



This is an unofficial English translation of the Royal Decree 1344/2007 revised by the Spanish Agency for Medicines and Medical Devices

ROYAL DECREE 1344/2007, of 11 October, regulating pharmacovigilance of medicinal products for human use.

This Royal Decree develops Title II, Chapter VI, of Law 29/2006 of 29 July on guarantees and rational use of medicinal products and medical devices, which lays down the guarantees with regard to the monitoring of the risk-benefit balance of medicinal products and therefore regulates the Spanish Pharmacovigilance System and pharmacovigilance for medicinal products for human use.

In addition, this Royal Decree updates and adapts to technical progress the regulation in force concerning these matters until now, contained in Royal Decree 711/2002 of 19 July, regulating pharmacovigilance of medicinal products for human use, which is now repealed, and incorporates into Spanish law the novelties introduced by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

The novelties introduced in Title IX “Pharmacovigilance” of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, are a consequence of the changes arising as a result of international harmonization of definitions, terminology and technical developments, which requires that pharmacovigilance systems in the European Union are continually adapted to take into account of scientific and technical progress.

Most notable among these novelties introduced by the new European regulation and which are incorporated into Spanish law by this Royal Decree, is the requirement for electronic reporting of adverse reactions between the different agents (pharmaceutical industry, national agencies and European Medicines Agency), with the aim of making possible the creation and maintenance of a European database of suspected adverse reactions, which shall be managed by the European Medicines Agency, ensuring its accessibility to the Member States. Notable also is the introduction of the concept of risk management, understood as the planning of pharmacovigilance activities with the intention of anticipating the safety problems of medicinal products, as well as the introduction of measures to minimize the known risks of medicinal products and to allow their effective reporting, with special mention to pharmacoepidemiology and, in particular, to post-authorization studies that should help to identify and characterize the risks of medicinal products and to evaluate the effectiveness of these risk minimization measures. Also important is the modification of the definitions of “risks related to the

use of medicinal products” and “risk-benefit balance”, which are included in this provision.

Finally, it should be noted that Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, incorporates a new article 102a into Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, whereby the management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance is placed under the permanent control of the competent authorities in order to guarantee their independence, which is already operating in Spain should also be transferred to the field of pharmacoepidemiology, so that, with the necessary independence, studies are conducted from the public sector that are of particular interest to protect public health.

Taking into account this background, this Royal Decree first establishes the agents who participate in the Spanish Pharmacovigilance System for medicinal products for human use, as well as the obligations of each of the agents involved in this activity, whose objective is to provide continuously the best possible information on the safety of medicinal products, thus enabling the adoption of the appropriate measures and ensuring that the medicinal products available in the market have a favorable benefit-risk balance for the population under the authorized conditions of use. For the conduct of pharmacovigilance of medicinal products for human use, the European Commission has prepared and published the guidelines contained in Volume 9A of the Rules Governing Medicinal Products in the European Union, which shall be applicable, as well as their successive updates.

Secondly, it establishes the administrative consequences which for safety reasons can affect the marketing authorization conditions of medicinal products for human use, and, finally, it regulates post-authorization studies to ensure that evaluation of the risk-benefit balance of authorized medicinal products is continuous.

This provision was drawn up after hearing the sectors involved and consulting the Autonomous Communities.

This Royal Decree, which has the condition of legislation on medicinal products as established in Article 149.1.16.^a of the Constitution, incorporates into Spanish law sections 1.i) and 72-76 of Article 1 of Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

By virtue hereof, as proposed by the Minister of Health and Consumer Affairs, and after approval by the Minister of Public Administrations, in agreement with the Council of State and after deliberation of the Council of Ministers at its meeting of 11 October 2007,

I PROVIDE THAT:

CHAPTER I

General provisions

Article 1. *Scope of application.*

The provisions of this Royal Decree shall be applied to the pharmacovigilance of medicinal products for human use, as a public health activity aimed at the identification, quantification, evaluation and prevention of the risks associated with the use of these medicinal products once they are marketed.

Article 2. *Definitions.*

For the purposes of this Royal Decree, the following definitions are given:

- a) Spanish Pharmacovigilance System for medicinal products for human use: Decentralized scheme, coordinated by the Spanish Agency of Medicines and Medical Devices, integrating the activities fulfilled on a permanent and continuous basis by health administrations to collect, prepare and, where appropriate, process information useful for the supervision of medicinal products, and in particular, information on adverse reactions to medicinal products, as well as the carrying out of as many studies as considered necessary to evaluate the safety of the medicinal products.
- b) Spontaneous Reporting Program: Pharmacovigilance based on the reporting, collection and evaluation of suspected adverse reactions to medicinal products.
- c) Adverse reaction: Any response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. This term also includes all adverse clinical consequences resulting from dependence, abuse and misuse of medicinal products, including those caused by use of the product outside of authorized conditions and by medication errors.
- d) Serious adverse reaction: Any adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. For reporting purposes, suspected adverse reactions that are considered medically important, even if they do not meet the above criteria, such as those that are life threatening or require intervention to prevent one of the above outcomes, shall also be considered serious. As far as the notification process is concerned, any suspected transmission via a medicinal product of an infectious agent shall also be considered a serious adverse reaction.
- e) Unexpected adverse reaction: Any adverse reaction, the nature, severity or outcome of which is not consistent with the information laid down in the summary of product characteristics.

f) Periodic safety update report: A document prepared by the marketing authorization holder according to the guidelines laid down to this regard in the European Union, whose purpose is to update the safety information of the medicinal product which, among other elements, contains information on the suspected adverse reactions of which the holder has knowledge in the period of reference, as well as a scientific evaluation of the risk-benefit balance of the medicinal product.

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

h) Post-authorization safety study: A pharmacoepidemiological study or clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying, characterizing or quantifying the risks associated with authorized medicinal products.

i) Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

j) Yellow card: A form used to report suspected adverse reactions, distributed by the bodies in charge of pharmacovigilance in the Autonomous Communities to healthcare professionals.

k) Good pharmacovigilance practices: Set of rules or recommendations aimed at ensuring:

1. The authenticity and quality of the data collected in pharmacovigilance which allow the risks associated with the use of the medicinal products to be assessed at any time;

2. The confidentiality of the information relating the identity of the patients and healthcare professionals;

3. The use of uniform criteria in management of the pharmacovigilance information.

l) Risks related to the use of a medicinal product: Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health, as well as any risk with undesirable effects on the environment.

m) Risk-benefit balance of a medicinal product: An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks of its use.

n) Risk management plan: A document in which the applicant or marketing authorization holder specifies the important identified or potential risks of the medicinal product and notes the relevant safety information that is not available; sets out a plan to carry out the pharmacovigilance activities necessary to identify, characterize or quantify these risks; and incorporates, if necessary, a specific program to prevent or minimize risks, including activities of education and information to healthcare professionals and patients in the context of this plan and the evaluation of the effectiveness of the measures taken.

ñ) Medication error: An error through action or omission in the process of treatment with medicinal products that causes or has the potential to cause harm to the patient. Medications error that cause harm to the patient shall be considered adverse reactions for reporting purposes, except those caused by treatment failure due to omission of a treatment.

Article 3. Sources of pharmacovigilance information.

1. The information on the risks associated with the use of medicinal products can be obtained from the following sources:

a) Spontaneous reporting of individual cases of suspected adverse reactions by healthcare professionals.

h) Post-authorization studies.

c) Computerized health databases.

d) Preclinical information on animal studies.

e) Information from clinical trials with a medicinal product.

f) Information relating to the manufacture, storage, sales, distribution, dispensation, prescription and usage of medicinal products.

g) Scientific publications.

h) Other sources of information, such as those related to the inappropriate use and abuse of medicinal products or to medication errors that can provide relevant data for assessing the benefits and risks of the medicinal products.

i) Other international health authorities and health agencies

2. The Spanish Agency of Medicines and Medical Devices shall establish the necessary agreements with the competent bodies of the Autonomous Communities for shared use of the sources of information under their control specified in paragraphs c), f) and h) of the previous section.

3. In order to facilitate the exchange of information on individual case safety reports, the guidelines prepared and published by the European Commission in Volume 9A of the Rules Governing Medicinal Products in the European Union relating to the collection, verification and presentation of adverse reaction reports, including the technical requirements for the electronic exchange of pharmacovigilance information in accordance with internationally agreed formats and internationally agreed medical terminology shall be applied.

CHAPTER II

a) On the Spanish Pharmacovigilance System for medicinal products for human use

Article 4. a) Agents of the Spanish Pharmacovigilance System for medicinal products for human use

1. a) The Spanish Pharmacovigilance System for medicinal products for human use is formed by:

a) The Spanish Agency of Medicines and Medical Devices, which acts as the coordinating center.

b) The bodies in charge of pharmacovigilance in the Autonomous Communities and the autonomous pharmacovigilance units or centers attached to them.

c) Healthcare professionals.

2. The Technical Committee of the Spanish Pharmacovigilance System for medicinal products for human use, as the coordinating body formed by the Spanish Agency of Medicines and Medical Devices and the bodies in charge of pharmacovigilance in the Autonomous Communities, or their delegated units, shall unify the performance criteria of the spontaneous reporting program, evaluate the alert signals generated by the Spanish Pharmacovigilance System for medicinal products for human use, and discuss the methodological and practical aspects of any studies proposed to be undertaken.

Article 5. Duties of the Spanish Agency of Medicines and Medical Devices relating to pharmacovigilance of medicinal products for human use.

1. The duties of the Spanish Agency of Medicines and Medical Devices include:

a) Coordinate and evaluate the Spanish Pharmacovigilance System for medicinal products for human use, and also the tasks of its Technical Committee, in accordance with the “Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System for medicinal products for human use” drawn up by this Committee and published by the Ministry of Health and Consumer Affairs. It is also responsible for the planning and the development of this system in relation to the Autonomous Communities.

In the exercise of its coordinating functions, the Spanish Agency of Medicines and Medical Devices shall supervise the permanence and continuity of the spontaneous reporting program in the respective Autonomous Communities, and shall submit an annual report of activities of the Spanish Pharmacovigilance System to the Committee on Safety of Medicinal Products for Human Use.

b) Establish, in collaboration with the Autonomous Communities, a data processing network which enables the bodies in charge of pharmacovigilance in the Autonomous Communities, or their designated units, to have telematic access to all information collected by the Spanish Pharmacovigilance System for medicinal products for human use.

c) Manage the database of the Spanish Pharmacovigilance System for medicinal products for human use, ensuring its availability and it being updated at all times, monitoring its security and ensuring data confidentiality and integrity during the data transfer processes. The Ministry of Health and Consumer Affairs shall establish the terms under which this information shall be made available to the public.

d) Act as the reference center of the Spanish Pharmacovigilance System for medicinal products for human use with the marketing authorization holders of medicinal products and international bodies, without prejudice to the responsibilities of the Autonomous Communities regarding pharmacovigilance.

e) Make available to marketing authorization holders immediately and in no case later than fifteen calendar days following their receipt, the reports on suspected serious adverse reactions occurring in Spain and where medicinal products of which they are holders are involved.

Any other pharmacovigilance information not stated above should be expressly requested by the interested party, following the procedure established for that purpose.

f) Notify the European Medicines Agency and the Member States immediately and in no case later than fifteen calendar days following their receipt, the reports on suspected serious adverse reactions occurring in Spain.

This should be made through the data processing network established by the European Medicines Agency in collaboration with the Member States and the European Commission.

g) Promote the creation of computerized health databases to be used as a source of information in order to conduct pharmacoepidemiological studies with the participation of the health authorities of the Autonomous Communities and healthcare professionals.

h) Promote and perform the pharmacoepidemiological studies necessary to evaluate the safety of authorized medicinal products.

i) Evaluate the information received from the Spanish Pharmacovigilance System, as well as from other sources of information. Specially, the Agency shall evaluate the information from periodic safety update reports, risk management plans and post-authorization studies that have implications for the safety of medicinal products.

j) Establish appropriate measures for the management of identified risks, including the necessary education and information, with the aim of minimizing or preventing these risks.

k) Ensure public access to the information sent by marketing authorization holders or any other entity or person that is considered especially relevant for the protection of public health.

l) Establish, in collaboration with the Autonomous Communities, the pertinent inspection procedures in order to ensure compliance with the obligations of marketing authorization holders indicated in Article 8.

m) Any other duty that may be necessary within the scope of pharmacovigilance and that must be fulfilled by the Spanish Agency of Medicines and Medical Devices.

2. The Spanish Agency of Medicines and Medical Devices shall ensure, within the area of its responsibilities, the necessary means to carry out pharmacovigilance and risk

management, as well as the independent conduct of whatever studies may be necessary to evaluate the safety of medicinal products.

Article 6. Participation of the Autonomous Communities in the Spanish Pharmacovigilance System for medicinal products for human use.

1. The Spontaneous Reporting Programs that shall be developed permanently and continuously by the Autonomous Communities shall be accordance with the Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System for medicinal products for human use which shall be published by the Ministry of Health and Consumer Affairs.

2. The Autonomous Communities shall record suspected serious adverse reactions in the database of the Spanish Pharmacovigilance System within 10 calendar days from receipt of the information.

The Spanish Agency of Medicines and Medical Devices may require the health authorities of the Autonomous Communities to provide the information required to evaluate the safety of medicinal products.

3. The Autonomous Communities shall cooperate with the Spanish Agency of Medicines and Medical Devices on the implementation and development of programs and studies about the evaluation and management of risks of medicinal products, in accordance with the agreements made by the Committee on Safety of Medicinal Products for Human Use and the Technical Committee of the Spanish Pharmacovigilance System for medicinal products for human use.

4. The Autonomous Communities shall cooperate with the Spanish Agency of Medicines and Medical Devices on the dissemination of knowledge relating to the safety of medicinal products in the healthcare setting.

Article 7. Obligations of healthcare professionals.

Physicians, pharmacists, dentists, nurses and other healthcare professionals have the obligation:

a) Report suspected adverse reactions of authorized medicinal products, including those of medicinal products used under conditions different from those under which they were granted marketing authorization and medicinal products not marketed in Spain, but whose importation was authorized in accordance with Article 24.4 of Law 29/2006 of 26 July. These reports shall be sent as soon as possible to the body in charge of pharmacovigilance in the relevant Autonomous Community through the suspected adverse reaction reporting form (“yellow card”).

Priority shall be given to reports of serious or unexpected adverse reactions to any medicinal product and those related to new medicinal products identified by the yellow triangle described in Article 8.2.

When suspected adverse reactions are the result of a medication error according to the definition given in article 2.ñ), reporting may be made by the special procedures that shall be agreed by the Technical Committee of the Spanish Pharmacovigilance System

and included in the document “Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System for Medicinal Products for Human Use”.

- b) Keep the clinical documentation on suspected adverse reactions to medicinal products in order to complete or perform the follow-up, if necessary.
- c) Cooperate with the Spanish Pharmacovigilance System for medicinal products for human use, providing the necessary information that they request to identify, characterize or quantify adverse reactions or to extend or complete the information on reported adverse reactions.
- d) Keep informed on the safety data relating to medicinal products commonly prescribed, supplied or administered, and implement in their care area the risk prevention measures set out in the summary of product characteristics of the medicinal product, including measures to inform and educate patients.
- e) Collaborate with risk management plans, in particular for medicinal products classified as requiring special medical control.
- f) Collaborate with the qualified person responsible for pharmacovigilance of marketing authorization holders in the event of a suspected adverse reaction to one of their medicinal products, providing the information required for subsequent reporting to the Spanish Pharmacovigilance System.
- g) Collaborate as experts with the Spanish Agency of Medicines and Medical Devices and the competent bodies of the Autonomous Communities in the evaluation of safety problems of medicinal products for human use.

CHAPTER III

On marketing authorization holders

Article 8. *Obligations of the marketing authorization holder.*

1. The marketing authorization holder, in accordance with the “Good Pharmacovigilance Practices for Medicinal Products for Human Use for the Pharmaceutical Industry”, published by the Ministry of Health and Consumer Affairs, shall:

- a) Maintain detailed records of all suspected adverse reactions occurring in Spain or in the European Union or a third country. Save in exceptional circumstances, such as technical impossibility, individual cases safety reports on suspected adverse reactions meeting the criteria specified in paragraphs b) to g) shall be communicated electronically in accordance with the guidelines published in Volume 9A of the Rules Governing Medicinal Products in the European Union. In accordance with these guidelines, marketing authorization holders shall use internationally agreed medical terminology.
- b) Record and report suspected serious adverse reactions occurring in Spain to the body in charge of pharmacovigilance in the Autonomous Community where the healthcare professional reporting the case practices. This report must be made immediately and in

no case later than 15 calendar days following the receipt of the information. Report suspected adverse reactions of authorized medicinal products, including both those of medicinal products used under conditions different from those under which they were granted marketing authorization and medicinal products not marketed in Spain, but whose importation was authorized in accordance with Article 24.4 of Law 29/2006 of 26 July. Report also any other suspected serious adverse reaction occurring in Spain of which they can reasonably be expected to have knowledge.

If the report is submitted on paper, it should use any of the official languages of the respective Autonomous Community.

When the report is submitted in the standard European electronic format, it should be transmitted directly via the data processing network of the Spanish Pharmacovigilance System for medicinal products for human use specified in Article 5.1.b) according to European Union standards, including a case narrative, which should be provided in the official language of the State and include a translation into the English language. The Spanish Agency of Medicines and Medical Devices shall publish at the appropriate time the guidelines to be followed with regard to electronic reporting.

When suspected adverse reactions are the result of a medication error according to the definition given in article 2.ñ), reporting may be made by the special procedures that shall be agreed by the Technical Committee of the Spanish Pharmacovigilance System and included in the document “Good Pharmacovigilance Practices for Medicinal Products for Human Use for the Pharmaceutical Industry”.

c) Ensure that all suspected serious unexpected adverse reactions to medicinal products authorized in Spain occurring outside of the European Economic Area and which are brought to his attention by a healthcare professional are reported immediately to the Spanish Agency of Medicines and Medical Devices and in no case later than 15 calendar days following the receipt of the information. When the reports included in this section are submitted in the standard European electronic format, they shall be considered as having been notified to Spain, if they are sent to the database of the European Medicines Agency, and specific notification to Spain shall not be necessary.

d) Perform a follow-up of worldwide scientific literature in order to identify the published cases of adverse reactions in which are reasonable suspicions that the causal agent is an active ingredient of a medicinal product for which he is the marketing authorization holder in Spain. These cases shall be reported in accordance with the criteria specified in paragraphs b) y c).

e) Ensure that all suspected serious adverse reactions occurring during a post-authorization study of which he can reasonably be expected to have knowledge are reported using the criteria specified in paragraphs b) and c) in accordance with the criteria established in the guidelines contained in Volume 9A of the Rules Governing Medicinal Products in the European Union.

f) When advanced therapy medicinal products are involved, reporting of the suspected adverse reactions shall be done in accordance with the criteria specified in paragraphs b) and c). However, when the suspected adverse reaction involves transmission of a disease or other problem either because of contamination during the process or because

it was already contained in the tissue or cellular group, the marketing authorization holder shall ensure that the reaction is reported within no later than 48 hours, indicating in the report the unique European identifying code of the donation laid down in Royal Decree 1301/2006 of 10 November, establishing the rules of quality and safety for the donation, obtaining, assessment, processing, preservation, storage and distribution of human tissues and cells and approving the rules of coordination and functioning for human use.

g) In the case of medicinal products where the Reference Member State is Spain, which have been authorized by the mutual recognition or decentralized procedure, or which have been the object of a Community decision, ensure that all suspected serious adverse reactions occurring outside of Spain but within European Union territory are reported in the format and at intervals to be indicated by the Spanish Agency of Medicines and Medical Devices, for analysis and follow-up of these adverse reactions for all the European Union. When the reports included in this section are submitted in the standard European electronic format, they shall be considered as having been notified to Spain, if they are sent to the database of the European Medicines Agency or the competent authority of the corresponding Member State if it occurs within the European Union, and specific notification to Spain shall not be necessary.

h) Submit to the Spanish Agency of Medicines and Medical Devices the records of all suspected adverse reactions in the form of a periodic safety update report as indicated in the guidelines included in Volume 9A of the Rules Governing Medicinal Products in the European Union.

This should be done immediately upon request of the Spanish Agency of Medicines and Medical Devices or periodically according to the following periods, unless other requirements have been laid down as a condition of the granting of the marketing authorization for the medicinal product.

The time period for the presentation of such reports shall be every six months from authorization until marketing. Once marketed, they shall be submitted every six months for the first two years after initial marketing in any country of the European Union and annually for the subsequent two years. Thereafter, the periodic safety update reports shall be submitted at three-yearly intervals. These periods shall be applicable to all medicinal products regardless of their date of authorization.

The marketing authorization holder may request the amendment of the periods referred to above either at the time of submission of the application for marketing authorization or following the granting of the marketing authorization in accordance with the procedure laid down in the regulation governing the evaluation, registration, authorization and dispensing conditions for medicinal products for human use manufactured industrially.

The circumstances under which it is required to restart the periodicity of submission of periodic safety update reports are described in Volume 9A. If in these circumstances the holder considers that it is not necessary to restart the periodicity of periodic safety update reports, he should request an exemption at the time of submission of marketing authorization or following the granting of the marketing authorization in accordance with the procedure laid down in the regulation governing the evaluation, registration,

authorization and dispensing conditions for medicinal products for human use manufactured industrially. In any case, restarting of periodicity shall be mandatory when an indication for pediatric use is added to a medicinal product that did not have this indication.

The marketing authorization holder shall follow the instructions in Volume 9A regarding the submission of the periodic safety update report for renewal of the marketing authorization.

i) Perform post-authorization studies to generate additional information on the characteristics of use of the medicinal products, to confirm, quantify or characterize potential risks, or to provide new scientific information on the risk-benefit balance of medicinal products authorized in Spain.

j) Perform a continuous evaluation of the risk-benefit balance of the medicinal products authorized in Spain and immediately inform the Spanish Agency of Medicines and Medical Devices of any new information which might influence the overall risk-benefit evaluation or require a change in the summary of product characteristics and/or package leaflet.

The marketing authorization holder should 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.

k) Provide a report on the risk-benefit balance upon request by the Spanish Agency of Medicines and Medical Devices.

l) Carry out the pharmacovigilance and risk management plans established for each medicinal product, including the studies judged necessary by the competent authorities to assess its safety or to evaluate the effectiveness of risk minimization measures.

m) Not to communicate to the public information relating to pharmacovigilance concerns in relation to its authorized medicinal product without giving at least 24 hours prior notification to the Spanish Agency of Medicines and Medical Devices. The marketing authorization holder shall ensure that the information is presented objectively and is not misleading, and without omitting relevant safety information. Failure to notify the Agency or disseminating the information without respecting the terms established in this section shall be considered as noncompliance with the pharmacovigilance obligation established in Article 101.2.b. 14) of Law 29/2006, of 26 July. The Agency shall take the necessary measures to ensure compliance with this obligation.

n) Carry out in Spain the regulatory measures adopted for safety reasons for the medicinal products of which it is the marketing authorization holder, as well as all the measures and studies included in the risk management plan that are planned to be carried out in Spain.

ñ) Establish appropriate procedures to ensure that sales representatives comply with the obligation to notify them of all information relating to the use of the medicinal products

they are in charge of promoting, indicating especially the adverse reactions reported to them by the persons visited.

2. For medicinal products containing active ingredients not previously authorized in Spain, the marketing authorization holder shall be required to include the pictogram shown in the appendix in all catalogs, promotional materials and any other type of material for dissemination to healthcare professionals during the first five years after their authorization. For medicinal products with previously authorized active ingredients, the pictogram shall appear for the first five years from the granting of the authorization of the first medicinal product containing them.

When significant changes are introduced that may affect the safety profile of the medicinal product, such as new routes of administration, new combinations, new indications for populations other than the usual ones, or any others based on a reasoned decision of the Spanish Agency of Medicines and Medical Devices, a longer period may be established.

3. This article shall not apply to marketing authorization holders of homeopathic medicinal products registered by the special simplified procedure, except for the obligations contained in paragraphs j) y k) of section 1.

Article 9. *Qualified person for pharmacovigilance.*

1. The marketing authorization holder of a medicinal product for human use must have in Spain permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance. The marketing authorization holder shall notify the Spanish Agency of Medicines and Medical Devices and the bodies in charge of pharmacovigilance in the Autonomous Community where it is located, the name of this qualified person. The Spanish Agency of Medicines and Medical Devices shall keep a record of these qualified persons.

2. The qualified person for pharmacovigilance will fulfill the following duties:

a) Create and maintain a system to collect, treat and assess the information about all suspected adverse reactions notified of company staff and sales representatives, so that it is accessible at least at one point in the European Union.

b) Prepare and submit to the Spanish Agency of Medicines and Medical Devices the periodic safety update reports referred to in Article 8.1.h).

c) Ensure that any request from the Spanish Agency of Medicines and Medical Devices for additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned.

d) Provide the Spanish Agency of Medicines and Medical Devices with any other information of interest for the evaluation of the benefits and risks afforded by a medicinal product, including information about post-authorization safety studies.

e) Ensure the necessary mechanisms to carry out in Spain the regulatory measures adopted for safety reasons for the medicinal products whose pharmacovigilance is his responsibility, as well as all measures and studies included in the risk management plan that are planned to be carried out in Spain.

f) Act as the contact person for pharmacovigilance inspections carried out in Spain.

3. The previous paragraphs shall not apply to marketing authorization holders of homeopathic medicinal products registered by the special simplified procedure.

Article 10. Information provided by the marketing authorization holder for safety reasons.

1. The marketing authorization holder is required to disseminate among healthcare professionals the updated summary of product characteristics of the medicinal product, along with the information established in Article 15.2 of Law 29/2006 of 26 July. It shall also submit to the health administrations the summary of product characteristics authorized by the Spanish Agency of Medicines and Medical Devices.

2. When in the judgment of either the marketing authorization holder or the Spanish Agency of Medicines and Medical Devices it is considered necessary for the former to inform healthcare professionals about new data relating to the safety of the medicinal product or risk prevention, and it is decided to send an individual letter to each healthcare professional concerned, the text and where appropriate any supplementary material as well as the timetable for sending the text and the type of healthcare professional addressed should be previously agreed with the Spanish Agency of Medicines and Medical Devices. In all cases, a marking should be included on the envelope indicating the nature of the information it contains.

CHAPTER IV

On administrative intervention

Article 11. Advisory committee and participation of experts in the evaluation of the safety of medicinal products.

1. As established in Royal Decree 520/1999 of 26 March approving the Charter of the Spanish Agency of Medicines and Medical Devices, the Committee on Safety of Medicinal Products for Human Use shall advise in pharmacovigilance matters and its composition shall be made public.

2. The Spanish Agency of Medicines and Medical Devices may request advice from experts in medicinal product safety and in other medical and scientific areas, including the experts from the Spanish Pharmacovigilance System for medicinal products for human use designated by the competent bodies of each Autonomous Community.

These experts may evaluate specific safety problems, post-authorization studies, periodic safety update reports, risk management plans and applications for changes in the summary of product characteristics.

Article 12. Variation of the marketing authorization for pharmacovigilance reasons.

1. In accordance with Article 17.9 of Law 29/2006 of 26 July, when the holder of a marketing authorization of a medicinal product is acquainted with new relevant information affecting the safety of this medicinal product, including its knowledge through a circular or individualized notification from the Spanish Agency of Medicines and Medical Devices, he shall update without delay the authorization and application dossier by means of the procedures of variations of the terms of a marketing authorization for medicinal products for human use. Noncompliance with this obligation may be grounds for suspension or revocation of the authorization. This variation shall be subject to payment of the corresponding fees.

2. The Spanish Agency of Medicines and Medical Devices, for reasons of public interest, health defense or the safety of individuals based on evaluation of pharmacovigilance data, may restrict the terms of an authorization for a medicinal product and establish some of the reservations or restrictions of its scope of use that are listed below, as defined in the regulation governing the authorization, registration and dispensing conditions of medicinal products for human use manufactured industrially:

a) Medicinal products for hospital use (H).

b) Medicinal products for hospital diagnosis or prescription by certain specialists (DH).

c) Medicinal products under special medical control (ECM).

Article 13. Suspension or revocation of the marketing authorization for pharmacovigilance reasons.

1. The Spanish Agency of Medicines and Medical Devices, on the basis of the evaluation of the pharmacovigilance data, may temporarily suspend or permanently revoke the authorization for a medicinal product when:

a) It has an unfavorable risk-benefit balance under normal conditions of use.

b) For any reason, it involves a foreseeable risk for the health or safety of individuals.

c) It fails to comply with pharmacovigilance regulations, in accordance with the provisions of Article 22.1.d) of Law 29/2006 of 26 July.

d) It has so been agreed by the European Medicines Agency.

2. For reasons of public health and until the suspension or revocation procedure is settled, a precautionary suspension may be imposed on marketing by a reasoned resolution. In these cases, the interested party shall withdraw the product from the market at his expense, without prejudice to action taken by the Spanish Agency of Medicines and Medical Devices when the urgency of the case demands it. The expenses incurred by these measures shall be paid by the interested party, without this being a penalty in any case.

Article 14. Evaluation and procedure for cases that may lead to a suspension or revocation of the marketing authorization or significant variation of authorized conditions of use.

1. When for pharmacovigilance reasons, the Spanish Agency of Medicines and Medical Devices considers that any of the circumstances foreseen in Articles 12.2 and 13 are present as grounds for a significant variation of authorized conditions of use or for revocation or suspension of the authorization, respectively, the following actions shall be taken:

a) The Agency shall request from the marketing authorization holder a report evaluating the safety problem detected and, if appropriate, the risk-benefit balance of the medicinal products for the conditions of use authorized in Spain, including proposed reasons for reducing the risk. This report shall be consistent with the structure and issues specified in the request of the Spanish Agency of Medicines and Medical Devices. The report should be submitted within no later than 60 days from the receipt of the request, unless a shorter period is established by the Agency due to the urgency of the problem, or in exceptional cases and at the request of the marketing authorization holder, a longer period is agreed with the Agency.

b) Based on the report, the Spanish Agency of Medicines and Medical Devices shall draw up an assessment report on the safety problem.

c) If based on the previous report, the Agency determines that there is a need for suspension or revocation of the authorization or for a significant variation of the conditions of use for safety reasons, the corresponding procedure shall be automatically initiated. In all cases that may result in suspension or revocation of the marketing authorization, the Committee on Safety of Medicinal Products for Human Use shall issue a non-binding but mandatory opinion.

In specific cases where the interests of the European Union are involved, the Spanish Agency of Medicines and Medical Devices or the marketing authorization holder may submit the matter to the Committee for Medicinal Products for Human Use of the European Medicines Agency for the adoption of a Community decision.

d) After hearing the interested party, the Spanish Agency of Medicines and Medical Devices shall issue a decision specifying the applicable appeals and notify it to the interested party. This procedure shall be resolved and notified within a maximum of six months, without prejudice to interruption of the period for issuing of the report by the Committee on Safety of Medicinal Products for Human Use, and by the Committee of Medicinal Products for Human Use of the European Medicines Agency in cases where the interests of the European Union are involved, in accordance with Article 83.3 of Law 30/1992 of 26 November, on the Legal Regime of the Public Administrations and Common Administrative Procedure.

2. In the case of the procedure for variation of the authorization, the decision shall note the changes to be made in the summary of product characteristics, package leaflet, labeling and scope of use of the medicinal product, and also other measures aimed at reducing the risk or informing healthcare professionals and users.

In accordance with these indications, the marketing authorization holder shall apply for the appropriate variation to the terms of the marketing authorization of the medicinal product according to the procedures laid down in the regulation governing the

evaluation, registration, authorization and dispensing conditions for medicinal products for human use manufactured industrially.

3. The procedure laid down above shall not apply to medicinal products authorized by the centralized procedure established in Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products and establishing a European Medicines Agency, which shall be governed by their specific regulations.

Article 15. *Urgent variations for safety reasons and applicable procedure.*

1. When new information is received indicating a serious risk for public health associated with use of the medicinal product or a significant impact on the safety of the medicinal product, the Spanish Agency of Medicines and Medical Devices may decide a provisional and urgent change to the medicinal product information concerning particularly one of the following sections of the summary of product characteristics: indications, posology, contraindications, or warnings and special precautions for use.

2. When the marketing authorization holder considers necessary an urgent change to the terms of authorization of a medicinal product for safety reasons, he shall request this change to the Spanish Agency of Medicines and Medical Devices, accompanied by the following documents:

- a) Report on the risks detected that make the change necessary.
- b) Proposed change to summary of product characteristics and package leaflet.
- c) Proposed information to healthcare professionals and to patients/consumers where appropriate.
- d) Proposed complementary actions, as well as any other information considered necessary for effective application of the change.

If the Spanish Agency of Medicines and Medical Devices has not raised any objection within 24 hours following receipt of the information, the urgent changes for safety reasons shall be deemed to have been accepted provisionally. The holder of the marketing authorization shall submit an application for the change in the summary of product characteristics not later than 15 calendar days after the date of acceptance. The Spanish Agency of Medicines and Medical Devices shall establish the specific procedures to be followed.

3. When the urgent safety restriction is imposed on the holder by the Spanish Agency of Medicines and Medical Devices, the holder shall be obliged to submit an application for a variation in the terms set out by the Agency immediately and in no case later than 15 calendar days after receipt of the notification from the Agency.

4. In the circumstances specified in paragraphs 2 and 3 above, the timeframe and terms of the information addressed to healthcare professionals, as well as effective application of the variation by the holder, including the changes in the packaging materials, shall be agreed with the Spanish Agency of Medicines and Medical Devices.

5. In the case of products authorized via the mutual recognition or decentralized procedure, the harmonization mechanisms established for this purpose in the European Union shall be taken into account through the corresponding guidelines. In the case of centrally authorized medicinal products, the procedure to be followed shall be that provided for in Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to terms of a marketing authorization for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State, and the guidelines developing it.

Article 16. Communications and precautionary measures.

1. If the Spanish Agency of Medicines and Medical Devices, on the basis of the pharmacovigilance data, considers that a marketing authorization must be subject to suspension, revocation or variation involving a significant restriction in use of the medicinal product, it shall immediately notify the Autonomous Communities, the European Medicines Agency, the other Member States and the marketing authorization holder.

2. In cases where urgent action to protect public health is considered essential, the Spanish Agency of Medicines and Medical Devices may suspend the marketing authorization of a medicinal product informing the health administrations of the Autonomous Communities, the European Commission, the European Medicines Agency, the other Member States and the marketing authorization holder at the latest one working day after the suspension.

3. The decisions concerning the suspension, revocation or a significant change to the marketing authorization that may affect public health in third countries shall be made known to the World Health Organization.

Article 17. Variation, suspension and revocation of marketing authorization of medicinal products authorized by the mutual recognition and decentralized procedures.

1. Without prejudice to the provisions of Article 14, when the Spanish Agency of Medicines and Medical Devices, according to the evaluation of the pharmacovigilance data, considers necessary for public health reasons to vary, suspend or revoke the marketing authorization or medicinal products authorized by the mutual recognition or decentralized procedures, it must submit the matter to the Committee for Medicinal Products for Human Use of the European Medicines Agency for the adoption of a Community decision.

2. After the Community decision is notified, with no more procedures than hearing the interested party, the Spanish Agency of Medicines and Medical Devices shall adopt and notify the appropriate decision, indicating the applicable appeals, within 30 days from notification of the Community decision.

3. In cases where a precautionary suspension of the medicinal product is justified, the provision of Article 16.2 shall be applied, and the reasons for the suspension shall be notified at the latest one working day after adoption of the measure to the health administrations of the Autonomous Communities, the European Commission, the

European Medicines Agency, the other Member States and the marketing authorization holder .

Article 18. *Communication to Autonomous Communities, healthcare professionals and the public.*

1. The Spanish Agency of Medicines and Medical Devices shall inform the Autonomous Communities and other responsible bodies of the adoption of the measures provided for in this Chapter that have relevance for public health.

2. The Spanish Agency of Medicines and Medical Devices and the Autonomous Communities shall provide healthcare professionals and the general public, in an appropriate fashion, with information about the risks of medicinal products.

CHAPTER V

On post-authorization studies

Article 19. *Applicable system.*

1. Post-authorization studies should be aimed to complement the information obtained during clinical development of the medicinal products prior to authorization. The planning, conducting of financing of post-authorization studies, with the purpose to promote the prescription of medicinal products is forbidden.

2. The health administrations shall establish by mutual agreement the conditions under which post-authorization observational studies should be conducted with the aim of favoring those studies which can contribute to the knowledge of the medicinal product or improve clinical practice. The Spanish Agency of Medicines and Medical Devices shall coordinate the actions carried out in this area and shall create the Coordinating Committee for Post-Authorization Studies with the participation of representative from all Autonomous Communities and the Agency, where the guidelines on the common procedures to be implemented by each community in their territory shall be discussed. The functioning of this Committee shall be governed by the regulations provided in Law 30/1992 of 26 November on the Legal System of the Public Administrations and Common Administrative Procedure for government bodies.

3. The Spanish Agency of Medicines and Medical Devices shall keep a record of all proposals of post-authorization observational studies, which shall be accessible to the competent bodies of the Autonomous Communities, and shall inform each sponsor about the procedures to be followed in each case. For this purpose, the study sponsor must send the study protocol to the Spanish Agency of Medicines and Medical Devices.

4. When the post-authorization study, in accordance with the provisions of Article 58 of Law 29/2006 of 26 July, is a clinical trial and not an observational study, it shall not be subject to the provisions of this Chapter, but to those of Royal Decree 223/2004 of 6 February regulating clinical trials with medicinal products for human use.

5. When the conduct of a post-authorization observational study is a condition established at the time of authorization of a medicinal product, or is required by the competent authority to clarify issues concerning the safety of the medicinal product, or

is part of the risk management plan which should be carried out by the holder, the holder shall only require authorization from the Spanish Agency of Medicines and Medical Devices according to the procedures set out for this purpose. The Spanish Agency of Medicines and Medical Devices shall notify these studies to the Autonomous Communities where they are to be conducted and shall include them in the record referred to in paragraph 3.

6. When these studies are sponsored by the health administrations or financed with public funds, simplified procedures shall be established in order to facilitate their conduct to be agreed by the Coordinating Committee for Post-Authorization Studies referred to in paragraph 2.

7. The study sponsor shall notify the Autonomous Communities where the study is to be conducted and the Spanish Agency of Medicines and Medical Devices of the effective start date of the study and shall submit annual progress and final reports as well as any relevant protocol amendments when appropriate.

8. In any case, the sponsor of a post-authorization safety study shall take into account the guidelines included in Volume 9A of the Rules Governing Medicinal Products in the European Union.

Single additional provision. *Cities with Statutes of Autonomy.*

The references made to the bodies in charge of pharmacovigilance in the Autonomous Communities shall be understood as having also been made to the cities with a statute of autonomy, with the scope foreseen in their respective statutes of autonomy and royal decrees on the transfer of public health responsibilities.

Single repealing provision. *Repeal.*

Royal Decree 711/2002 of 19 July regulating pharmacovigilance of medicinal products for human use is repealed.

First final provision. *Legislative nature.*

This Royal Decree is enacted in development of Law 29/2006 of 26 July on Guarantees and the Rational Use of Medicinal Products and Medical Devices and has the status of legislation on pharmaceutical products for the purposes foreseen in Article 149.1.16.^a of the Constitution.

Second final provision. *Power of development.*

The Minister of Health and Consumer Affairs is empowered to lay down the necessary provisions for appropriate application and development of this Royal Decree.

Third final provision. *Incorporation of European Union law.*

This Royal Decree incorporates into Spanish law paragraphs 1.i) and 72 to 76 of Article 1 of Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, amending 2001/83/EC on the Community Code relating to medicinal products for human use.

Fourth final provision. *Effective date.*

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

Done at Madrid, 11 October 2007.

JUAN CARLOS R.

The Minister of Health and Consumer Affairs,
BERNAT SORIA ESCOMS

ANNEX

Pictogram identifying medicinal products with new active ingredients

The pictogram consists of an equilateral triangle with the tip pointing upwards. It is a black triangle on yellow background.



This pictogram shall appear in a visible place, to the left of the name of the medicinal product, and at least in the heading of the information provided. It shall be of similar size to the font of the name and shall measure at least 0.5 cm on each side.