratio of drugs, surveillance of new drugs and drugs with a potential security issue that involves the need for studies or specific measures to minimize the identified risk is also enhanced. These drugs have an additional follow distinctive for both the healthcare professional and the citizen, in order to prioritize the reporting of suspected adverse reactions; a list of these drugs under additional monitoring will be made public. (Art.12).

Art. 13 deals with the information disclosed by the MAHs for security reasons. This information shall be provided to the Spanish Agency before distribution to the public in order to ensure that the information is presented objectively and not misleading. The MAH should agree with the Spanish Agency the text, any supporting material, the communication strategy, the distribution procedure, the timing and type of health professional that must be addressed and the number of health professionals who have made the communication. The text should incorporate a distinctive indicating the nature of the information it contains. This shall also apply to the material aimed at minimizing risks included in risk management plans need to be made known to health professionals and, through these, to patients.

In Spain we should highlight the figure of the Local Contact Person for Pharmacovigilance, regulated by Art.14. The MAH must have permanently and continuously a contact person for pharmacovigilance in Spain, and provide the Spanish Agency the contact details of this person who will be available to the competent bodies of the Autonomous Communities. This person will collect the information about adverse reactions happening in Spain and cooperate with regional pharmacovigilance centers to provide all available information, transmit any request from the Spanish Agency to the MAH related to benefits and risks of a drug and to answer any information requested about the volume of sales, act as point of contact for safety reasons, as well as for actions taken in Spain concerning the provisions of the risk management plan, ensure the proper functioning of local pharmacovigilance activities and act as contact person for pharmacovigilance inspections in Spain.

Author's Biography

José Alberto Ayala Ortiz (M.Sc. Pharm. and M.Sc. IT) is an expert in the field of Pharmacovigilance and Drug Safety. He has experience both from the Regulatory (Danish Medicines Agency), and from the Pharmaceutical Industry, where he has been responsible for Pharmacovigilance IT systems, databases and Electronic transmissions. Besides his day-to-day Pharmacovigilance work as a consultant, he is an active trainer of the EVWeb and XEVMPD training courses since 2003, and collaborates together with the training team, the EMA and the DIA in the development of these training courses. He provides also EU QPPV services and local QPPV services in Spain for Pharmaceutical Companies.