Royal Decree 577/2013 of July 26, regulating the Pharmacovigilance of Medicinal Products for Human Use

Law 29/2006 of July 26 on the Guarantees and Rational Use of Medicines and Medical Devices sets out, under Title II, Chapter VI, the guarantees as regards the monitoring of the benefit-risk balance of medicinal products, and therefore regulates the Spanish Pharmacovigilance System and the pharmacovigilance of medicinal products for human use.

Law 29/2006 was implemented by Royal Decree 1344/2007 of October 11 governing the Pharmacovigilance of Medicinal Products for Human Use, which specifically regulates: (1) the agents involved in the Spanish Pharmacovigilance System for Medicinal Products for Human Use, as well as the obligations of the individual agents involved in this activity, whose goal is to continuously provide the best possible information on the safety of medicinal products to enable the adoption of appropriate measures, thus ensuring that the medicinal products available on the market have a favorable benefit-risk balance for the population under the approved conditions of use; (2) the administrative consequences that may affect the terms of the marketing authorizations for medicinal products for human use for safety reasons; and (3) post-authorization studies in order to ensure continuous evaluation of the benefit-risk balance of authorized medicinal products.


However, in the light of experience gained, it became evident, following assessment of the pharmacovigilance system of the European Union by the European Commission that measures were needed to improve the functioning of European Union laws on pharmacovigilance of medicinal products, and that amendment of Directive 2001/83/EC was appropriate. This was effected by Directive 2010/84/EU of the European Parliament and of the Council of December 15, 2010 and Directive 2012/26/EU of the European Parliament and of the Council of October 25, 2012, which amend, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.


Consequently, this Royal Decree updates and adapts to technical progress the hitherto existing legislation on this matter, contained in Royal Decree 1344/2007 of October 11 governing the pharmacovigilance of medicinal products for human use, which is hereby repealed, and incorporates into national law the developments brought about by Directive 2010/84/EU of the European Parliament and of the Council of December 15, 2010 and Directive 2012/26/UE of the European Parliament and of the Council of October 25, 2012. These developments are numerous and of great significance.

The developments introduced by the new European legislation, which have been incorporated into this Royal Decree, include notably: the expansion of the definition of the term “adverse reaction” that covers any noxious and unintended response to a medicinal product, including adverse reactions resulting from any use outside the terms of the marketing authorization, abuse, and medication errors; the establishment of clear criteria concerning the obligations and functions of the responsible parties involved; the strengthening of the obligations of marketing authorization holders aimed at proactively identifying potential safety concerns, which shall be reflected in a risk management plan that shall become part of the marketing authorization, and at collecting any new data that may affect the benefit-risk balance of the medicinal products, which should be communicated to the Spanish Agency of Medicines and Medical Devices.

In addition, new measures to improve transparency and communication on the safety of medicinal products have been incorporated. Among them, the right of patients and healthcare professionals to information, increasing their participation and confidence in the healthcare system. In that regard, the participation of citizens in the reporting of suspected adverse reactions to medicinal products has been enabled.

The surveillance of new medicinal products and of those in which an identified potential safety issue requires the conduct of studies or the adoption of specific measures to minimize the risk is encouraged. These medicinal products subject to additional monitoring shall be identified by a symbol in the summary of product characteristics and package leaflet, so that both healthcare professionals and citizens may prioritize the reporting of suspected adverse reactions. The list of medicinal products subject to additional monitoring shall be made publicly available. The need to assess the impact of measures adopted to minimize the risks of medicinal products is introduced for the first time into legislation.

It is also important to highlight, due to its importance in the decision-making process about the risks of medicinal products, the establishment of a new European committee —the Pharmacovigilance Risk Assessment Committee— intended to streamline and harmonize decision-making after assessing the risks associated with medicinal products, so that decisions are
implemented equitably, comprehensively, and simultaneously in all Member States. Current administrative procedures are simplified and the periodic safety update reports prepared by marketing authorization holders may be submitted electronically. These reports shall be available to all medicines regulatory agencies in the Member States, which shall conduct their assessment in accordance with new procedures aimed at improving the efficiency of the system. This will result in a closer cooperation between the authorities of the Member States in assessing the risks of medicinal products and making decisions, as well as in the clarification of the coordinating role of the European Medicines Agency.

The pharmacovigilance activities of the Member States shall be reviewed by the European Commission on a biennial basis to ensure compliance with the established functions. This review shall include the functions in this field of both the Spanish Agency of Medicines and Medical Devices and the Autonomous Communities. In addition, the Spanish Agency of Medicines and Medical Devices shall fulfill the minimum quality requirements laid down in the implementing measures of the European Commission —Commission Implementing Regulation (EU) No. 520/2012 of June 19, 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No. 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council—.

Guidelines on good pharmacovigilance practices have been developed by the European Medicines Agency in coordination with the Member States. This guideline, as well as its subsequent updates, shall apply to the performance of pharmacovigilance of medicinal products for human use. Directive 2010/84/EU, transposed by this Royal Decree, also provides in Article 108 a series of implementing measures that were developed by the European Commission in the relevant regulation.

Finally, it should be noted that Article 105 of the Directive 2010/84/EU of the European Parliament and of the Council of December 15, 2010 imposes the permanent control of the authorities on the management of funds intended for activities related to pharmacovigilance, the operation of communication networks and market surveillance, as a fundamental guarantee to preserve their independence. Although this is already in operation in Spain, it shall also be applied to the field of pharmacoepidemiology so that studies that are of particular interest for the protection of public health may be conducted within the public sector with the necessary independence.

On this basis, this Royal Decree establishes the responsibilities of the Spanish Agency of Medicines and Medical Devices, the Autonomous Communities, healthcare professionals and citizens, and the obligations of marketing authorization holders. These responsibilities and obligations are aimed at continuously providing the best possible information on the safety of medicinal products to enable the adoption of appropriate measures, ensuring that the medicinal products available on the market have a favorable benefit-risk balance for the population, under the authorized conditions of use.

Publication of all recommendations made by the European Pharmacovigilance Risk Assessment Committee has been provided for, as well as a summary of the risk management plan.
that marketing authorization holders are required to prepare. The option to hold public hearings
during the process of assessing safety concerns of particular importance has been also foreseen.

In addition, this Royal Decree establishes the possibility to impose on the marketing authorization
holders the obligation to conduct post-authorization safety and efficacy studies of medicinal products in
everyday medical practice. These obligations will be a condition of the marketing authorization, and
the marketing of a medicinal product may be suspended by regulatory authorities in case of failure to
fulfill the obligation. These obligations shall be specified in the risk management plan.

Furthermore, this Royal Decree lays down the administrative consequences that for safety
reasons may affect the terms of the marketing authorization for medicinal products for human use,
and incorporates a new urgent procedure for Union-wide assessment of safety issues. Lastly, it
regulates post-authorization studies with medicinal products.

Also, the functions of some of the committees attached to the Spanish Agency of Medicines and
Medical Devices —specifically, the Committee on Safety of Medicinal Products for Human Use and
the Committee for Coordination of Post-Authorization Studies— need to be adapted.

In accordance with the provisions of Article 149.1.16.a of the Spanish Constitution, this Royal
Decree is issued within the competence of the Government on pharmaceuticals legislation, and
partially incorporates Directive 2010/84/EU of the European Parliament and of the Council of
December 15, 2010 into domestic law, while ensuring, as regards the processing of personal data,
compliance with Organic Law 15/1999 of December 13 on the Protection of Personal Data and its
implementing regulations.

As set out in Article 24.3 of Law 50/1997 of November 27 (Government Law), the Ministry of
Finance and Public Administration previously issued a report on this rule. Also, in accordance with
the provisions of Articles 67.2 and 71 of Law 16/2003 of May 28 on Cohesion and Quality of the
National Health System, the Advisory Committee and the Plenary of the Inter-Regional Council of the
National Health System issued a report on this Royal Decree.

The Autonomous Communities and the cities of Ceuta and Melilla were consulted and sectors
involved were heard in the preparation of this rule. Also, the Spanish Data Protection Agency issued
a report on this rule and the mandatory report by the Council of Consumers and Users was obtained.

Accordingly, on proposal of the Minister of Health, Social Services, and Equality, with the prior
approval of the Minister of Finance and Public Administration, in agreement with the Council of State,
and following deliberation by the Council of Ministers during the meeting held on July 26, 2013,

I HEREBY DECREE AS FOLLOWS:

CHAPTER I

General Provisions
Article 1. Scope

The provisions of this Royal Decree shall apply to the pharmacovigilance of medicinal products for human use, defined as a public health activity aimed at identifying, quantifying, assessing, and preventing the risks associated with the use of authorised medicinal products.

These provisions shall, in turn, conform to the provisions of the Commission Implementing Regulation and comply with the European guidelines on good pharmacovigilance practices.

Article 2. Definitions

For the purposes of this Royal Decree, the following definitions shall apply:

1. Spanish Pharmacovigilance System for Medicinal Products for Human Use: A decentralized body, coordinated by the Spanish Agency of Medicines and Medical Devices, that integrates the activities permanently and continuously conducted by the Health Administrations for the purpose of collecting, preparing and, where appropriate, processing information on suspected adverse reactions to medicinal products to identify previously unknown risks or changes in known risks, as well as for conducting as many studies as considered necessary to confirm and/or quantify these risks. It is composed of the competent pharmacovigilance bodies of the Autonomous Communities and their attached regional pharmacovigilance units or centers, the Spanish Agency of Medicines and Medical Devices, healthcare professionals, and citizens.

2. Spontaneous reporting program: A pharmacovigilance method based on the transmission, collection, recording, and evaluation of reports of suspected adverse reactions to medicinal products.

3. Regional Pharmacovigilance Center: A unit responsible for implementing the Spontaneous Reporting Program and any other task entrusted to it by the relevant Autonomous Community, whatever the unit may be called in each of them.

4. Adverse reaction: A response to a medicinal product which is noxious and unintended.

5. Serious adverse reaction: An adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in significant or persistent disability or incapacity, or is a congenital anomaly/birth defect. For reporting purposes, those suspected adverse reactions that are considered medically important shall also be regarded as serious even if they do not meet the above criteria, such as those that jeopardize the patient or require intervention to prevent one of the above outcomes and any suspected transmission of an
infectious agent via a medicinal product.

6. Unexpected adverse reaction: An adverse reaction, the nature, severity or outcome of which is not consistent with the information contained in the summary of product characteristics.

7. Medication error: An unintended mistake in the prescribing, dispensing, or administration of a medicinal product while the medicinal product is under the control of healthcare professionals or consumer. Medication errors that cause harm to patients are considered adverse reactions except those resulting from therapeutic failure due to non-treatment.

8. Pharmacovigilance system master file: A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized medicinal products.

9. Signal: Pharmacovigilance information arising from one or multiple sources, which suggests a new potentially causal association or a new aspect of a known association between a medicinal product and an event or set of related adverse events, which is judged to be of sufficient likelihood to justify a verification action.

10. Yellow card: A form used for reporting suspected adverse reactions, either in paper or electronic format.

11. Medicinal products subject to additional monitoring: Medicinal products included in the list created and maintained by the European Medicines Agency according to the criteria set out in Article 23 of the Regulation (EC) No. 726/2004 of the European Parliament and of the Council of March 31, 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Such a list shall be developed after consultation with the European Pharmacovigilance Risk Assessment Committee and shall include all medicinal products containing new active substances or biological medicinal products, including biosimilars. The list may also include medicinal products that are subject to the obligation to conduct a post-authorization study or to conditions or restrictions with regard to the safe and effective use of the medicinal product.

12. Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System: A set of rules and recommendations developed by the Technical Committee of the Spanish Pharmacovigilance System according to the European guidelines on good pharmacovigilance practices, which are intended to ensure:

(a) The authenticity and quality of the data on suspected adverse reactions collected by the
Spanish Pharmacovigilance System;

(b) The confidentiality of the information relating to the identity of the patients and healthcare professionals; and

(c) The use of uniform criteria in the management of information collected through the spontaneous reporting program.

13. Good Pharmacovigilance Practices for the Pharmaceutical Industry: A set of quality standards regarding the organization and operation of the holders of marketing authorizations for medicinal products intended to ensure the authenticity and quality of the safety data for continuous assessment of the risks associated with the medicinal products for which they hold marketing authorizations.

14. Risks associated with the use of a medicinal product: Any risk for patient's health or public health related to the quality, safety or efficacy of the medicinal product and any risk of undesirable effects on the environment.

15. Periodic safety update report: A document prepared by the marketing authorization holder according to the relevant legislation and guidelines in the European Union, to update the new information on the medicinal product that becomes known during the reporting period. The periodic safety update report shall contain a scientific evaluation of the benefit-risk balance of the medicinal product.

16. Post-authorization study: Any clinical or epidemiological study carried out during the marketing of a medicinal product in accordance with the terms of the summary of product characteristics or under normal conditions of use, in which the medicinal product(s) of interest are the main exposure factor investigated. This study may take the form of a clinical trial or an observational study.

17. Post-authorization safety study: Any post-authorization study conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of an authorized medicinal product, or of measuring the effectiveness of risk management measures.

18. Prospective follow-up post-authorization study: Any post-authorization study in which patients are followed over time, in relation to the event of interest, for a period that includes time after the start of the study.

20. Risk management system: A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.


Article 3. Sources of information for pharmacovigilance

1. Information on the risks associated with the use of medicinal products can come from the following sources:
   
   (a) Study results provided by applicants or holders of marketing authorizations for medicinal products, or independent researchers, whether quality or preclinical (pharmacology or toxicology) studies, pre-authorization studies, post-authorization studies, or meta-analyses.
   
   (b) Individual cases of suspected adverse reactions reported through spontaneous reporting programs.
   
   (c) Computerized healthcare databases.
   
   (d) Registries of patient populations defined by a particular disease or drug treatment, and any other systematic collection of safety information on medicinal products.
   
   (e) Information involving the manufacturing, storage, sale, distribution, dispensing, prescription, and use of medicinal products, including drug utilization studies.
   
   (f) Information concerning the misuse or abuse of medicinal products, medication errors, or occupational exposure, which is relevant to the evaluation of the benefits and risks of medicinal products.
   
   (g) Published scientific reports of individual cases, case series, pharmacology and toxicology studies, clinical trials, pharmacoepidemiology studies, and meta-analyses.
   
   (h) Information from other health authorities and international health organizations.
   
   (i) Any other source that may provide information on the risks associated with the use of medicinal products.

2. The Spanish Agency of Medicines and Medical Devices shall establish the necessary agreements with the competent bodies of the General Government Administration and Autonomous Communities to facilitate the sharing of the information sources under their jurisdiction specified in paragraphs (c), (d), (e), and (f) above.
Article 4. **Functions of the Spanish Agency of Medicines and Medical Devices as regards the pharmacovigilance of medicinal products for human use**

1. The functions of the Spanish Agency of Medicines and Medical Devices include:
   
   (a) To coordinate and evaluate the operation of the Spanish Pharmacovigilance System for Medicinal Products for Human Use in accordance with the Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System.

   In exercising its coordinating functions, the Spanish Agency of Medicines and Medical Devices shall supervise the continuity and quality of the spontaneous reporting program in the respective Autonomous Communities, and submit an annual report on the activities of the Spanish Pharmacovigilance System to the Committee on Safety of Medicinal Products for Human Use. In addition, it shall, upon report to the Committee on Safety of Medicinal Products for Human Use, inform the competent pharmacovigilance bodies of the Autonomous Communities of any deviation from correct operation so that they can take the necessary corrective actions.

   (b) To provide secretariat services to the Committee on Safety of Medicinal Products for Human Use, the Technical Committee of the Spanish Pharmacovigilance System, and the Committee for Coordination of Post-authorization Studies. The objectives, functions and composition of these committees are set out in Royal Decree 1275/2011 of September 16 establishing the State agency known as “Spanish Agency of Medicines and Medical Devices” and approving its Statute.

   (c) To establish and maintain, in coordination with the Autonomous Communities, a data processing network that enable electronic access by the competent pharmacovigilance bodies to all information on suspected adverse reactions known to have occurred in Spain. This information shall be integrated into the database known as *Farmacovigilancia Española, Datos de Reacciones Adversas* (Spanish Pharmacovigilance, Data from Adverse Reactions), hereinafter referred to as FEDRA.

   (d) To administer FEDRA database, ensuring its continuous availability and updating, guaranteeing its security, the protection of personal data, and the integrity of data during data transfer processes. The Spanish Agency of Medicines and Medical Devices shall define, in cooperation with the Technical Committee of the Spanish Pharmacovigilance System, the terms under which this information shall be made publicly available.

   (e) To serve as the reference center of the Spanish Pharmacovigilance System for medicinal product marketing authorizations holders and international organizations, without prejudice to the pharmacovigilance competences of the Autonomous Communities.

   (f) To submit to the European Medicines Agency database (hereinafter referred to as EudraVigilance) information on all serious suspected adverse reactions reported to the Spanish Pharmacovigilance System by healthcare professionals and citizens, within fifteen calendar days of receipt.

   (g) To submit to EudraVigilance information on all non-serious suspected adverse reactions
reported to the Spanish Pharmacovigilance System by healthcare professionals and citizens, within ninety calendar days of receipt.

(h) To establish, in coordination with the Regional Pharmacovigilance Centers, a system for the reporting of suspected adverse reactions by health professionals and citizens, via web-based electronic reporting forms.

(i) To biennially provide the European Commission with information on the pharmacovigilance activities, including those under the competence of the Spanish Pharmacovigilance System.

(j) To promote the development and use of computerized healthcare databases that serve as a source of information for conducting pharmacoepidemiology studies with the participation of the Health Administrations of the Autonomous Communities and health professionals, and to encourage the creation and maintenance of a unified registry of all available databases.

(k) To promote, in cooperation with the Autonomous Communities and health professionals, the creation of independent registries that provide information on the safety of authorized medicinal products.

(l) To promote and conduct pharmacoepidemiology studies aimed at assessing the benefit-risk balance of authorized medicinal products.

(m) To evaluate the information received from the Spanish Pharmacovigilance System and other sources of information.

(n) To assess, in coordination with the competent authorities of the Member States, the emergence of new risks or changes in existing risks, periodic safety update reports, risk management plans, post-authorization study results that may alter the benefit-risk balance of medicinal products, and any other reports on the safety of medicinal products. For this purpose, it shall prepare reports for the network of National Agencies of the European Union when applicable, and submit such reports to the Member States and the European Medicines Agency within the established timeframes.

(n) To establish the appropriate measures to minimize or prevent identified risks, including the necessary training and information, and assess the impact of such measures.

(o) To publish on its website the summaries of the risk management plans, the list of medicinal products subject to additional monitoring, information on the ways available to healthcare professionals and citizens for the reporting of suspected adverse reactions together with a web-based reporting form, and any other information that is relevant to minimize the risks associated with medicinal products.

(p) To disseminate information deemed relevant to the protection of public health including, where appropriate, information received from marketing authorization holders or any other entity or person.

(q) To cooperate within the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency and execute the assigned tasks.

(r) To establish, jointly with the Autonomous Communities within the Technical Committee on Inspection, appropriate inspection procedures to ensure compliance with the obligations of marketing
authorization holders laid down in Chapter IV, and carry out the inspections required to verify compliance within its sphere of competence.

(s) Any other functions that may be necessary in the field of pharmacovigilance and should be carried out by the Spanish Agency of Medicines and Medical Devices.

2. The Spanish Agency of Medicines and Medical Devices shall ensure, within its sphere of competence, the necessary means to perform the above tasks while fulfilling the minimum quality system requirements established by the European Commission in the implementing measures, and the conduct of independent studies aimed at evaluating the safety of medicinal products.

Article 5. Functions of the Autonomous Communities

The functions of the Autonomous Communities, through their competent bodies or delegated units, include:

1. To establish a permanent and continuous spontaneous reporting program in accordance with the Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System, and provide the Spanish Agency of Medicines and Medical Devices with the name of the unit responsible for this task in the Autonomous Community.

2. To promote and carry out the pharmacovigilance activities, studies, and programs agreed within the Technical Committee of the Spanish Pharmacovigilance System.

3. To enable the reporting of suspected adverse reactions by health professionals and citizens through various means, including electronic reporting, in accordance with the terms agreed within the Technical Committee of the Spanish Pharmacovigilance System.

4. To implement various strategies to facilitate the reporting of suspected adverse reactions by physicians, pharmacists, and other healthcare professionals and citizens. These strategies shall be designed in coordination with the Spanish Agency of Medicines and Medical Devices within the Technical Committee of the Spanish Pharmacovigilance System. Participation of consumer and patient organizations, scientific societies, and professional organizations may be requested for this purpose.

5. To record suspected adverse reactions received into FEDRA database. Suspected adverse reactions shall be recorded within ten calendar days of receipt for serious cases, or eighty calendar days of receipt for non-serious cases.
6. To provide the Spanish Agency of Medicines and Medical Devices with information to assess the benefit-risk balance of medicinal products or the impact of regulatory measures adopted for safety reasons, when requested.

7. To evaluate the information contained in the FEDRA database and other accessible databases of suspected adverse reactions for detecting signals.

8. To collaborate with the Spanish Agency of Medicines and Medical Devices and marketing authorization holders in the detection of possible duplicates of suspected adverse reaction reports.

9. To cooperate with the Spanish Agency of Medicines and Medical Devices in implementing and developing programs and studies on the assessment and management of risks of medicinal products, in accordance with the agreements adopted by the Committee on Safety of Medicinal Products for Human Use.

10. To cooperate with the Spanish Agency of Medicines and Medical Devices in disseminating the knowledge on the safety of medicinal products.

11. To establish cooperation procedures with the units responsible for patient safety, so that suspected adverse reactions resulting from medication errors are recorded on the FEDRA database and those units are in turn informed of the cases received directly in the Regional Pharmacovigilance Centers.

12. To implement the appropriate measures agreed in the Technical Committee of the Spanish Pharmacovigilance System for identifying the name and batch number of the medicinal product on reports involving biological or biotechnological products.

13. To implement the appropriate measures to collect the information required for proper scientific evaluation of suspected adverse reaction reports by involving marketing authorization holders, healthcare professionals, or citizens, as appropriate, in obtaining follow-up information.

14. To prepare an annual activity report to be submitted to the Spanish Agency of Medicines and Medical Devices, conduct biennial internal audits of the Regional Pharmacovigilance Center, and submit the audit reports to the Spanish Agency of Medicines and Medical Devices.

15. To carry out the functions relating to post-authorization studies referred to in Chapter VI.
16. To conduct the necessary inspections to assure compliance with the provisions of Chapter V within their territory and communicate the results of inspections, both favorable and unfavorable, to the Spanish Agency of Medicines and Medical Devices, indicating any non-compliance identified.

17. To contribute to scientific advances by improving pharmacovigilance methods, the knowledge and understanding of the nature and mechanisms of adverse reactions, and the safety profile of medicinal products.

18. Any other functions that may be necessary in the field of pharmacovigilance and should be carried out by the Autonomous Communities.

19. The Autonomous Communities shall ensure the necessary means to perform the above tasks.

CHAPTER III

Healthcare Professionals and Citizens

Article 6. Participation of healthcare professionals

The obligations of the healthcare professionals include:

1. To report suspected adverse reactions to authorized medicinal products, including medicinal products used outside the terms of the marketing authorization. These reports shall be submitted as promptly as possible to the relevant Regional Pharmacovigilance Center by any of the means made available for reporting. The web address for electronic reporting shall be indicated in the summary of product characteristics of the medicinal product.

   Priority shall be given to the reporting of suspected serious or unexpected adverse reactions to any medicinal product and those involving medicinal products subject to additional monitoring. Medicinal products subject to additional monitoring shall be identified as such by a symbol, the same in all of the European Union, which shall be included in the medicinal product information in accordance with Article 12.5.

2. To report suspected adverse reactions to medicinal products that are not marketed in Spain and have been obtained through the procedures set out in Royal Decree 1015/2009 of June 19 governing the availability of medicinal products in special situations, in accordance with the provisions therein.
3. If a suspected adverse reaction is a result of a medication error, such circumstance shall be stated on the yellow card. For this purpose, special procedures shall be established and incorporated into the document on Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System.

4. To keep clinical documentation on suspected adverse reactions to medicinal products for at least five years in order to complete or conduct the follow-up, if necessary.

5. To cooperate with the Spanish Pharmacovigilance System, providing the required information on request to expand or complete the information on reported cases of suspected adverse reactions.

6. After reporting a suspected adverse reaction to a marketing authorization holder, to cooperate with it by providing the information required for proper scientific evaluation.

7. To keep informed on the safety of the medicinal products that they commonly prescribe, dispense or administer, and to implement, within their healthcare setting, the measures indicated in the summary of product characteristics aimed at preventing risks and any procedures designed to facilitate compliance with these measures, including training and information for users.

8. To cooperate with the Spanish Agency of Medicines and Medical Devices and the Autonomous Communities in any request for systematic collection of information aimed at assessing the risks of medicinal products or the impact of risk minimization measures, including measures contained in the risk management plans.

9. To cooperate, in their capacity as experts, with the Spanish Agency of Medicines and Medical Devices and the Regional Pharmacovigilance Centers when requested.

**Article 7. Participation of citizens**

Citizens can report suspected adverse reactions to medicinal products, either by bringing them to the attention of the healthcare professionals who, after their clinical assessment, shall report them to the Spanish Pharmacovigilance System, or directly to the Spanish Pharmacovigilance System. Direct reporting shall be made possible through a web-based electronic form, the address of which shall be specified in the package leaflet of each medicinal product.

**CHAPTER IV

Marketing Authorization Holders**
Article 8.  Pharmacovigilance system of the marketing authorization holder

The marketing authorization holder shall have an adequate system in place to fulfill its pharmacovigilance responsibilities, designed to monitor the safety of authorized medicinal products and to identify any changes in their benefit-risk balance. The marketing authorization application shall include a summary of the pharmacovigilance system.

For this purpose, the marketing authorization holder shall:

1. Produce a pharmacovigilance system master file: The Spanish Agency of Medicines and Medical Devices may at any time ask the marketing authorization holder to submit a copy of this file. The marketing authorization holder shall submit the copy within seven calendar days of receipt of the request. The pharmacovigilance system master file shall also be available for inspection.

2. Perform a regular independent audit of its pharmacovigilance system and record the main findings of the audit on the master file. Based on the audit findings, it shall ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the reference to the audit findings may be removed.

3. Have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance for the European Union. This person shall reside and operate in the European Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorization holder shall submit the name and contact details of the qualified person responsible for pharmacovigilance to the Spanish Agency of Medicines and Medical Devices and the European Medicines Agency.

4. Evaluate all information scientifically, consider options for risk minimization and prevention, and take appropriate measures as necessary.


Article 9.  Obligations regarding suspected adverse reactions

In relation to suspected adverse reactions, marketing authorization holders shall:

1. Record electronically the suspected adverse reactions occurring in Spain, the European Union, or third countries which are brought to their attention, both those spontaneously reported by
healthcare professionals or citizens and those collected during a post-authorization study.

2. Report electronically individual cases of suspected adverse reactions in accordance with the European Union requirements laid down in the documents referred to in the second paragraph of Article 1.

3. Submit electronically to the EudraVigilance database:
   (a) All serious suspected adverse reactions that occur in the European Union and in third countries within fifteen calendar days following the day on which the marketing authorization holder gained knowledge of the event.
   (b) All non-serious suspected adverse reactions that occur in the European Union within ninety calendar days following the day on which the marketing authorization holder gained knowledge of the event.

   For suspected adverse reactions reported by healthcare professionals practicing in Spain or by citizens who are in Spain, the marketing authorization holder shall include information identifying the Autonomous Community where the reporting healthcare professional practices or the reporting citizen resides, respectively.

   Suspected adverse reactions collected within a clinical trial shall be reported in accordance with relevant legislation.

4. Report to the Spanish Agency of Medicines and Medical Devices the suspected adverse reactions to investigational medicinal products obtained on a compassionate use basis that they are aware of.

5. Appropriately identify those suspected adverse reactions explicitly stated by the reporter to have resulted from a medication error.

6. Screen the worldwide scientific literature to identify cases of suspected adverse reactions associated with an active substance of a medicinal product for which it holds a marketing authorization in Spain that occurred in the European Union or in third countries where it holds a marketing authorization for such medicinal product. These cases shall be reported electronically in accordance with the European Union requirements laid down in the documents referred to in the second paragraph of Article 1. However, for medicinal products containing an active substances from the list monitored by the European Medicines Agency pursuant to Article 27 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council, marketing authorization holders shall not be required to report to EudraVigilance database the suspected adverse reactions recorded in the medical literature referred to in the list of publications monitored by the European Medicines Agency.
7. Establish procedures in order to obtain accurate and verifiable information for the scientific evaluation of suspected adverse reaction reports. For this purpose, they shall also collect follow-up information on these reports if considered necessary by the marketing authorization holder or the Spanish Pharmacovigilance System, and submit the updates in accordance with point 3 of this article.

8. Cooperate with the Spanish Pharmacovigilance System in the detection of duplicates of suspected adverse reaction reports.

9. Include in the suspected adverse reaction reports, the complete original verbatim narrative and textual descriptions in Spanish and a summary thereof in English.

10. The holders of marketing authorizations for homeopathic medicinal products authorized pursuant to Article 57 of Royal Decree 1345/2007 of October 11 are exempt from establishing a pharmacovigilance system. However, they shall immediately report to the Spanish Pharmacovigilance System any incident resulting in harm to a patient through the regular channels available for this purpose.

Article 10. Obligations regarding periodic safety update reports


2. Periodic safety update reports shall be submitted in the format agreed in the European Union. Periodic safety update reports shall include summaries of relevant data on the risks and benefits of the medicinal product, results from all the studies, an assessment of their potential impact on the marketing authorization, and a scientific evaluation of the benefit-risk balance of the medicinal product, as well as any data available to the marketing authorization holder relating to the volume of sales and the number of prescriptions for the medicinal product, together with an estimate of the population exposed to the medicinal product.

3. As regards the frequency and dates of submission of periodic safety update reports:
   (a) The frequency and dates of submission of periodic safety update reports shall be specified in the terms of the marketing authorization and may be amended after the marketing authorization has been granted.
   (b) The dates of submission of periodic safety update reports shall be calculated from the date of the authorization of the medicinal product.
(c) Periodic safety update reports shall be submitted immediately upon request by the Spanish Agency of Medicines and Medical Devices, and also periodically at the intervals specified in this section, unless other frequency has been established as a condition of the marketing authorization for the medicinal product. The periodic safety update reports shall be submitted every six months after authorization and until the placing on the market. After the medicinal product has been placed on the market, periodic safety update reports shall be submitted every six months during the first two years following the initial placing on the market in any country of the European Union, and once a year for the next two years. Thereafter, periodic safety update reports shall be submitted at three-year intervals.

4. Subject to the provisions of point 3 above and in order to conduct a single harmonized assessment of periodic safety update reports for medicinal products containing the same active substance or the same combination of active substances, authorized in more than one Member State, the frequency and dates of submission may be amended and harmonized according to an European Union reference date. This reference date shall be agreed by the competent European authorities on the basis of the date of the first marketing authorization for a medicinal product containing that active substance or that combination of active substances in the European Union. In this regard:

(a) The frequency, reference date, and submission dates shall be published on the web-portal of the Spanish Agency of Medicines and Medical Devices and on the European medicines web-portal.

(b) Marketing authorization holders shall submit an application for a variation to the terms of the marketing authorization for modifying the submission of periodic safety update reports according to the European Union reference date.

(c) Marketing authorization holders shall be allowed to request changes of the European Union reference date or the frequency of submission of periodic safety update reports for a medicinal product on the following grounds: (1) in order to avoid a duplicate assessment, (2) in order to achieve international harmonization, or (3) for reasons relating to public health.

(d) Any change to the dates or the frequency of submission of periodic safety update reports as a result of the application of this point 4 shall take effect six months after the date of publication.

(e) The single assessment shall be conducted in a harmonized fashion across the countries of the European Union. Within thirty calendar days of receipt of the assessment report, the marketing authorization holder may submit comments to the European Medicines Agency and to the lead Member State. The European Pharmacovigilance Risk Assessment Committee shall adopt the final assessment report and issue a recommendation. Any regulatory measures derived from that recommendation shall be made available to the marketing authorization holder. In the event that those measures require a variation to the terms of the authorization, the marketing authorization holder shall submit an appropriate application for variation to the marketing authorization according to the established timetable.
5. Submission of periodic safety update reports should not be required for medicinal products authorized as generics, for homeopathic medicinal products authorized through a simplified registration procedure, for traditional-use herbal medicinal products, or for medicinal products authorized as well-established medicinal use, unless this obligation has been imposed as a condition to the marketing authorization. However, the Spanish Agency of Medicines and Medical Devices shall require periodic safety update reports for such medicinal products when pharmacovigilance concerns arise or as a result of the lack of periodic safety update reports for their active substances.

Article 11. Obligations regarding risk management systems and post-authorization studies

In relation to risk management systems and post-authorization studies, marketing authorization holders shall:

1. Operate a risk management system for each medicinal product for which marketing authorization is sought after the entry into force of this Royal Decree. For authorized medicinal products, the Spanish Agency of Medicines and Medical Devices may impose an obligation on the marketing authorization holder to operate a risk management system if there are concerns about new risks affecting the benefit-risk balance. In this case, the marketing authorization holder may present observations within thirty calendar days of receipt of the request. If, after considering the observations, the Spanish Agency of Medicines and Medical Devices confirms the obligation to operate a risk management system, the marketing authorization shall be varied to include the risk management system. In this regard, the marketing authorization holder shall:

   (a) Incorporate into the risk management system the conditions imposed during the authorization procedure for the medicinal product or subsequently.

   (b) Monitor the outcome of risk minimization measures contained in the risk management system.

   (c) Update the risk management system.

   (d) The risk management plan shall be submitted to the Spanish Agency of Medicines and Medical Devices, together with a summary in Spanish in the established format.

2. Conduct post-authorization safety studies required by the Member States or the European Commission:

   (a) As a condition to the marketing authorization. The marketing authorization shall lay down deadlines for the fulfillment of the condition where necessary.

   (b) Where there are safety concerns about an authorized medicinal product. If the same concerns apply to more than one medicinal product, the Spanish Agency of Medicines and Medical Devices shall, following consultation with the European Pharmacovigilance Risk Assessment
Committee, encourage the marketing authorization holders concerned to conduct a joint study.

3. Conduct post-authorization efficacy studies required by the Member States or the European Commission, under the following circumstances:

(a) As a condition to the marketing authorization, where concerns relating to the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. The marketing authorization shall lay down deadlines for the fulfillment of the condition where necessary.

(b) After the granting of a marketing authorization, when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly.

The obligation to conduct such studies shall be based on the circumstances stated by the European Commission.

Article 12. **Obligations for continuous evaluation of the benefit-risk balance and updating of the authorization conditions**

The marketing authorization holder shall:

1. Conduct a continuous evaluation of the benefit-risk balance of the medicinal products authorized in Spain and immediately communicate the Spanish Agency of Medicines and Medical Devices any new information that might influence the overall evaluation of the benefit-risk balance or entail an amendment to the summary of product characteristics and/or package leaflet.

   It shall also immediately inform the Spanish Agency of Medicines and Medical Devices of any restriction, suspension, or prohibition imposed by the competent authorities of any country.

2. Provide a report on the benefit-risk balance upon request of the Spanish Agency of Medicines and Medical Devices, as well as any additional information necessary for the evaluation of the benefit-risk balance of a medicinal product, including information about the volume of sales or prescriptions of the medicinal product concerned. The marketing authorization holder shall answer fully and promptly such requests.

3. Implement in Spain regulatory measures adopted for safety reasons, including those contained in the risk management plan.

4. Evaluate the impact of regulatory measures adopted for safety reasons, including, where appropriate, specific studies.

5. For medicinal products included in the list of medicinal products subject to additional
monitoring published in the European medicines web-portal and on the web-portal of the Spanish Agency of Medicines and Medical Devices, the marketing authorization holder shall include in the summary of product characteristics and in the package leaflet the symbol and the explanatory sentence agreed by the competent authorities of the European Union. Information on additional monitoring status shall also be included in any material distributed to healthcare professionals, including materials distributed to patients through healthcare professionals.

**Article 13. Information provided by the marketing authorization holder for safety reasons**

1. The marketing authorization holder shall give prior notice to the Spanish Agency of Medicines and Medical Devices of any public announcement relating pharmacovigilance concerns of its medicinal product. The marketing authorization holder shall ensure that the information is presented objectively and is not misleading, and that relevant safety information is not omitted. Disseminating the information without complying with the terms established in this section shall be considered an infringement of the pharmacovigilance obligations laid down in Article 101.2.(b)(14) of the Law 29/2006 of July 26 on the Guarantees and Rational Use of Medicines and Medical Devices.

2. Where the marketing authorization holder, the Spanish Agency of Medicines and Medical Devices, or the European Medicines Agency consider that the marketing authorization holder should submit information on the safety of the medicinal product or risk prevention to healthcare professionals, and that this information should be submitted to them individually, the marketing authorization holder shall:

   (a) Previously agree the text and any other supplementary materials with the Spanish Agency of Medicines and Medical Devices.

   (b) Agree the communication strategy, which shall include at least the distribution procedure, the timetable, and the targeted healthcare professional groups. The Spanish Agency of Medicines and Medical Devices shall, in addition, notify marketing authorization holders of the organizations and institutions to which the communication should be submitted in all cases.

   (c) Inform the Spanish Agency of Medicines and Medical Devices of the number of healthcare professionals to whom the communication was submitted.

   (d) Duly state in the communication that the text was agreed with the Spanish Agency of Medicines and Medical Devices, and include a warning indicating the nature of the information contained.

   The obligations laid down in this section shall also apply to the materials referred to in the risk management plan aimed to minimize risks that are to be distributed to healthcare professionals and/or to patients through healthcare professionals.

**Article 14. Contact person for pharmacovigilance**
1. The marketing authorization holder shall have permanently and continuously at its disposal in Spain a contact person for pharmacovigilance and shall submit his/her contact details to the Spanish Agency of Medicines and Medical Devices through an electronic system that shall be provided for that purpose. The designated contact person for pharmacovigilance shall have the appropriate experience and training to perform his/her duties. The Spanish Agency of Medicines and Medical Devices shall maintain a database of contact persons for pharmacovigilance, which shall be available to the competent bodies of the Autonomous Communities.

2. The contact person for pharmacovigilance shall assist the qualified person responsible for pharmacovigilance in the European Union referred to in Article 8.3 in his/her assigned functions and cooperate in the following tasks:

(a) To collect information about all suspected adverse reactions brought to the attention of the personnel of the company, so that such information is included in the record referred to in Article 9.1, ensuring that:

1st - Accurate and verifiable information is obtained, enabling the scientific evaluation of suspected adverse reaction reports.

2nd - Follow-up information is collected.

3rd - Duplicates of suspected adverse reaction reports are detected in cooperation with the Spanish Pharmacovigilance System.

4th - Suspected adverse reactions explicitly stated by the reporter to have resulted from a medication error are appropriately identified.

(b) To transmit to the qualified person responsible for pharmacovigilance in the European Union referred to in Article 8.3 any request from the Spanish Agency of Medicines and Medical Devices for additional information necessary to evaluate the benefits and risks of a medicinal product, and provide any information requested by the Spanish Agency of Medicines and Medical Devices about the volume of sales or prescriptions in Spain of the medicinal product concerned.

(c) To serve as a point of contact to provide information to the Spanish Agency of Medicines and Medical Devices on the implementation in Spain of regulatory measures adopted for safety reasons and actions relating to the provisions of the risk management plan.

(d) To establish the procedures required to ensure proper execution of local pharmacovigilance activities.

(e) To serve as the contact person for pharmacovigilance inspections conducted in Spain.

(f) To cooperate with the Regional Pharmacovigilance Centers in providing all available information concerning the reports of suspected adverse reactions to medicinal products.

CHAPTER V

Administrative Intervention
Article 15. Advisory body and participation of experts

1. The Committee on Safety of Medicinal Products for Human Use, a collegiate body provided for in the Statute of the Spanish Agency of Medicines and Medical Devices approved by Royal Decree 1275/2011 of September 16, shall provide advice to the Agency on pharmacovigilance issues.

2. The Spanish Agency of Medicines and Medical Devices may request the advice of experts in the safety of medicinal products and other medical and scientific fields, including the technicians of the Spanish Pharmacovigilance System.

Article 16. Variation to the marketing authorization for pharmacovigilance reasons

1. In accordance with Article 17.9 of Law 29/2006 of July 26, when new relevant information that affects the safety of a medicinal product is brought to the attention of the marketing authorization holder, it shall, without delay, update the marketing authorization dossier following the procedures for variation to the terms of marketing authorizations. Failure to fulfill this obligation shall result in suspension or revocation of the authorization. These variations shall be subject to payment of the appropriate fee.

2. The marketing authorization holder shall ensure that the medicinal product information is kept up to date with the current scientific knowledge, including the conclusions of the assessments and recommendations published in the European medicines web-portal established in accordance with Article 26 of the Regulation (EC) No. 726/2004 of the European Parliament and of the Council of March 31, 2004, and on the web-portal of the Spanish Agency of Medicines and Medical Devices.

   The conclusions indicated above shall include, as appropriate, those agreed by the Coordination Group or those issued by the European Commission. They shall be based on the recommendations of the European Pharmacovigilance Risk Assessment Committee arising from the assessment of periodic safety update reports, post-authorization studies, results of risk management plans, and any information on new risks or changes in known risks. In order to facilitate the fulfillment of the obligations of the marketing authorization holder, the Spanish Agency of Medicines and Medical Devices shall publish an implementation timetable in its web-portal and shall also inform the marketing authorization holder of any other measure intended to reduce the risk.

3. Where reasons of public interest, health protection, or human safety arise from the evaluation of pharmacovigilance data, the Spanish Agency of Medicines and Medical Devices may restrict the terms of the authorization for a medicinal product and impose some of the below listed conditions or restrictions of use, as defined in the regulations governing the procedure for authorization,
registration, and dispensing conditions of industrially produced medicinal products for human use:

(a) Medicinal product for hospital use (H)
(b) Medicinal product for hospital diagnosis or prescription by specific medical specialists only (DH)
(c) Medicinal product under special medical control (ECM)

These conditions or restrictions of use may also be applied to medicinal products authorized by the European Commission subject to restricted medical prescription.

Article 17. Urgent safety restriction and applicable procedure

1. When new information becomes available indicating a significant public health risk associated with the use of a medicinal product or having a significant impact on the safety of the medicinal product, the Spanish Agency of Medicines and Medical Devices may decide an urgent provisional amendment to the medicinal product information, particularly involving some of the following sections of the summary of product characteristics: indications, posology, contraindications, adverse reactions, special warnings and precautions for use, including warnings relating to the use of the medicinal product during pregnancy and lactation.

2. Where the marketing authorization holder considers that urgent variation to the terms of the authorization for a medicinal product is needed for safety reasons, a variation application shall be submitted to the Spanish Agency of Medicines and Medical Devices, together with the following documents:
   (a) A report on the new risks that make the variation necessary.
   (b) The proposed amendment to the summary of product characteristics and package leaflet.
   (c) The proposed information to healthcare professionals and, where appropriate, information to be provided by healthcare professionals to users.
   (d) The proposed additional actions and any other information considered necessary for effective implementation of the variation.

   If the Spanish Agency of Medicines and Medical Devices has not raised any objection within one working day of receipt of the information, the urgent safety restriction shall be considered provisionally accepted, and the marketing authorization holder shall submit an application for variation of the summary of product characteristics within fifteen calendar days of the date of acceptance. The Spanish Agency of Medicines and Medical Devices shall establish the specific procedures to be followed.

3. Where the urgent safety restriction is imposed by the Spanish Agency of Medicines and Medical Devices, the marketing authorization holder shall submit an application for variation in
accordance with the terms specified by the Agency, immediately and not later than fifteen calendar days of receipt of the notification.

4. In the circumstances specified in points 2 and 3 above, the timeframe and the information for healthcare professionals and the effective implementation of the variation by the marketing authorization holder, including the changes to the packaging shall be agreed with the Spanish Agency of Medicines and Medical Devices.

5. For medicinal products authorized under the mutual recognition or decentralized procedures, the mechanisms established for this purpose in the relevant guidelines shall be taken into account. For medicinal products authorized under the centralized procedure, the Commission Regulation (EC) No. 1234/2008 of November 24, 2008 and their implementing guidelines shall be followed.

Article 18. Suspension or revocation of the authorization for pharmacovigilance reasons

Based on the assessment of pharmacovigilance data, the Spanish Agency of Medicines and Medical Devices may temporarily suspend or permanently revoke the authorization of a medicinal product if:

1. The medicinal product has an unfavorable benefit-risk balance.
2. The medicinal product poses an unacceptable risk to human health or safety.
3. There is non-compliance with pharmacovigilance legislation according to the provisions of Article 22.1 (d) of Law 29/2006 of July 26.
4. It is a requirement under current legislation.

Article 19. Urgent European Union procedure

1. The Spanish Agency of Medicines and Medical Devices shall initiate the procedure provided for in this article by informing the other Member States, the European Medicines Agency, and the European Commission when, as a result of the evaluation of a safety concern and upon advice of the Committee on Safety of Medicinal Products for Human Use, it considers suspending or revoking a marketing authorization, prohibiting the supply of a medicinal product or refusing the renewal of a marketing authorization.

2. The Spanish Agency of Medicines and Medical Devices shall consider initiating the procedure provided for in this article by informing the other Member States, the European Medicines Agency, and the European Commission if, as a result of the evaluation of a safety concern, the Spanish Agency of Medicines and Medical Devices:

(a) Considers, upon advice of the Committee on Safety of Medicinal Products for Human Use,
that a new contraindication, a reduction in the recommended dose, a restriction to the indications, or any of the conditions or restrictions of use referred to in Article 16.3 is necessary; or

(b) Is informed by a marketing authorization holder that, on the basis of safety concerns, it has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorization withdrawn or intends to do so, or has not applied for the renewal of a marketing authorization.

3. If the medicinal products concerned contain active substances authorized in more than one Member State of the European Union, the European Pharmacovigilance Risk Assessment Committee shall assess the matter in order to reach a European Union-wide common decision. In this regard:

(a) The Spanish Agency of Medicines and Medical Devices shall make available to the European Pharmacovigilance Risk Assessment Committee all relevant scientific information that it has at its disposal and any assessments performed.


(c) The European Pharmacovigilance Risk Assessment Committee shall make a recommendation within sixty calendar days of the information being submitted.

For medicinal products authorized under the centralized procedure established in Regulation (EC) No. 726/2004 of the European Parliament and of the Council of March 31, 2004, where the Spanish Agency of Medicines and Medical Devices considers that measures or decisions envisaged in Article 20 of that Regulation should be adopted on the basis of the evaluation of pharmacovigilance data, the matter shall, upon advice of the Committee on Safety of Medicinal Products for Human Use, be referred to the European Pharmacovigilance Risk Assessment Committee for assessment.

4. If the medicinal products concerned contain active substances authorized only in Spain and not in other Member States of the European Union, the matter shall be assessed according to the following procedure:

(a) The Spanish Agency of Medicines and Medical Devices shall request the marketing authorization holder to submit a report assessing the identified safety concern and, where appropriate, the benefit-risk balance of the medicinal product for the conditions of use authorized in Spain, including the proposed risk minimization measures. Such report shall conform to the structure and matters specified in the request. The report shall be submitted, at the latest, within sixty calendar days of receipt of the request. However, this period may be reduced having regard to the urgency of
the matter or, in exceptional circumstances and at the request of the marketing authorization holder, extended in agreement with the Spanish Agency of Medicines and Medical Devices.

(b) On the basis of the above report, the Spanish Agency of Medicines and Medical Devices shall prepare an assessment report on the safety concern.

(c) In all cases where any of the restrictions of use referred to in Article 16.3 or a suspension or revocation of the marketing authorization may apply, the Committee on Safety of Medicinal Products for Human Use shall issue a mandatory opinion upon hearing the marketing authorization holder concerned.

**Article 20. Administrative measures resulting from the urgent European Union procedure**

1. Administrative measures arising from the evaluation shall be agreed by the Spanish Agency of Medicines and Medical Devices within the Coordination Group, or determined by decision of the European Commission, which shall be communicated to the Member States and the marketing authorization holder, as appropriate. A timetable for implementation of such measures shall be provided.

2. In the event that the marketing authorization should be varied as a result of the procedures described in the previous article, the amendments to be made to the summary of product characteristics and package leaflet, together with the implementation timetable shall be made available to the marketing authorization holder concerned in the web-portal of the Spanish Agency of Medicines and Medical Devices. The marketing authorization holder shall be informed by the Spanish Agency of Medicines and Medical Devices of any other measure intended to minimize the risk.

   The marketing authorization holder shall submit an application for variation to the terms of the marketing authorization for the medicinal product following the procedures foreseen in Royal Decree 1345/2007 of October 11 governing the procedure for authorization, registration, and dispensing conditions of industrially produced medicinal products for human use.

3. In the event that, as a result of the procedures described in the previous article, the marketing authorization should be suspended or revoked, or the terms of the marketing authorization should be varied in accordance with the provisions of Article 16.3, a decision shall be issued and the marketing authorization holder concerned shall be notified of its right to appeal and of the implementation timeframe.

4. These administrative measures shall not apply to medicinal products authorized under the centralized procedure established in Regulation (EC) No. 726/2004 of the European Parliament and of the Council of March 31, 2004, which are governed by specific regulations.
Article 21. Precautionary measures

1. On the basis of the pharmacovigilance data, the Spanish Agency of Medicines and Medical Devices may adopt the precautionary measures provided for in Article 99 of the Law 29/2006 of July 26. In addition, the Agency may, at any stage of the procedure laid down in Article 19, adopt such measures on its own initiative, or at the request of the European Commission.

The Spanish Agency of Medicines and Medical Devices shall inform the Autonomous Communities, the Member States, the European Commission, and the European Medicines Agency of the precautionary measures adopted, at the latest on the following working day.

2. Summaries of product characteristics and package leaflets containing information related to the safety variations decided as a result of urgent European Union procedures may be published by the Spanish Agency of Medicines and Medical Devices on its web-portal, even if the marketing authorization holder has not yet submitted the corresponding variation. Such publication shall not, in any case, relieve the marketing authorization holder from submitting the corresponding application for variation.

Article 22. Communications to Autonomous Communities, healthcare professionals, citizens, and international organizations

1. The Spanish Agency of Medicines and Medical Devices shall inform the Autonomous Communities and other competent bodies about the adoption of those regulatory measures foreseen in this chapter that are relevant to public health.

2. The Spanish Agency of Medicines and Medical Devices and the Autonomous Communities shall appropriately submit information on the risks of medicinal products to healthcare professionals and citizens. The information submitted by the Spanish Agency of Medicines and Medical Devices shall be available on its web-portal.

3. The decisions involving suspensions, revocations, and significant variations to authorizations, shall be brought to the attention of the World Health Organization in as much as they may affect the protection of public health in third countries.

Article 23. Pharmacovigilance inspections

1. The Spanish Agency of Medicines and Medical Devices and competent health authorities of the Autonomous Communities shall, within their respective spheres of competence, verify
compliance with the provisions of Chapter IV through inspection of the sites, files, documents, and the pharmacovigilance system master file of the marketing authorization holder or of any company contracted by the marketing authorization holder to carry out the activities referred to in that chapter.

2. Following every inspection, which shall be conducted in accordance with the procedures agreed within the Technical Committee on Inspection, the inspectors shall prepare a report conforming to the format agreed in the European Union, and the inspected entity concerned shall be given the opportunity to submit comments.

3. If the outcome of these inspections is that the marketing authorization holder has failed to comply with the pharmacovigilance system as described in its master file, or with any other obligation established, the deficiencies shall be brought to the attention of the marketing authorization holder for correction. The Spanish Agency of Medicines and Medical Devices or the competent health authorities of the Autonomous Communities, as appropriate, shall impose the applicable penalties.

4. The Spanish Agency of Medicines and Medical Devices shall inform the other Member States, the European Medicines Agency, and the European Commission of these cases of non-compliance.

CHAPTER VI

Post-Authorization Studies

Article 24. Scope and general aspects

1. Post-authorization studies shall aim to complement the information obtained during the clinical development of the medicinal products prior to authorization. Post-authorization studies shall not be planned, conducted, or funded for the purpose of promoting the prescription of medicinal products.

2. The remuneration to healthcare professionals who participate in post-authorization studies shall be restricted to compensation for any additional time and expenses incurred, subject to the regulations applying to the remuneration of public employees and the relevant internal rules of the institutions employing the researchers.

3. In order to ensure the welfare and the rights of the subjects, post-authorization studies must receive a favorable opinion from a Research Ethics Committee prior to initiation. Such opinion shall be unique and, therefore, shall be recognized throughout the national territory.
4. The provisions of this chapter shall not apply to those post-authorization studies that, in accordance with the provisions of Law 29/2006 of July 26, qualify as clinical trials and not as non-interventional studies. Instead, Royal Decree 223/2004 of February 6 governing clinical trials of medicinal products for human use shall apply.

Article 25. Administrative procedure

1. Through the Committee for Coordination of Post-Authorization Studies, Health Administrations shall harmonize the criteria and requirements for post-authorization studies with medicinal products and favor those of greater scientific interest, which may contribute to the knowledge of the medicinal product or to the improvement of clinical practice.

2. The Spanish Agency of Medicines and Medical Devices shall, in cooperation and coordination with the Autonomous Communities, provide a unique access point for the electronic processing of applications for post-authorization studies and electronic exchange of information, documents, and official communications. The competent bodies of the Autonomous Communities shall have access to the data entered into the information system established by the Spanish Agency of Medicines and Medical Devices. They shall keep the information on marketing authorization applications, as well as the results of their assessments updated.

3. Prior to the initiation in Spain of studies that fulfill the criteria established by the Spanish Agency of Medicines and Medical Devices, the sponsor shall request the Agency to classify the study. These studies shall be included in the public clinical studies registry established by the Spanish Agency of Medicines and Medical Devices.

4. Subject to the necessary approval by service and healthcare providers in whose jurisdiction the post-authorization studies are to be conducted, post-authorization studies shall require prior authorization in accordance with the following:

   (a) Post-authorization studies that conform to the provisions of Article 11.2 shall be evaluated by the European Pharmacovigilance Risk Assessment Committee, which shall issue a decision within sixty calendar days after the submission of the draft protocol.

   The Spanish Agency of Medicines and Medical Devices shall be responsible for evaluating post-authorization studies in the following cases:

   1st - Studies requested by the Spanish Agency of Medicines and Medical Devices for safety reasons after the granting of the marketing authorization, which are to be conducted only in Spain.

   2nd - Prospective follow-up post-authorization studies included in the risk management plan for a medicinal product that are to be conducted in Spain and have not been referred to in the previous sections.
(b) Post-authorization studies promoted by Health Administrations or supported by public funds shall require authorization by the Spanish Agency of Medicines and Medical Devices, which shall request the Committee for Coordination of Post-Authorization Studies to submit a report.

(c) The competent bodies of the Autonomous Communities shall evaluate those applications for authorization of prospective follow-up post-authorization studies that do not conform to the provisions of the previous sections. The Committee for Coordination of Post-Authorization Studies shall establish a system for mutual recognition among the Autonomous Communities in order to harmonize the evaluations and approve a common protocol.

5. After a post-authorization study has been approved, substantial amendments shall require the prior authorization of the bodies that conducted the initial evaluation.

6. The sponsor shall notify the Spanish Agency of Medicines and Medical Devices of the effective date for study initiation and shall submit annual follow-up reports as established and a final report within twelve months after the completion of data collection. This information shall be made available to the Autonomous Communities through the information system referred to in point 2 above.

First additional provision.  

Data protection

The rules contained in this Royal Decree shall be interpreted subject to the provisions of Organic Law 15/1999 of December 13 on the Protection of Personal Data and its implementing regulations, so that confidentiality, personal and family privacy of citizens, and protection of their personal data shall be guaranteed in the computer and electronic processing of data collected as a result of pharmacovigilance activities, in accordance with the specific applicable regulations.

Second additional provision.  

The cities of Ceuta and Melilla

References to the competent pharmacovigilance bodies of the Autonomous Communities shall also apply to the cities of Ceuta and Melilla, within the scope provided for in their respective Statutes of Autonomy and Royal Decrees on the transfer of functions and services.

Third additional provision.  

No increase in personnel costs

The application of this Royal Decree shall not result in any increase in personnel costs. New human resource requirements, if any that may arise as a result of the regulatory obligations set out in this Royal Decree shall be fulfilled through redistribution of personnel.
Fourth additional provision. **Healthcare centers of the Ministry of Defense**

The Inspectorate-General of Health Care of the Armed Forces shall submit to the Spanish Agency of Medicines and Medical Devices, through the Spanish Pharmacovigilance System, as established, any information on suspected adverse reactions occurring in Spain brought to the attention of the Inspectorate-General.

The Inspectorate-General shall directly submit to the Spanish Agency of Medicines and Medical Devices any information relating to hospitals or healthcare units of Spanish Armed Forces that are participating in international missions.

First transitional provision  **Electronic reporting of suspected adverse reactions**

The provisions of Article 9.3 shall enter into force six months after the date on which the functionalities of the EudraVigilance database are established. Until that time, marketing authorization holders shall electronically submit to the Spanish Pharmacovigilance System only serious suspected adverse reactions reported to the Spanish Pharmacovigilance System by healthcare professionals and citizens. Serious suspected adverse reaction reports shall be electronically submitted to EudraVigilance by the Spanish Agency of Medicines and Medical Devices.

However, serious suspected adverse reactions occurring outside the European Union that are brought to the attention of the marketing authorization holder shall be electronically submitted to EudraVigilance by the marketing authorization holder.

During this transitional period, non-serious suspected adverse reactions shall not be submitted to EudraVigilance or to the Spanish Pharmacovigilance System.

Once the functionalities of the suspected adverse reaction database have been established, the Spanish Agency of Medicines and Medical Devices shall notify the date on which point 3 of Article 9 shall enter into force as regards the submission of suspected adverse reactions to the EudraVigilance database.

Second transitional provision  **Electronic submission of periodic safety update reports**

Point 1 of Article 10 shall enter into force twelve months after the functionalities of the repository for periodic safety update reports have been established. Until that time, marketing authorization holders shall submit periodic safety update reports to the Spanish Agency of Medicines and Medical Devices by electronic means, using the software application developed for that purpose and according to the requirements established in previously applicable regulations.

Once the functionalities of the repository for periodic safety update reports have been established, the Spanish Agency of Medicines and Medical Devices shall notify the date on which point 1 of Article 10 shall enter into force.
Third transitional provision  

*Updating of the contact details of the contact person*

The contact details of the contact person for pharmacovigilance provided for in point 1 of Article 14 shall be electronically recorded and updated once the Spanish Agency of Medicines and Medical Devices informs that a software application is available for that purpose. Until that time, marketing authorization holders shall submit the contact details of the contact person to the Spanish Agency of Medicines and Medical Devices and to the competent bodies of the relevant Autonomous Communities.

Fourth transitional provision  

*Pharmacovigilance master file*

For medicinal products authorized before the entry into force of this Royal Decree, the obligation of the marketing authorization holder to produce and maintain a pharmacovigilance system master file and submit a summary thereof provided for in Article 8 shall be fulfilled at the time of renewal of the marketing authorization, and in any case before July 21, 2015.

Fifth transitional provision  

*Amendment to the summary of product characteristics and package leaflet*

The amendments to the package leaflet and summary of product characteristics foreseen in Articles 6.1, 7 and 12.5 of this Royal Decree shall be incorporated when instructed by the Spanish Agency of Medicines and Medical Devices on a public announcement that shall be published on its website. The exceptions and reductions provided for in Articles 109.4 and 111.6 of Law 29/2006 of July 26 shall apply.

Single repeal provision  

*Regulatory repeal*

Any provisions of equal or lower status conflicting with the provisions of this Royal Decree are hereby repealed, in particular, Royal Decree 1344/2007 of October 11 governing the pharmacovigilance of medicinal products for human use.

First final provision  

*Amendment to Royal Decree 1015/2009 of June 19 governing the availability of medicinal products in special situations*

Royal Decree 1015/2009 of June 19 governing the availability of medicinal products in special situations is hereby amended as follows: paragraph (c) of point 1 of Article 11 is replaced by the following:
“(c) To report immediately suspected adverse reactions to the Spanish Agency of Medicines and Medical Devices.”

Second final provision. *Amendment to the Statute of the Spanish Agency of Medicines and Medical Devices, approved by Royal Decree 1275/2011 of September 16 establishing the State agency known as “Spanish Agency of Medicines and Medical Devices” and approving its Statute*

The Statute of the Spanish Agency of Medicines and Medical Devices, approved by Royal Decree 1275/2011 of September 16 establishing the State agency known as “Spanish Agency of Medicines and Medical Devices” and approving its Statute is hereby amended as follows:

One. Paragraphs (c) and (d) of point 3 of Article 19 are replaced by the following:

“(c) To inform mandatorily during the procedure for suspension or revocation of a marketing authorization for medicinal products for human use in the circumstances foreseen in current regulations on pharmacovigilance of medicinal products for human use.

(d) To provide technical advice to the Spanish representatives in the European Pharmacovigilance Risk Assessment Committee.”

Two. Two new paragraphs, (f) and (g), are added to point 3 of Article 19 as follows:

“(f) To prepare the recommendations of use described in Article 13.2 of Royal Decree 1015/2009 of June 19 governing the availability of medicinal products in special situations.

(g) To recommend the conduct of studies aimed at assessing the impact of measures adopted to minimize the risks of medicinal products.”

Three. Points 3 and 4 of Article 23 are replaced by the following:

“3. The Committee for Coordination of Post- Authorization Studies shall be composed of the following members:

(a) Two members *ex officio*:

1. The Head of the Department of Medicinal Products for Human Use.
2. The Chief of the Division of Pharmacoepidemiology and Pharmacovigilance of the Department of Medicinal Products for Human Use.

(b) Seventeen members, each one representing one competent body on post-authorization
studies from the Autonomous Communities, officially designated by that body.

(c) One member representing the Secretariat-General of Penitentiary Institutions of the Ministry of Home Affairs.

4. The Chairperson and the Vice-Chairperson of the Committee for Coordination of Post-Authorization Studies shall be elected by the members of the Committee from among the representatives of the Autonomous Communities and the Secretariat-General of Penitentiary Institutions. The Chief of the Division of Pharmacoepidemiology and Pharmacovigilance of the Department of Medicinal Products for Human Use shall act as Secretary of the Committee for Coordination of Post-Authorization Studies."

Four. A new point 5 is added to Article 29 as follows:

“5. The human, technical and budgetary resources for the functioning of the Committees shall be allocated by the Spanish Agency for Medicines and Healthcare Products.

Third final provision Legislative competence

This Royal Decree is issued under Article 149.1.16.a of the Spanish Constitution, which confers to the Government exclusive competence on pharmaceuticals legislation.

Fourth final provision Rule-making powers

The Minister of Health, Social Services, and Equality is empowered to issue the provisions that may be necessary for proper enforcement and implementation of this Royal Decree.

Fifth final provision Incorporation of European Union legislation


Sixth final provision Entry into force

This Royal Decree shall enter into force on the day after the date its publication in the “Official
State Journal”.

Done at Madrid, July 26, 2013.

The Minister of Health, Social Services, and Equality,
ANA MATO ADROVER

JUAN CARLOS R