The Royal Spanish Pharmacopoeia Legal Analysis

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1. Historical background towards the creation of a supranational Pharmacopoeia.

Etymologically, the word `pharmacopoeia´ derives from the compound Greek word (*φαρμακο*, medicine, and *ποιΐα*, to do, to prepare)[1] and alludes to that written text, with legal force in a certain territory, which relates the characteristics and the form of elaboration of the medicines that contain it. There have been many denominations, with different nuances and appreciations, therefrom. However, we could include other meanings in the previous definition such as *compositiones*, *antidotarium*, *concordia*, *receptario*, etc., among others.

The doctrine is uniform among historians when they state that the first official pharmacopoeia was the so-called *Antidotarium Florentinum*, whose full name was *Nuovo receptario composto dal famosissimo Chollegio degli eximii Dottori della Arte et Medicina della ciptá di Firenze* printed in Florence in 1498. The official nature of this text, and therefore its innovative appearance, results from the fact that it was compiled ad *istatia delli Signori Consoli della univerità delli spetiali* and, moreover, it possesses the guild's seal that grants it that exclusivity, unprecedented so far[2]. That text is divided into four sections: one for the identification of simple forms, another for the identification of compounds, the way in which the most complex forms are elaborated and a final chapter dedicated to weights, measures and synonyms.[3]. On the other hand, the first Spanish Pharmacopoeia (and second worldwide after the one mentioned above)

[1] PONTES ROSALES, José. (1898). *Concept of Pharmacopoeias or Medicines Codes at the end of this century*. Speech of the Royal Academy of Medicine. Madrid: Printing Sons of José Ducazcal, p. 46.

[2] URDANG, George. (1952). "Evolución de las Farmacopeas. Repaso con referencia especial a la Pharmacopoea Internationalis." [Translation Ibero-American Healthcare Office]. *Bulletin World Health Organitation*, vol. 4, p. 545.

[3] CASTILLO GARCÍA, Benito del. (2014). *De las Farmacopeas de ayer y hoy*. Academic reception speech at the Academy of Pharmacy "Reino de Aragón". Zaragoza: Ed. Professional Association of Pharmacists of Zaragoza, p. 18.

was the so-called *Concordia Pharmacopolarum Barcinonensium*, published in Barcelona in 1511; two more editions were published in 1535 and 1587.

There are numerous texts that would fit, partially or totally, with the previous and current definition of pharmacopoeia. However, the definition transcribed by Gómez Saavedra *et als.*[4]is more specific and meticulous:

> "that text written or requested by an authority (national or regional) or by any organization with power to govern itself, which may or may not have the term pharmacopoeia engraved on its presentation, has as its mission to establish the quality standards and specifications for medicines used in a given region or country, and which has legal force, or has been accepted to harmonize professional practice, in that territory or political unit".

2. The challenge of a supranational regulation of pharmacopoeias

Both the medicine and the health and non-health professionals who intervene in its legal life[5] have a vocation aimed at globalization, since these products must contribute to all people reaching the highest degree of health[6].

This new conception of the term, from a supranational perspective, originated a definition of medicine[7] promulgated by the European regulation. That directive defined medicine, in its first article, as:

[4] GÓMEZ SAAVEDRA, I. *et als*. (2016). "History, Present and Projections of the Pharmacopoeia". *Anales de la Real Academia Nacional de Farmacia*, Vol. 82, 3, p. 283-296.

[5] The concept of legal life of the medicine has been studied by different authors. We highlight the one pointed out by BOMBILLAR SÁENZ, Francisco Miguel. (2010). *Intervención administrativa y régimen jurídico del medicamento en la Unión Europea*. Granada: Ed. Universidad de Granada. This author states that the legal life of the medicine for human use comprises: "the manufacture and importation, labeling and leaflet, classification, wholesale distribution, information, advertising and pharmacological surveillance of that product."

[6] *Constitution of the World Health Organization*. (1946). In: Basic documents. 45ª ed. Geneva: World Health Organization, pages 1-18.

[7] [European Union]. Directive 2001/83/EC on the Community code relating to medical products for human use, *Official Journal of the European Union* 28th November 2001, number 311, pp. 67-128, transposed in Spain by the Royal Legislative Decree 1/2015 of 24th July, approving the consolidated text of the Law on guarantees and rational use of medicines and medical devices, *Spanish official gazette (BOE)* of 25th July 2015, N. 177, pp. 62935 to 63030.

> "any substance or combination of substances presented as having curative or preventive properties with regard to human diseases; shall also be regarded as a medicine any substance or combination of substances which may be administered to humans in order to make a medical diagnosis or to restore, correct or modify physiological functions in a person."

With this definition of medicine, the concept was harmonized in all European States. Such fact, from a legal perspective, is of significant importance as it was a further step in the dizzying and dynamic evolution of pharmaceutical legislation. Although it is true that previously, have been remarkable facts such as the enactment of Directive 65/65/EEC which led, according to the doctrine, to the birth of the Community Pharmaceutical Law[8], which, in Bombillar's words:

> "It has sought, since its origin, to remove the remaining barriers to the free movement of medicines within the European Union and [...] to ensure the highest level of health protection for European citizens, ensuring that only those medicines that meet the minimum requirements of quality, safety and efficiency circulate within the European Union.

After that, two European Directives were enacted: Directive 75/318/EEC, on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, and Directive 75/319/EEC, on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products.

Therefore, the enactment of the above standards provided a clear progress towards the creation of a common legislation around the medicine. The figure of the "qualified person" emerged as well, as the responsible for the pharmaceutical industry, who had to possess a minimum knowledge on the medicine.

However, this harmonizing idea around the medicines could not have been carried out without the existence of a Global Pharmacopoeia or *Pharmacopoea Internationalis*[9], an European Pharmacopoeia[10] and the different initiatives enacted by

[8] *Cfr.* by BOMBILLAR SÁENZ, Francisco Miguel. (2010). *Intervención administrativa y régimen jurídico del medicamento en la Unión Europea*, *op. cit*., p.112.

[9] The Third World Health Assembly, held in May 1950, decided on the publication of the International Pharmacopoeia and, by virtue of article 23 of the WHO Constitution, recommended "the possible inclusion of its provisions in the national pharmacopoeias, once such provisions have been adopted by the competent authorities".

the Organization of the United Nations (hereinafter UN) through the World Health Organization (hereinafter WHO) related to the medicine[11]. The idea of a text, at a global level, that will house a lowest common denominator around the medicine had been raised previously[12], however, this work would only serve as a recommendation or reference and, in no case will it be the official pharmacopoeia of any country. While it is true that the UN Member States may incorporate the whole or part of its provisions in their national pharmacopoeias. To date, eight editions of the International Pharmacopoeia have been published, including a series of monographs on testing and analysis methods to comply with the quality standards applied to pharmaceutical substances. Its purpose is to serve as a guide for the establishment of control standards in the WHO Member States.

To this end, quality standards are required for pharmaceutical forms developed according to the WHO Model List of Essential Medicines. In addition, it includes monographs on the preparation of different products and the requirements for quality control, as well as the appropriate and effective techniques regarding the characterization and minimization of impurities. For this reason, this text has had significant relevance at an international level, since it has meant the harmonization of concepts, from a legal and scientific perspective, around public health.

3. The Royal Spanish Pharmacopoeia

Through the instrument of accession of Spain to the Convention on the elaboration of a European Pharmacopoeia, Spain became part to that international

[10] One of the main purposes of the European Pharmacopoeia was and is the promotion of public health through the promulgation of recognized common standards that can be used regarding safety and quality of medicines.

[11] We highlight, among others, the creation of the WHO Global Surveillance and Monitoring System for Medical Products [Resolution 16.36 formulated at the XVI World Health Assembly in 1968 and the enactment of the *Good Manufacturing Practice*. approved at the XXII World Health Assembly (*Resolution WHA* 22-50 of 1969).

[12] This idea emerged in 1865 at the 1st International Pharmaceutical Congress in Brunswick (Germany) and at subsequent international meetings and congresses (since 1912) organized by the International Pharmaceutical Federation (FIP).

convention[13]. Previously, the European states of Belgium, France, Germany, Italy, Luxembourg, the Netherlands, Switzerland and Great Britain considered the objective of progressively establish a common pharmacopoeia[14]. The main reason originating this idea was the interest of the European Council in promoting economic and social progress through the adoption of agreements, mainly in the economic, social, cultural, legal and administrative fields. For this reason, and since such harmonizing measures were necessary with regard to medicines, it was considered to progressively establish a common pharmacopoeia, of official applicability, in the mentioned nations.

The responsible bodies for the elaboration of the European Pharmacopoeia were, on the one hand, the Public Health Committee (with main functions of supervision, control and approval of proposals) and, on the other hand, a European Pharmacopoeia Commission[15] whose functions were:

- Determine the general principles relevant to the elaboration therefrom;
- Decide on methods of analysis;
- Prepare and approve the monographs to be included in the mentioned Pharmacopoeia.

At present, the ninth edition, plus eight additional supplements, of the European Pharmacopoeia, is elaborated by the European Directorate for the Quality of Medicines

[13] [Spain]. Instrument of accession of Spain to the Convention on the elaboration of a European Pharmacopoeia, *Spanish official gazette of* 3rd June 1987.

[14] *Treaty Number 50* [ETS No. 050]. *Convention on the Elaboration of a European Pharmacopoeia*. [on-line:[https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168006ff4c]. 22nd July, 1964.

[15] The elaboration of the Pharmacopoeia is the responsibility of the European Pharmacopoeia Commission, established in accordance with article 5 of the above mentioned Convention. It is composed of delegations named by the contracting parties. Each delegation shall consist of no more than three members chosen for their competence in the matters for which the Commission is responsible.
The meetings of the Commission are open to observers from non-member States and international organizations, in accordance with their rules of procedure. The observers currently admitted come from: Albania, Algeria, *[Beginning of amendment]* Argentina, Armenia, *[End of amendment]* Australia, Belarus, Brazil, Canada, China, Georgia, Israel, Kazakhstan, Madagascar, Malaysia, *[Beginning of amendment]* Moldova, *[End of amendment]*, Morocco, Russian Federation, Senegal, Syria, Tunisia, Ukraine, United States of America and the World Health Organization.
The Convention is open for signature by European countries and the observer status can be used by the European countries intending to sign the Convention to familiarize with the Commission's working methods. The Commission recognizes that relations with other non-European countries are essential due to the globalization of the pharmaceutical products supply chain. The observer status for non-European countries serves to promote these relationships by facilitating cooperation and the exchange of information and work documents.

(EDQM) under the auspices of the European Council. It is an official reference work in thirty-eight European countries and, furthermore, is estimated to be used as a reference work in around a hundred more countries. The said text contains 2406 monographs, 365 general texts and around 2730 reagents. Its purpose is to promote public health through common guidelines regarding the quality of the medicines, in order to guarantee their safe use by the patients.

The incorporation of Spain to the European Economic Community (nowadays the European Union) took place on the 1st of January 1986, when the Treaty of Accession of Spain entered into force[16]. Through the signature of this international treaty, the Republic of Portugal also became a member of the said supranational organization.

From a legal perspective, as a result of this incorporation, Spain was subjected to a series of requirements, in some cases mandatory, that originated, among others, changes in their enacted regulations thanks to the legal mechanisms pre-established, as it is the case of the European Pharmacopoeia.

In this case, the Official Pharmacopoeia in Spain when it fully fledged joined the European Economic Community, was the Spanish Official Pharmacopoeia in tis ninth edition, in force since 1954[17] and published by the Academy of Medicine. It was an outdated text for that time, that did not contain most of the medicines that were present in the market. Such was its obsolescence that the Spanish Socialists Workers Group presented a motion[18] in the Congress of Deputies, affirming that the said text:

> "The 75 per cent, at least, of the ingredients contained in the most used Spanish medicines do not appear […] the Spanish Pharmacopoeia and its futility have led the Administration […] to declare that it was not mandatory in pharmacies, therefore it could be argued that, in fact, there is currently no pharmacopoeia in force in our country."

[16] Ratification instrument of the Treaty signed in Lisbon and Madrid on the 12th June 1985, regarding the accession of the Kingdom of Spain and the Republic of Portugal to the European Economic Community and to the European Atomic Energy Community, *Spanish official gazette (BOE)* of 1st January 1986, no. 1, pp. 3-687.

[17] *Spanish Pharmacopoeia* (1954). Ninth edition. Madrid: Estades, Artes Gráficas.

[18] [Spain]. Motion on the Spanish Pharmacopoeia. *Parliament official gazette (BOCG)* of 28th October 1981, no. 771-I, pp. 1967-1968.

In addition to the above, this situation led to a proposal to publish "a Spanish Pharmacopoeia updated until 1981", within a period of three months. However, the said Pharmacopoeia was in force until 1987, when the European Pharmacopoeia was established as the official pharmacopoeia, pursuant to the Convention on the Elaboration of a European Pharmacopoeia. More than four years had to pass by (since the accession of Spain to the EEC) for the enacting, in 1990, of the Law 25/1990[19], of 20th December, which focused exclusively in medicines. That standard established that the Royal Spanish Pharmacopoeia "will be composed by the particular Spanish monographs and those contained in the European Pharmacopoeia of the European Council. The International Pharmacopoeia of the WHO will have a residual character".

However, it was not until the end of 1996 that the longed for text was published. The Order of 26th December 1996 approved the Royal Spanish Pharmacopoeia (its first edition). It was a text in paper format that contained 1128 monographs (two of them were Spanish particular monographs[20] and, the rest, came from the third edition of the European Pharmacopoeia) which entered into force on the 1st January 1997. Although, its regulation described in detail its functions and the explanations of its monographs, that had already been regulated previously[21]. The competent State organization in charge of its elaboration was the Ministry of Health and Consumption, due to the exclusive competence that article 149.1.16.ª of the Spanish Constitution of 1978 assigns to the State in terms of legislation on pharmaceutical products.

Later, the first edition of the Royal Spanish Pharmacopoeia, logically, was subject to some changes due to the publication of new updates and additions in the European Pharmacopoeia[22]. The said text, a must have in every pharmacy,

[19] [Spain]. Law 25/1990, of 20th December, on medicines, *Spanish official gazette (BOE)* of 22nd December 1990, no. 306. In the fifth chapter (on the Pharmacopoeia and the quality control) appeared a definition of the Royal Spanish Pharmacopoeia.

[20] The monograph of *Meliloti herba* y *Centellae Asiaticae herba* [entered into force on the 1st July 1997].

[21] [Spain]. Royal Decree 294/1995 of 24th February, regulating the Royal Spanish Pharmacopoeia, the National Formulary and the consultative bodies of the Ministry of Health and Consumption in this matter. *Spanish official gazette (BOE)* of 12th April 1995, no. 87.

[22] [Spain]. Order of 23rd December 1997 approving the additions and updates of the Royal Spanish Pharmacopoeia, *Spanish official gazette (BOE)* of 30th December 1997, no. 312 [112 new monographs and 107 updated monographs, 10 new texts of general methods and 13 updated texts

pharmaceutical service, distribution entity and pharmaceutical lab, was replaced by the second edition of the Royal Spanish Pharmacopoeia. The reason for that change was logical, given that the first edition had been modified in so many occasions, a standardized text (and easy to consult) was needed. Then, the second edition of the Royal Spanish Pharmacopoeia was approved (which included the fourth edition of the European Pharmacopoeia completely), composed by 1605 monographs and 266 general chapters. The text was again modified in 2003[23] and in 2004[24], highlighting the careful selection of analysis instrumental methods.

Despite the institutional crisis[25] that was going on in the European Union, it did not affect, in any case, any of the tasks of the European Council regarding the European Pharmacopoeia. This way, after several updates and additions (most of them coming from the European text), in the second edition of the Royal Spanish Pharmacopoeia, it was decided to repeal this edition, in accordance with the currently repealed Law of Medicines, to approve the third edition of the Royal Spanish Pharmacopoeia[26], which was composed by 1852 monographs and 286 general texts (including monographs and

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of general methods approved], Order of 30th December 1998 approving the additions and updates of the Royal Spanish Pharmacopoeia, *Spanish official gazette (BOE)* of 31st December 1998, no. 313 [97 monographs and 9 new general chapters, in addition to 118 monographs and 14 new chapters are approved. Furthermore, by way of an urgent procedure, 8 monographs and 2 general chapters are included, and the monographs of Ethisterone and Sterile reconstituted collagen suture are eliminated], Order of 17th February 2000 approving the additions and updates of the Royal Spanish Pharmacopoeia, *Spanish official gazette (BOE)* of 24th February 2000, no. 47 [208 monographs and 42 new and updated general chapters approved, in addition to the national monograph of *Merbromin*], Order of 17th April 2001 approving the additions and updates of the Royal Spanish Pharmacopoeia, *Spanish official gazette (BOE)* of 20th April 2001, no. 103 [101 monographs and 11 new general chapters approved, 179 monographs and 12 general chapters revised, in addition to 89 monographs and 23 general chapters corrected].

[23] [Spain]. Order SCO/575/2003, of 10th March, approving the additions and updates of the Royal Spanish Pharmacopoeia, *Spanish official gazette (BOE)* of 19th March 2003, no. 67 [48 monographs and 1 new general chapter approved, 128 monographs revised and corrected and 7 general chapters revised and corrected].

[24] [Spain]. Order SCO/869/2004, of 17th March, approving the additions and updates of the Royal Spanish Pharmacopoeia, *Spanish official gazette (BOE)* of 3rd April 2004, no. 81 [71 monographs and 3 general chapters approved and 250 monographs revised and 32 new general chapters].

[25] The non-entry into force of the Treaty establishing a Constitution for Europe, signed in Rome on the 29th October 2004, due to the refusal of the French Republic and the Netherlands, was the fact that triggered this European politic institutional crisis.

[26] The said text included all the whole European Pharmacopoeia (5th edition). That edition was composed by 3230 monographs and 330 general methods.

analysis methods). The institution in charge of its publication was the Ministry of Health and Consumption.

In 2006, after enacting the Law 29/2006 of 26th July, on guarantees and rational use of medicines and healthcare products, a detailed definition of the Royal Spanish Pharmacopoeia was established, which differed in little nuance with the previous standard dedicated to medicines. Due to this significant change, in addition to the enactment of the Treaty of Lisbon[27], and the publication of the sixth edition of the European Pharmacopoeia, it was deemed necessary to elaborate a fourth edition of the Royal Spanish Pharmacopoeia[28], following the report of the Council of Consumers and Users and the National Commission of the Royal Spanish Pharmacopoeia, and after consultation with the Autonomous Communities.

The purpose of the European Pharmacopoeia[29] is to promote public health through the establishment of common and recognized standards, that healthcare professionals can use in the right circumstances, respecting the safety, quality and efficiency of medicines. This is why, especially given the wide range of new medicinal products that have emerge in recent years, that the EDQM of the European Council decided to publish the sixth edition of the European Pharmacopoeia. As a consequence, it was considered appropriate to elaborate the fifth edition of the Royal Spanish Pharmacopoeia[30], which included the European text mentioned, in addition to only one

[27] One of the main developments of the Treaty of Lisbon was the recognition of the binding nature of the Charter of Fundamental Rights signed in 2000 [*Official Journal of the European Union* C364/1 of 18th December 2000]. In this text, the "protection of health" was recognized in article 35. On this matter it is recommended to consult Cavas Martínez, F. and Sánchez Triguero, C. (2005). "La protección de la salud en la Constitución Europea", *Revista del Ministerio de Trabajo y Asuntos Sociales*, no. 57: 401-418.

[28] [Spain]. Order SPI/2891/2010, of 3rd November, approving the fourth edition of the Spanish Pharmacopoeia, *Spanish official gazette (BOE)* of 11th November 2010, no. 272.

[29] The European Pharmacopoeia is elaborated by the European Directorate for the Quality of Medicines (EDQM), which is part of the European Council, based in Strasbourg (France). The organization chart includes a scientific secretariat, a publication service, a laboratory and a reference patterns division.

[30] [Spain]. Order SSI/23/2015, of 15th January, approving the fifth edition of the Royal Spanish Pharmacopoeia and the second edition of the National Formulary, *Spanish official gazette (BOE)* of 21st January 2015, no. 18. This new edition is composed by 3246 monographs and 332 general methods. The Royal Decree 520/1999 approved the Statute of the Spanish Agency of Medicines, assigning to this autonomous organization, among other competences, the elaboration, updating and publishing of the Royal Spanish Pharmacopoeia. The last modification

Spanish monograph, with the purpose to better meet the needs and facilitate the cooperation between Member States, ensuring an effective dissemination of the quality standards. Furthermore, with the aim to achieve an international harmonization regarding medicines, it was considered appropriate to include several general chapters and monographs on excipients, harmonized from the Pharmacopoeias from the US, Japan and Europe. In order to implement this international approach, the work is done in coordination with the International Conference on Harmonization (ICH).

The harmonization approach provided by the ICH has its origin in Europe, Japan and the US, as its aim was, mainly, to regulate and harmonize the different scientific and technical methods used in the production of medicines. The said institution was created in April 1990, it consist of an agreement between the three regions mentioned to harmonize the different regional requirements regarding the specific guidelines of medicines which, along with the commitment of consolidation, has allowed an important contribution in the public health protection field at a global level[31]. That agreement, at an international scale, must head for the economization of resources in order to eliminate unnecessary barriers in the production of new medicines (keeping their guarantees regarding its quality, safety and efficiency) in order to, ultimately, protect the public health of patients.

The ICH itself has developed four sets of guidelines for specific topics, as quality, safety, efficiency and multidisciplinary processes, as the medical terminology of the ICH (MedDRA) or the Common Technical Document (CTD), that the member regulatory authorities implement.

As a conclusion we could determine that the Royal Spanish Pharmacopoeia is the code that establishes the quality that the active ingredients and excipients composing the medicines of human and veterinary use must meet[32]. The Royal Pharmacopoeia is

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was introduced with the Royal Decree 1275/2011, creating the state agency "Spanish Agency of Medicines and Healthcare Products" and approving its Statute, which expressly mention the composition and functions of the Pharmacopoeia Committee and the National Formulary.

[31] For more information visit their official *website* https://www.ich.org/home.html

[32] This is how it is defined in article 11 of the Royal Legislative Decree 1/2015, of 24th July, approving the consolidated text of the Law on guarantees and rational use of medicines and medical devices, *Spanish official gazette (BOE)* of 25th July 2015 [amended the 23rd December 2015].

composed by the monographs contained in the European Pharmacopoeia of the European Council and, in some justify cases, by the Spanish particular monographs[33].

The Royal Pharmacopoeia includes monographs, properly organized and coded, specifying the identity, purity and richness of, at least, the active ingredients and excipients, as well as the official analytic methods and general texts necessary to correctly apply the monographs. The defined specifications in the monographs are the minimum requirements that must be complied with, therefore, all raw materials presented under a scientific or common designation of the Royal Pharmacopoeia in force must comply with the specifications of the latter.

The monographs composing the Royal Spanish Pharmacopoeia indicate, for every active ingredient or excipient, the following specifications[34]:

- Nomenclature.
- Characteristics.
- Means that allow it identification.
- Testing and analytic methods that allow the quality control.
- Preparation procedures.
- Standards for the preparation and proper storage.
- Special standards of labeling.

This monographs also include the names of the impurities that can be controlled with this procedures, as long as the confidential details of the manufacturer of the substance are not revealed.

The general scheme of the Royal Spanish Pharmacopoeia is the following:

- Introduction
- General standards
- Analytic methods
- Materials and containers
- Reagents

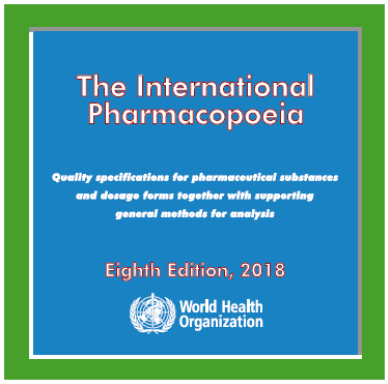
[33] The Ministry in charge of the affairs related with health can recognize the validity of certain monographs of foreign pharmacopoeias in Spain.

[34] [Spain]. OM/SSI/23/2015 of 15th January, *Spanish official gazette (BOE)* of 21st January 2015, approving the fifth edition of the Royal Spanish Pharmacopoeia and the second edition of the National Formulary.

- General monographs and texts
- Pharmaceutical forms
- Vaccines
- Antiserums
- Radiopharmaceutical preparations
- Suture threads
- Homeopathic preparations
- Plant drugs

All pharmacies, pharmaceutical services, distribution entities and pharmaceutical laboratories must have *on-line* access to the Royal Spanish Pharmacopoeia, and it must be a reference work for all public or private bodies that are related with the medicines.

9th edition of the European Pharmacopoeia



8th edition of the International Pharmacopoeia

5th edition of the Royal Spanish Pharmacopoeia