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Review Article

A Journey through the History of Drug Quality Control, from Greece to Costa Rica

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Abstract

This review describes the evolution and development of drug quality control throughout different times in history. A bibliographic research was conducted from the database JSTOR from the University of Costa Rica. This database contains information from academic journals and books from XIX to date. It covers different fields, such as anthropology, arts, biology, botany, health sciences, politics, pharmacy, history. Information was retrieved when the following words were present: pharmacy, quality, quality control, drugs, medicines, pharmacopoeia.

In ancient history India, China, Greece, Egypt, Africa and America used different medicinal plants to cure or alleviate disease. In some of these regions, methods were developed to make medicinal preparations as safe and effective as possible. In ancient Greece, the need to have a complete knowledge of drugs to carry out their proper preparation and detect adulterations was emerging. In Europe there was a constant development in the field, from books containing simple lists of preparations and medicines to more complex pharmacopoeias that included quality of the medicines. In America, the United States Pharmacopoeia (USP) first appeared in 1820. In Costa Rica, the Specialized Laboratory for Drug Analysis, actually the Laboratory for Analysis and Pharmaceutical Consulting (LAYAFA), was created in 1965, to ensure the quality and safety of medicines registered and marketed in Costa Rica.

Differences between regulations and quality standards across centuries and countries, and their impact on the commercialization of medicines, have promoted regulations to harmonize the requirements related to different activities of the processes of manufacture, registration and quality control of medicines.

Keywords: Quality Control of Medicines, Costa Rica, Pharmacy, medicines, drugs, pharmacopoeia, LAYAFA

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1. Introduction

The interest in the quality of medicines is as old as medicines themselves; since prehistoric times, mankind has had the need to search for substances that could help them to treat their ailments and diseases, as well as prevent and avoid intoxication and counteract the undesirable effects of treatments. Evidence suggests that since ancient times, in various regions such as India, China, Greece, Egypt, Africa and America, observation resulted in the use of medicinal plants, then appeared the need to develop techniques and methods to use these plants in preparations that were as safe and effective as possible.(1) In fact, the word pharmacy (Ph-ar-maki), in ancient Egypt meant "that provides security". (2)

Ayurvedic medicine, practiced in India since 4000 BC, has already demonstrated the use of a large collection of medicinal plants and combinations of them to create therapeutic synergies. It had methods that sought to guarantee the quality of the preparations through rudimentary processes of purification and characterization of their effects, according to the most appropriate preparation, such as decoctions, cold or hot infusions, powders, liquid extracts, resins, balms and oils, among others. Besides, they had relevant information regarding the administration, safety and adverse reactions of these preparations described in the texts of Ayurveda medicine. Currently, this wide knowledge has been compiled in the Ayurvedic Pharmacopoeia of India, which includes official monographs of a great number of combinations of medicinal plants in order to enhance the pharmacological activity and minimize their adverse effects. (1-3)

In China, the practice of medicine and pharmacy evolved significantly from the hand of its first emperors Yu Siung and Shen Nung, the former describing the origin of diseases and the latter treating them. Yu Siung wrote The Canon, the basis of all Chinese medical literature. (4) Shen Nung (3000-2200 BC), considered the founder of pharmacy and Chinese medicine, is credited with the discovery of tea, a plant he used as an antidote to the poisoning of various plant species and the writing of Pen Tsao, the Great Chinese Herbarium or Chinese Medical Matter, considered by some as one of the first herbal pharmacopoeias. (5) This book contained information on 365 drugs, subdivided according to their toxicity; among them were ephedra, cinnamon, rhubarb, cannabis, ginseng, ephedra and ginkgo. With the passage of time, Chinese medicine was influenced by Lao Tse and Confucius which, coupled with interaction with other cultures such as Arabic, led to the development of alchemy, the ancestor of pharmaceutical science. Later, in the 7th century, several books on the cultivation and use of plants appeared and during the Tang Dynasty several official herbal pharmacopoeias emerged, (4) in which the use of different plants was documented and recorded.

The Egyptians collected in various papyri such as those of Ebers, Kahun, Ramesseum, Hearst (1550 BC) and Chester Beatty (1300 BC) (6) description of gastrointestinal and parasitic diseases, eye diseases; treatment of dermatological disorders and description of contraceptive methods, among others. (7) The Ebers Papyrus is one of the oldest medical texts (1500 BC), these documents included 811 prescriptions and the classification of 700 drugs of mineral, vegetable and animal origin, such as cassia, which they used for the treatment of diarrhea and internal bleeding; aloe vera for skin conditions, which is still used today (8); the use of laudanum and castor oil for the treatment of eye diseases; belladonna atropa for the relief of pain and fever; and a combination of honey and acacia seeds for contraception. (5,7,9) Also, they described the conservation of drugs, the proper storage of medicinal substances (5) and the preparation of formulas by a "Chief Pharmacist". (6)

The objective of this review is to describe the evolution and development of drug quality control throughout different times in history, from Greece to Costa Rica.

2. Results

Greek and Arabic contributions to drug quality control

In Greece, the influence of Egyptians, Indians and other cultures led to the study of diseases and their treatment, and they were said to be interested in separating the two. In the second century A.D., Greek and Roman medicine were complemented by the contributions of Hippocrates, Dioscorides and Galen. It was at this time that three of the oldest pharmaceutical forms of humanity appeared: the Hiera Picra, the Triaca and the Terra Sigillata, which is the first medicine with a "registered trademark"; they were clay tablets used as astringents and antidotes. (5)

Teofrasto (300 BC), "father of botany", in his book Historia Plantarum made the first classification of plants based on their therapeutic properties, which included their description, forms of preparation and uses.(4-5,10) In this book the first reference is made to the use of opium or poppy juice. He also wrote the Causis Plantarum, which mentions the appropriate ways to obtain the different substances from plants. (11)

Dioscorides (40-90 AD), a Greek physician, pharmacologist, botanist and philosopher, considered an excellent pharmacognosist, warned of the danger of adulteration; he also explained and suggested methods for the identification, collection and classification of plants and established detailed rules for the storage of various types of drugs. (5) He wrote the book "De Materia Medica" between the years 60-78 AD, a document about botany and pharmacology that includes 500 plants and 72 preparations or substances of plant, animal or mineral origin; 4740 medical uses; 61 animal species, among other aspects. It is considered the "widest pharmaceutical guide of antiquity", (4-5) included medicinal uses, side effects, posology, methods of detecting adulteration of the preparation, veterinary uses, non-medical uses, conditions of preservation and storage, potential toxicity and the explanation of the use of bain-marie or distillation to make medicinal preparations.(11-12)

Galen (130-200 AD), a doctor who followed the Hippocratic humoral doctrine and the father of polypharmacy, received his patients in the "Apoteca", a room in which he prepared, dispensed and stored the magisterial preparations he had made (5); he believed that it was imperative to have a thorough knowledge of drugs in order to know their correct preparation and whether or not they were adulterated. He wrote Methodo Medendi in which he names the properties of the drugs and possible combinations according to the location of the disease and made a classification of the drugs according to their pharmacological properties. (13) The phrase "galenic of the medicines" is attributed to his legacy and currently refers to the active ingredients and excipients contained in the medicines. He was the last doctor to be recognized by Christians, Jews and Arabs. (4)

Arab medicine and pharmacy have been recognized for having collected some of the eastern and western wisdom on diseases and medicines. They improved it, systematized it, practiced and taught it in their hospitals, always located next to the mosques. (4)

Cosmas and Damian (200-303 AD), twins born in Arabia, (14) studied medicine in Syria and were known for the unique symbiosis that they formed during their lifetime between medicine and pharmacy. Their names have a Greek origin: Cosmas came from Kosmas which meant "beautiful, ordered"; while Damian came from Damyan which meant "tamer". (15) They practiced their profession in Aegean and Cilicia; Cosmas practiced medicine, while his brother Damian made preparations for the treatment of his patients' ailments, (5) totally free and altruistic. One of his great miracles was the transplant of a black Ethiopian's leg to the guardian of a

church suffering from gangrene. (16-17) Because of their condition as Christians they were persecuted by the governor of Cilicia, Lysias, in the time of the Roman Emperor Diocletian, tortured and finally beheaded for their religious beliefs. They were considered the best and most miraculous saints of ancient times. (16) Currently, the following are considered patron saints of general practitioners, medical surgeons, and especially pharmacists. (17) They are always represented along with their attributes, containers for medicines, medical, pharmaceutical, surgical and barbering instruments. Their religious festivity is celebrated on September 26th every year. (14)

Figure 1. Leg transplant by Cosme and Damian (14)

Before the fourth century, the Arab world expanded through Greece, Syria, Persia, Alexandria, absorbing the knowledge of those cultures. The Caliphs built academies, mosques and schools in each of the cities they conquered. They translated and disseminated works of authors such as: Hippocrates, Dioscorides, Aristotle, Galen, among others. With this, they also achieved progress in mathematics, alchemy and astrology in addition to pharmacy. Around the years 600 to 700 A.D., the first private commercial establishments dedicated to the preparation and trade of drugs appeared in Baghdad. For the first time in written history, the pharmacy profession has a definitive place as part of a public health system. (5)

In the ninth century, "The House of Wisdom" was built where the knowledge of the world was collected and translated; a hospital and a pharmacy were built next to it.(13) In this same century, Serapion the Elder, made a treaty on medicinal substances from Greece and Arabia, which specified the form of preparation of medicines with these substances, as well as their conservation and possible falsifications. (13)

Muhammad ibn Zakariya al-Razi (Rhaces) (854-925 A.D.) contributed to the pharmacy by developing a series of laboratory supplies such as: mortars, bottles, spatulas and vials, used in pharmacy even today. In his book "Liber medicinallis" al Almanzorem", he deals with the description of medicines and chemical compounds used in pharmacy such as iron and copper salts and mercury chloride, among others. He was the first to recommend the pills as an effective route of administration. (13)

Ibn Sahl, director of the Medical School of Djondisabur (approximately 850 AD), gave birth to the Agrabadhins. These documents were codes that described the correct elaboration of the medicines, including raw materials, formulations and doses, (18) for what are considered the ancestors of pharmacopoeias (19); During this time, it was established that official pharmaceutical formulas should be supervised by governments. During this period numerous works were written about medicines such as the Collection of Medicines and Simple Medicaments by Ibn al-Baitar which included more than a thousand references to the preparation of medicines; in addition, the famous triacs, apricots and the distillation. (18)

Ibn Sina, known as Avicenna (980-1037 AD) studied therapeutics, drugs and medicinal plants. Two of the volumes of his book "Canon medicinae" are devoted to pharmacy. He included the methods of preparation of drugs, their efficacy and the need to test their effects on animals before generalizing their use in humans; as well as the importance of dosage, route of administration and frequency of use of the drug. It also introduced gold and silver for the pills, to mask unpleasant scents and flavours. (4-5,13)

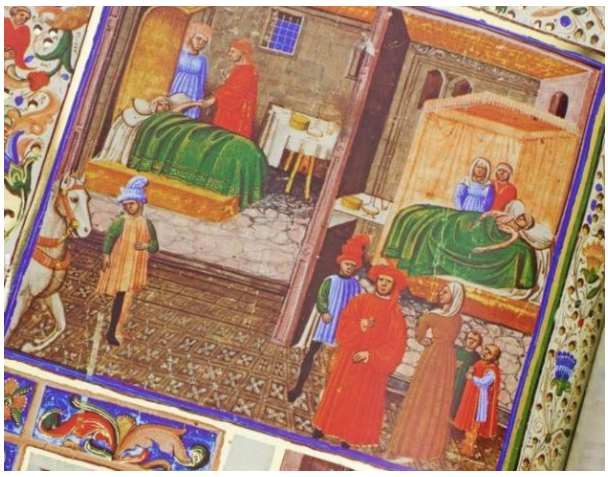


Figure 2. Canon Medicinae by Avicenna

(orbismedievalis.com/canon-medicinae-avicena)

Abu al Muna Kohen al Attar was a Hebrew pharmacist, in 1259 he wrote a Manual for Pharmacy, in which he referred to professional ethics. In his book he warned of special care in the instruments of weights and measures, in the cleanliness when making preparations and in the discarding of medicines in bad condition. (13)

During the pre-Islamic era, the figure of the Muhtasib was used to serve as the official inspector of

pharmaceutical practice, they took care of good customs, weights and measures, and to watch that the medicines were not adulterated, for this they used the hisba, Arab writings on the control of good commercial practices. The Muhtasib played a very important role in controlling the quality of medicines and in detecting possible pharmaceutical fraud. (20)

During the pre-Islamic era, the figure of the Arab science conserved the medical and pharmaceutical knowledge and contributed with its own knowledge and others from India. Although it is true, it is during the period of the Arabs in which pharmacy is separated from medicine, it is not until 1240 A.D., during the reign of the Emperor of Germany and King of Sicily Frederick II, of Hohenstaufen, Germany, that this division becomes official in Europe, when this monarch gives the profession of pharmacy the legal independence of medicine, the fact took place in a meeting of pharmacists and doctors, in his palace in Palermo. In addition, the mandatory use of a prescription form, a type of pharmacopoeia, was established in order to ensure the uniformity of drugs. (4-5,18)

3. History of the pharmaceutical industry and quality control in Europe and America

Continental Europe, now under the control of Germanic people, was under the influence of Christianity, which dispersed through the Roman Empire, when Theodosius divided his empire in two, starting the Middle Ages; during this period, the practice of medicine and pharmacy was moved to monasteries, where these knowledges were preserved while they cultivated medicinal plants. With this, the art of healing returned to priestly hands, where monks were in charge of preparing medicines and administering them to the sick. This is how monks and saints were related to medieval European medicine. (4-5)

The apothecary monks were linked to the healing of the soul and body, the use of medicinal plants, the preservation of knowledge, learning and research in the area of pharmacy, one example was St. Galls of Switzerland, who cultivated in his monastery: lily, sage, fennel, pennyroyal, mint, rosemary, and cumin among others. St. Albert the Great (1192-1280) wrote about medicinal plants. (5)

The School of Medicine of Salerno, founded around the ninth century, had a major breakthrough with the involvement of the Carthaginian Constantine the African (1015-1087), who devoted his life to translating into Latin the most important Arabic and Greek works. (4)

The connection of Arab and European medicine was made by Nicolas de Salerno and Montpellier who had great influence on the first two medical schools in Europe. Nicholas of Salerno (11th century), wrote the "Antidotarium", constituted like the book of the apothecaries and that reunited an important collection of galenic formulas; many of them Arabic. (4) Arnaldo de Vilanova (1235-1311), a physician in medieval Europe, in his search for the elixir of life, made much use of the liquor he prepared and called "acqua vitae". He extracted the active elements of the medicinal plants through alcohol, so he was the true inventor of the tinctures. (4)

With the Renaissance, absolute truths are questioned. Figures such as Theophrastus Philippus Aureolus Bombastus von Hohenhim, known as Paracelsus (1493-1541), a medical alchemist from Switzerland, who also emphasized the importance of the relationship between the dose of the drug and the route of administration, was the one who said: "Nothing is poison, everything is poison, the difference is the dose". He also generalized the use of opium in Europe and established a difference between learning based on theory (received in the universities) and practice, as did the so-called master of anatomy, Andres Vesalius (1514-1564), who established direct observation and experimentation as fundamental questions of scientific thought. (5)

A feature of the Renaissance pharmacist is that he conducted his own studies examined by courts of Promedicates, allowing him to establish pharmacy as a science, carrying out all kinds of studies and publications, constituting an important moment for the emergence of the first pharmacopoeias. With respect to the pharmaceutical literature, the most important thing of the time was the increase of the number of pharmacopoeias published in Europe. These pharmacopoeias defined the formulas that were considered definitive, which were written by doctors and followed by the pharmacists who carried out the preparation. However, during this century numerous works appeared written by pharmacists for the use of other pharmacists, such as the "Dispensarium ad aromaticus" by Nicole Prévost (Lyon, 1478 and 1488) which contained a properly pharmaceutical vocabulary and in which simple elements and 575 compounds were described. (13)

Another important work was written by Saladin di Asculi, the "Compendium Aromatarum" (Bologna, 1488) in which all possible and important aspects of the pharmaceutical profession were compiled and which came to be considered an indispensable reference work for pharmaceutical practice. This work was important, since it was written at the request of the pharmacists themselves; it contained the definition of pharmacy, as well as the requirements for practicing it, among which were: to be knowledgeable about the secrets of their art, to ask a fair price for the medicines they prepared, without committing fraud or selling abortive or poisonous preparations. The influence of this work can be seen in the "Institutionum pharmaceuticarum" (Jean Renou, Paris, 1608). Later, the work by Quiricus de Augustus, "Light of the Apothecaries" (Turin, Venice 1492), appeared, followed by the "Luminaria Mayor" by Jacobus Manlüs. (13)

In 1498, the first pharmacopoeia appeared in the city of Florence, *Nuovo Receptario Composito*, with the aim of guaranteeing the uniformity of content of the preparations and the purity of the substances to be used as medicines. Its use was compulsory for all the apothecaries of this city. Later (1511) in Barcelona, Spain, the first pharmacopoeia was published under the title *Concordia Apothecariorum.* (5)

Due to the great epidemics that hit the world in the mid-14th century, a large number of healers, spice makers, herbalists, and other characters emerged, who were dedicated to the manufacture and sale of preparations based on natural products from plants such as poppy, mandrake, opium and belladonna, among others, many of which lacked therapeutic effect. This situation was maintained until 1523, when Emperor Charles V ordered that only doctors and pharmacists were authorized to work in apothecaries. They also had to meet defined requirements such as: being a 25-year-old male, knowing Latin and having at least 4 years of professional experience. It is interesting to note that during this period, women were excluded from these professional areas. (5)

At this time, the first medical academies in France and England and the first English medical college are formed, whose objective would be to prevent the practice of medicine by monks and healers; to exercise a regulatory role over other professions related to medicine, such as pharmacy, and to examine medicines and prescriptions in the apothecaries of the time. In 1617, in England, with the creation of the Society of Masters, Guardians and Society of the Art and Mystery of the Drugstores of the city of London, there was a separation of pharmacists from shopkeepers and traders, making the pharmacy a science and profession itself. (4)

In the 17th century, pharmacists achieved an undisputed role in the field of health sciences, joined the scientific academies and began their role as trainers, researchers and real or military pharmacists. They devoted themselves with greater interest in chemistry, resulting in the use of increasingly reliable raw materials and the introduction in Europe of some remedies such as quinine, ipecac and balsam from Peru. (18) The introduction of quinine was an important milestone in the treatment of malaria, curing King Charles II (1665-1700) from an attack of this disease, and ipecacuanha curing dysentery in the son of Louis XIV (1638-1715). (13)

In Spain, towards the 18th century, the pharmacist was increasingly different from other professionals such as doctors, they were dedicated to research on new drugs and led to the appearance of the Academies of Medicine and Science of Barcelona, from the apothecaries of José Ortega and Francisco de Sala, respectively. In 1737, Philip V of Spain approved the statutes of the Royal College of Apothecaries of Madrid (against the will of the medical profession) which established the dedication of pharmacists to the "cultivation, advancement of pharmacy, chemistry, botany and natural history". During the reign of Charles III, on April 13, 1780, the court of the Protopharmaceuticalate was created, made up of the king's major apothecary and three examining mayors, definitively separating the profession from pharmacy and medicine, by means of a promulgation that established (...) I have resolved and govern by themselves the faculties of medicine, surgery and pharmacy; that each one of them and without dependence of the other have their separate hearings (...). Each profession went on to run its own affairs. Thus, in 1799, the first pharmacopoeia written entirely by Spanish pharmacists appeared. (21)

Almost 200 years after the discovery of America, the exercise of Pharmacy begins in this continent with the Jesuits (1635), who built hospitals and pharmacies in their settlements, equipped with preparations imported from Europe and other medicines native to America, such as yerba mate, quinine and Santa Maria herb, joining the knowledge of both worlds, in terms of medicinal preparations. (22) These drugs were manufactured without any control of the proportion of ingredients and the quality of the products themselves. This was a big problem at the time, since the quantities of active ingredients were not controlled, the patient was given either too little or too much. Also, medicines were manufactured under the same name but with different ingredients, so they did not share the same properties. (23)

It is known that the first apothecary was established in Nova Scotia, Canada in 1605 (4, 13), by Louise Hérbert (probably the first pharmacist in America) and in 1640, by a small apothecary in Boston Massachusetts, where they sold prepared and imported medicines, as well as medicinal plants from the region. (4)

In 1616, a doctor and a pharmacist opened the first pharmacy in Central America, in the General Captaincy of Guatemala. (4) In Buenos Aires, Argentina in the year 1770, Don Agustín Pica, took the steps to register the first lay apothecary. (24)

In 1729, in Philadelphia, Marshall's pharmacy served as a base for the establishment of a large-scale pharmaceutical factory and as the first school for the training of these professionals. (4,5) In 1804, Elizabeth Marshall, the granddaughter of the founder of Marshall Pharmacy, inherited the business and became the first female pharmacist in North America. (5)

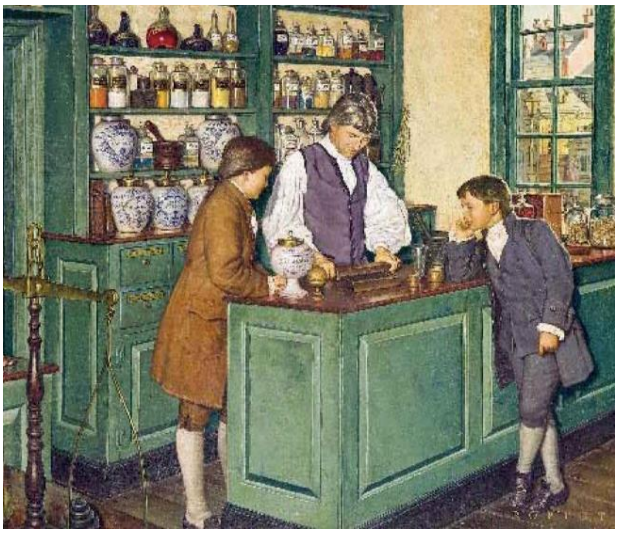


Figure 3. The Marshall Apothecary (5)

In 1752, the first hospital in the United States was created, the Pennsylvania Hospital, and with it the first hospital pharmacy, which received a shipment of medicines from London and had as its first hospital pharmacist Jonathan Roberts. (5)

The ineffectiveness and inconsistency of medicines, added to the mistrust towards health professionals that was beginning to emerge in patients, made that in 1820 eleven doctors met in the United States Capitol to create the United States Pharmacopoeia (USP), written in English and Latin, in which the first list of standard active ingredients was defined, with the purpose of improving the quality of medicines. (4, 23,25) This was the first book on standardized drugs to gain national acceptance. (5)

In 1821 the first association of pharmacists in the United States was established, the Philadelphia College of Pharmacy, to constantly monitor the quality of products sold in the market, creating a committee for the inspection of drugs and medicines. For the second edition of the American Pharmacopoeia, in 1831, the members of the Philadelphia College of Pharmacy are invited to participate in the elaboration of the new edition. (5)

Although the United States began its work to control medicines in 1820, Mexico was not left behind. By 1821, Garssicourt's National Formulary and Pharmaceutical Memorial was published, which is considered the antecedent of the Mexican pharmacopoeia. In 1846, the Pharmaceutical Academy of Mexico's capital published the first Mexican Pharmacopoeia. (26)

Other countries in Latin America began to be guided by existing pharmacopoeias such as the Spanish or French ones, however, they found themselves in the need to create their own pharmacopoeias to adjust them to the products manufactured in their respective countries. In Argentina they started to talk about the importance of creating an Argentine Pharmacopoeia since 1823, some attempts were made by several doctors who wrote their own works in order to be adopted as pharmacopoeias. (27) However, it was not until 1893 that the first edition of the Codex Medicamentarius of the Argentine Republic, also known as the Argentine Pharmacopoeia, was declared. (28)

In 1848, as concern about the quality of medicines consumed by American citizens grew, the United States Congress approved the "Drug Import Act" which indicated that medicines entering the country should be detained and analysed by the customs service to guarantee their quality and purity. It is until this year, 1848, that the Pharmacopoeia of the United States is officially recognized. (29)

In 1849, two German immigrants founded the Pfizer company in the United States, which was initially a chemical products industry, which during the civil war, was forced to change its production to medicines, due to the demand for antiseptics and painkillers. Edward Robinson Squibb, a union soldier, during the United States civil war, in 1858, opened his laboratory. The doctor Colonel Elli Lilly, in 1876, after the war, entered the pharmaceutical business creating a company that carries his name. (5)

Within the American Pharmaceutical Association (APhA), in 1852, the importance of ensuring the quality of imported drugs was discussed. Therefore, in 1853, they recommended to harden the federal and state laws to fight the traffic of adulterated and lower quality drugs. The use of the USP is requested, for the preparation of magisterial medicines. (5)

In 1887, the need to carry out a quality control of the substances contained in the preparations of that time was present, since therapeutic variability was being observed in medicinal preparations containing the same plants and prepared with the same method. Several publications arise describing the ways to carry out the quality control analyses, being the most important the Manual of Pharmaceutical Assaying of Dr. Lyons. (5)

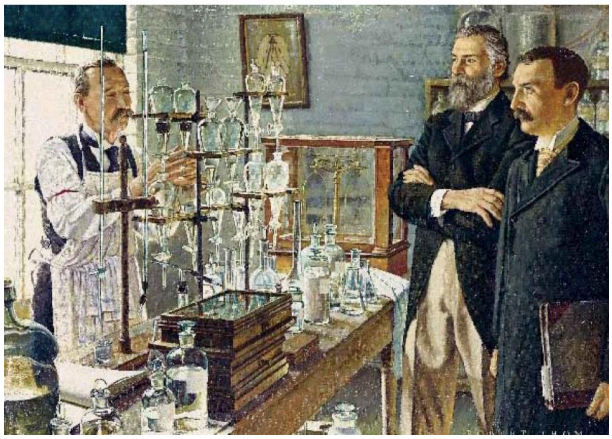


Figure 4. Standardization of pharmaceuticals circa 1883 (5)

During the 19th century, great transformations occurred that gave way to the industrial, political and scientific revolution, which radically transformed medicine, therapeutics and pharmacy and lead to a pharmaceutical revolution. (5)

While America was taking its first steps in the organization of its health services, in Europe, thanks to the invention of the steam engine and other advances in the production of goods, as a consequence of the Industrial Revolution, it was possible to obtain active principles of synthesis on a large scale, which originated the production of medicines on a massive scale and in this way the pharmaceutical industry appeared. This marked the beginning of the pharmaceutical revolution, product of the union between two important sciences of that time: industrial chemistry and pharmacy. (30-31) This pharmaceutical revolution was developed in three phases:

- The first was marked by the appearance of numerous substances extracted from medicinal plants, product of research by pharmacists and chemists, carried out in the backrooms of pharmacies. This is how narcotine (1803), emetine (1817), strychnine (1818), brucine (1818) and quinine (1820) appeared, whose results in terms of safety and effectiveness surpassed traditional natural remedies. (5,32)
- The second phase is characterized by the chemical synthesis of substances such as hyoscine, aspirin and ergotamine. (5,32)

- The third for the appearance of antiseptics such as phenol, sulphites and zinc chloride. (33)

On the other hand, during the 19th century humanity also went through a process of political transformation, the interest of the rulers in public health increased, which led to the development of public hygiene and social medicine. (32)

Germany played an important role in the emergence of the pharmaceutical industry, due to its superiority in the field of organic chemistry for industrial applications. Other nations in Europe competed with German industries for the large-scale elaboration of new pharmaceutical forms, and in countries like Italy, France and Spain appeared industries dedicated to the commercialization of medicines. (30) In Germany (1827), Emmanuel Merck turned the family pharmacy founded in 1668 into probably the first pharmaceutical industry, dedicated to the production of alkaloids. In 1859, the company Beecham, today part of the conglomerate GlaxoSmithKlineBeecham, became the first factory in the world to produce exclusively medicines. The Bayer Industry, founded in 1863 by Frederich Bayer and Johann Weskott, began as an industry for the production of artificial colorants. In 1885, produced and marketed the first analgesic medicine acetophenidine, then, in 1897 consolidated its pharmaceutical department. In 1899, Felix Hoffman, a chemist of this company, achieved the first pure and stable synthesis of acetylsalicylic acid. Switzerland became the third core of the pharmaceutical industry, with the Ciba-Geigy and Roche industries. (4)

In 1879, the Parke-Davis company introduced the first standardized pharmaceutical formulation, the Liquor Ergotae Purificatus. (5)

At the end of the 19th century, reforms in the training of pharmacists were taking place in Europe, through the evolution of higher education, in order to respond to the important changes in the way medicines were processed and manufactured in the large pharmaceutical industries. During this same period, experimental pharmacology was born, by Claude Bernard, through the study, in experimental animals, of chemically isolated active principles, such as morphine, strychnine and curare; and of substances obtained through chemical synthesis. This allowed the introduction of new therapies with more support, the birth of toxicology and the appearance of pharmacokinetics and pharmacodynamics. As a result of these studies, in 1857, Bernard published the book "Lessons on the effects of toxic and medicinal substances". Experimental pharmacology gave way to the application of experimental therapeutics, which consisted in the production of specific therapies for each disease. (32)

Returning to America, although the Drug Import Act was in place, many products manufactured in the United States were not quality controlled before being put on the market for use by the population, this led to some tragedies in the early 1900's. In 1901, the production of an antitoxin against diphtheria was contaminated with tetanus which caused the death of 14 children, a similar case also occurred with the vaccine for smallpox. From the tragedies that occurred, the Biological Control Act was drafted in 1902, which required the inspection of manufacturers and sellers of biological products and the performance of tests to determine the purity and strength of the product, in addition to complying with certain labelling guidelines such as showing the expiration date. (23,29)

In 1906, also under the concern that tragedies could happen again, the Food and Drug Act is written in the United States, (25) the act required the labelling of medicines with their respective ingredients (29), this put an end to many products containing alcohol, opium, or morphine, which were sold to relieve colic in babies and as tonics for adults. (34) It should be noted that this act was the starting point for the eventual creation of the Food and Drug Administration (FDA). (29)

In Brazil it is until 1926 that the first edition of the Brazilian Pharmacopoeia is born and made official, however, its use becomes mandatory until 1929, due to the need to control the quality control of drugs produced on a large scale. (35) Another South American country to make an official National Pharmacopoeia was Chile in 1905. (36)

Concerns about the quality of medicines in international trade took on a global dimension after the establishment of the WHO in 1948. In 1951, the WHO Executive Board adopted resolution EB7.R79, which requested the General Director to examine the advantages for health and international trade of more uniform inspection methods in different countries. (37)

4. Quality Control of Medicines in Costa Rica

In Costa Rica, during the pre-Columbian era, a system of magical and empirical healing predominated, led by the indigenous doctor, known in some regions as *Sukia* or *Shaman* and *Awáen*. (38)

Due mainly to economic poverty, Costa Rica had no medical or pharmaceutical professionals, thus perpetuating the system of shamans. (38) It was not until 1806 that the first doctor arrived in the country, Manuel del Sol, who collaborated in a vaccination campaign against smallpox, however, his stay was short as he was transferred by the Spanish Crown to another country. (38)

In the 1820s, the country's coffee activity became so important that it is considered that thanks to coffee Costa Rica developed economically, which attracted foreign doctors to our country. (38) In 1840 the doctor Nazario Toledo was established in Costa Rica. (38) President Braulio Carrillo, in 1841, allowed doctors and surgeons to run apothecaries, due to the lack of pharmacists. (38)

Under the administration of president José María Castro Madriz, in 1849, the chair of Pharmacy was opened at the first university in the country, the University of Santo Tomás, however, not a single pharmacist graduated from this university. (38) In this same year, the first pharmacist arrived, Don Fermín Meza Orellana, born and graduated in Guatemala. (39)

During the administration of president Juan Rafael Mora, in 1857, the first Protomedicato of Costa Rica was

created as a regulatory body for public health. It had twenty-four doctors and eight apothecaries. (40) The Protomedicatos date from the 15th century and were the technical body in charge of supervising the exercise of the health professions (doctors and pharmacists), as well as attending to the training of these professionals. The first Protomedicato was created in Spain, extending this organization to the colonies during the 16th century, specifically to Mexico, Peru and the region of *La Plata*. (41)

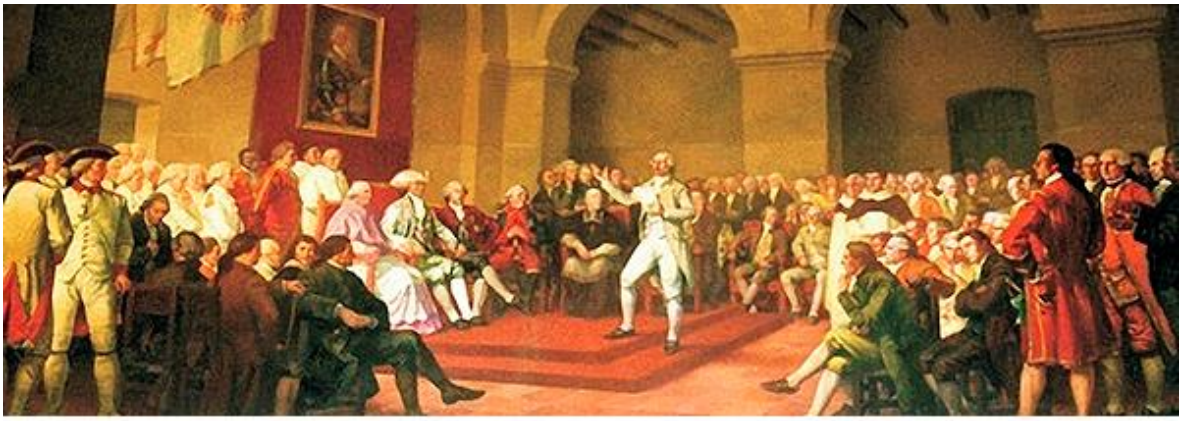


Figure 5. Protomedicato of the New World

(https://www.historiadelnuevomundo.com/el-protomedicato-de-indias-control-sanitario-en-el-nuevo-mundo/)

The Regulations of the Protomedicato were established on June 15, 1858, by Decree No. 8, giving it two functions: that of a court of theoretical-practical examinations for the medical sciences and of recognition of degrees obtained abroad, in addition to that of an inspectorate of public health and medical police; in this way the Protomedicato would be the antecedent/anchor of the Ministry of Health. Controls on wholesale imported drugs, in terms of price and quality, also began to be established. Among the functions of the Court of Medical Police that the Protomedicato assumed was that of classifying and analysing the "medicines" that were submitted to its knowledge (drinking and thermal waters, fermented beverages, natural or artificial wines, alcohols, oils, vinegars, honeys, preserved or fresh milk from different animals, gelatines, and others) and, in addition, recognizing medicines and authorizing their sale. (40)

By 1864, the country already had eighteen apothecaries (1 apothecary for every 6694 inhabitants). (40) In 1874 the first courses in pharmacy were given at the San Juan de Dios Hospital. The first Costa Rican pharmacist, Francisco Madriz, graduated in 1877. (42)

In spite of the efforts to professionalize the practice of pharmacy, in 1887, in the absence of medicines, there was still a tendency for the popular use of medicinal herbs for all illnesses, as observed in advertisements published by Bruno Carranza Ramírez. This situation changed significantly at the end of the 19th century, thanks to the inauguration of the railroad to the Atlantic on December 6, 1890, which allowed the overseas trade of drugs, certain medicines and patent medicines. These medicines were sold in grocery stores in both rural and urban areas, where natural products were also marketed, which led to errors and misfortunes resulting from inexperience of empiricists. (43)

Due to faults and abuses by various healers of the time, in response to a complaint made in 1887, the Protomedicato decided to cancel all patents granted to empiricists and agreed not to extend such permits again. However, this measure could not be made effective, which caused the resignation of some directors of the Protomedicato. This was partly due to the communication difficulties of the time, the inability to apply state controls. As well as the great identification of the population with natural products and the ambiguity of the state, which did not act effectively. On the contrary, in certain areas where the population had no possibility of accessing health services, it tolerated the use of these products in an empirical way. (43)

In 1895, the Constitutional Congress of the Republic created the Faculty of Medicine, Surgery and Pharmacy. Situations such as empiricism, the entry into the country of medicines with patents, the use of natural products by the population, the country's effort to professionalize medicine and pharmacy, led to the creation of the School of Pharmacy in 1897, under the administration of the Faculty of Medicine, Surgery and Pharmacy, during the administration of Rafael Iglesias. (40)

In 1902 the College of Pharmacists was created. "The creation of the College should be interpreted as part of the process of institutionalization of "public hygiene". By 1903 the new Pharmacy curriculum included, in the fourth year, the course of "Examination of Pharmaceutical and Food Substances". (40)

It was established, in 1917, as a graduation requirement that the students had to present, before a tribunal, an exam on the subject matter seen in the courses; then they had to present an incorporation exam to become part of the College, the exam included theoretical and practical tests on "...objective recognition of drugs and chemical products, chemical analysis of metallic compounds and recognition of alkaloids…". (40)

During the 1920s, the Costa Rican government developed its "public hygiene and health" policies, a fact that can be measured by the institutionalization of public health and the beginning of preventive health programs,

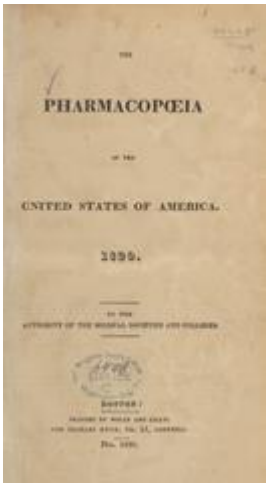
which marked a new stage in the treatment of sanitation in Costa Rica". The importation of foreign-patented medicines was controlled starting in the 1920s. Prior to that date, drug importers paid only one fee at customs. (40)

In 1923, the Law on the Protection of Public Health established that "the person applying for a sales permit must present the exact formula of the medicine or preparation to the College of Pharmacists, which, once accepted, may be submitted for sale by making its composition known on the label of the container". (40)

In 1929, the Regulation of Drugstores and Drugstores was approved, which requested the importer that two licensed pharmacists had to certify the information of the formula. The importer had to attach a sample of the presentation that the product would have, in order to send it to the Board of Directors of the Association; in order to register the drug, the name of the manufacturer and its address had to be submitted. For this purpose, the Office for the Registration of Pharmaceutical Specialties was established as a branch of the College of Pharmacists. (40)

In spite of the regulation of establishments and individuals who dispensed medicines, in 1930, the State implemented a control over the import, production and sale of "dangerous" drugs, however, these regulations were not clear, nor were the legal classifications about the trade of various drugs and there was great legal tolerance towards the trade and use of drugs. (40)

In 1934, the College of Pharmacists decided that new students of the School of Pharmacy must have a copy of the United States Pharmacopoeia to pursue their studies. In 1935, the register of medicines and the file of preparations samples were created. (40)


PHARMACOPŒIA

UNITED STATES OF AMERICA.

1930.

Figure 6. United States Pharmacopoeia

(resource.nlm.nih.gov/2567001R)

During 1938, the United States Pharmacopoeia was mainly used as a reference for preparing medicines, as were the British and the French Codex. In addition, the "Formulary of the Hospitals of Costa Rica" was adopted. (40)

In 1939, it was established that "...the drugs and medicinal preparations sold in the Republic must meet the purity and concentration requirements of the formulary". (40) By presidential decree, in 1945, measures were issued for the registration of medicines and disposal of pharmaceutical specialties, establishing a fee for the creation of a laboratory for the analysis of these specialties. (38)

In the 1960s, the Faculty of Pharmacy proposed a bill to establish the National Laboratory for the Analysis of Pharmaceutical Specialties to analyse the quality and properties of medicines, cosmetics and toiletries circulating in the country. This project was not initially approved in Congress. (43)

In collaboration with the customs administrators, in 1963, the public prosecutor of the College of Pharmacists was responsible for carrying out an ocular inspection of the imported shipments, to ensure that they complied with the requested requirements: "the name and address of the manufacturing laboratory, the consignee, the quantity contained in each container, the date of manufacture and the expiry date". (40)

In 1965 the Specialized Drug Analysis Laboratory was created, providing analysis services to the national pharmaceutical industry, the San Jose Social Protection Board and the General Direction of Social Medical Assistance and the Costa Rican Social Security Fund (CCSS), becoming the first laboratory in the country to guarantee the quality and safety of medicines, located in the Faculty of Medicine of the University of Costa Rica. In June 1971 the building of the Faculty of Pharmacy was inaugurated in the Gonzalo Gonzalez Auditorium, (140 students and 20 teachers), moving the Specialized Drug Analysis Laboratory from the Faculty of Medicine to the Faculty of Pharmacy. This Laboratory was later named Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA, by its acronym in Spanish). (43)

The Chemical-Pharmaceutical Quality Control Laboratory of the Ministry of Health was created in 1973. The General Health Law of 1973 restricts the importation and distribution of medicines only to persons registered with the Ministry of Health, previously registered with the College of Pharmacists. In addition, in order to register a drug, a proof of the Health Registration of the country of origin and a proof of the analysis of the product had to be presented. The analysis had to be made by a laboratory that guaranteed the quality of the drug according to the Official Pharmacopoeia. (40)

In January 1975, the Costa Rican social security office named Caja Costarricense del Seguro Social, initiated the purchase of equipment and facilities for a drug quality control laboratory. (44) In August 1976, it began operating in a building located behind the Mexico Hospital. This laboratory was created with the purpose of carrying out the analytical control of the medicines that entered this institution, verifying their quality before being dispatched. (45) In 1981, the Laboratory of Standards and Quality of Medicines were declared an Official Laboratory. (46)

At the same time, in the Faculty of Pharmacy of the University of Costa Rica, this situation was also the

reason for a deep analysis, which led to the strengthening and expansion of the Laboratory of Services to Industry and which implied a growth in infrastructure, equipment and highly trained human resources.

With the expansion of the laboratory, in 1985, the name was changed to Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA, by its acronym in Spanish), maintaining the services already offered and providing advice and training for the staff of the Ministry of Health and pharmaceutical professionals from other public and private institutions in the country.

In the 1990s, it was decided that state laboratories should be impartial. Therefore, in 1997, the Executive created the National Laboratory for Quality Control of Medicines (LANACCAME, by its Spanish acronym) as an official laboratory and the National Drug Certification Agency (ENACEM, by its Spanish acronym) as a body attached to the Ministry of Health, in order to carry out analyses, technical studies and certifications of medicines required by the Ministry of Health or third parties that requested it.

The National Laboratory for Quality Control of Medicines (LANACCAME) was integrated by the staff of the recently closed Laboratory for Chemical and Pharmaceutical Quality Control of the Ministry of Health and the Laboratory for Analysis and Pharmaceutical Consulting (LAYAFA) and served as a national reference laboratory for physical and chemical determinations in medicines, cosmetics, raw materials used in the pharmaceutical industry and narcotic drugs, as well as any other test or study considered by the Ministry of Health. National Drug Certification Agency (ENACEM), depended technically and administratively on the Division of Medical Services and Pharmacy of the Ministry of Health and was located in the Institute of Pharmaceutical Research (INIFAR, by its acronym in Spanish).

In 1998, after the closing of the Laboratory of Chemical and Pharmaceutical Quality Control of the Ministry of Health, the Executive, by means of Executive Decree Nº 26727, authorized the Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA) to carry out the analyses required by the Ministry of Health in the matter of medicines. That same year, the Pan-American Health Organization (PAHO) carried out evaluations of official laboratories of quality control in the Central American area and the Dominican Republic and granted recognition to LAYAFA, for having the technical and operative capacity necessary to be a reference laboratory.

In the year 2000, an agreement for the purchase and sale of laboratory services was signed between the Ministry of Health and the University of Costa Rica to continue the work that LAYAFA had been doing for the Ministry of Health. In this same year, at a regional level and during the II Pan-American Conference for the Harmonization of Pharmaceutical Regulations, it were created the Pan-American Network for the Harmonization of Pharmaceutical Regulations, the Working Group of Pharmacopoeias in the Americas and the Program for External Quality Control of Official Laboratories (PCEC, by its Spanish acronym), with the purpose of evaluating and improving the performance of official drug quality control laboratories in the Americas, in which LAYAFA has continuously participated.

The Executive by means of Executive Decree No. 28466-S of February 8, 2000, promulgated the Regulations for the Registration, Control, Import and Advertising of Medicines, which mentions the need for medicines to comply with recognized quality standards in order to be marketed.

Since 2002, when Costa Rica joined the Central American Customs Union process, LAYAFA has been actively participating in several of its meetings, as part of the Central American Economic Integration System (SIECA, by its acronym in Spanish).

In 2003, the National Official Laboratories of the Customs Union, within the process of Customs Union, granted the recognition of National Laboratory for Quality Control of Drugs of Costa Rica to the Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA), by demonstrating that it had adequate facilities, equipment and qualified personnel to perform physical, chemical and microbiological analysis of drugs and for having a quality system according to ISO/IEC 17025 to demonstrate its technical competence.

Likewise, in 2003, the World Health Organization established that each country, through its regulatory authority and through the corresponding legislation, should have an official quality control laboratory for medicines and other products of health interest, in order to guarantee patient safety.

In 2005 the Good Laboratory Practices Working Group (GLP WG) was established, the mission of this group was to strengthen the performance of the Quality Control of Medicines Official Laboratories in the region, this in order to guarantee the quality of the analytical results and to provide technical support for the implementation of Good Laboratory Practices. The network of official laboratories is formed by 28 Quality Control of Medicines Official Laboratories which belong to 23 countries of the region, among them is LAYAFA. (47, 48)

The Directorate of Registration and Control of the Ministry of Health considered it convenient to have an Advisory Commission on the quality of medicines made up of the parties involved in the topic, so that they can advise it on regulations to guarantee the quality of medicines. For this reason, the Regulations of the Advisory Commission on the Quality of Medicines were published in June 2006 by Executive Decree No. 33356. This Commission is made up of nine pharmaceutical members: two representatives of the Directorate of Registration and Control of the Ministry of Health, one of which will act as President and the other as Secretary, a representative of the Laboratory of Standards and Quality of Drugs of the Costa Rican Social Security Fund, a representative of the Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA) of the University of Costa Rica, two representatives of the Association of the National Pharmaceutical Industry (ASIFAN, by its

Spanish acronym), two representatives of the Central American Federation of Pharmaceutical Laboratories (FEDEFARMA, by its Spanish acronym) and a representative of the College of Pharmacists of Costa Rica. (49)

In 2008, a reorganization of the Ministry of Health was carried out and the National Drug Certification Agency was placed under the supervision of the Ministry's Customer Service Department. (49) In that same year, Executive Decree No. 26478-S was repealed, since the competencies established in that decree for the ENACEM and LANACCAME were assumed by the Customer Service Office of the Ministry of Health and the Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA) of the University of Costa Rica, respectively.

In 2010, LAYAFA obtained the accreditation of several tests of drug analysis and sampling, by the Costa Rican Accreditation Entity (ECA, by its Spanish acronym), in compliance with law No.8279 for the creation of the National System for Quality and in order to continue providing the service to the Ministry, resulted of a technical and managerial process that included a continuous quality system, which included aspects such as customer service, control of nonconformities, internal quality audits, internal controls, trained and supervised human resources, adequate installation conditions, accredited calibration tests and validation methods, suitable equipment, implemented security systems and research in new analysis methods.

According to 2011 data, the Laboratory of Standards and Quality of Medicines of the Caja Costarricense del Seguro Social already had a team of 64 workers, 21 of them pharmacists; who carried out in that year product analysis of 222 suppliers and 2145 deliveries. Four percent of the products analysed were rejected because they did not meet the necessary quality requirements. (50)

Aware of the importance of the work that LAYAFA carries out for the country, in 2015 the University of Costa Rica approved a significant investment of resources for the strengthening of INIFAR that will allow it to have modern laboratories, a pilot plant for the production of orphan drugs, cosmetics, natural products, among others. Thanks to this effort, LAYAFA will also have a new infrastructure in accordance with international standards, as well as more equipment and highly qualified human resources. This will allow LAYAFA to be recognized in the future as a reference laboratory of the World Health Organization.

In 2016, the scope of accreditation by ECA was extended and the Laboratory now has a greater number of accredited assays. This benefit both the Ministry as responsible for ensuring the quality of medicines, as well as the national pharmaceutical and cosmetic industry, for the benefit of the Costa Rican population to whom we demonstrate technical competence and commitment. In addition, LAYAFA continues to advise the Ministry of Health, with absolute reserve and in surveillance of intellectual property and confidentiality of information, through its participation in various commissions such as the Advisory Commission on Quality of Drugs and the National Commission against Illicit and Counterfeit Products; and participating in national and international working groups such as the Customs Union, in the writing and amendment of regulations.

Also, in 2016, The Laboratory of Standards and Quality of Medicines received the ISO 17025 accreditation, this is an international standard that accredits the quality processes carried out by laboratories where tests and calibrations are part of the inspection and certification of products. This accreditation gives greater support to the work that the laboratory carries out in the quality verification of the medicines that are offered to the insured ones. (51)

In 2018, the Caja Costarricense del Seguro Social was awarded with a Good Practice Award by the International Social Security Association (ISSA) for the implementation of a specialized information service on drug quality for health professionals working for the institution. This service in charge of the Laboratory of Standards and Quality of Medicines provides health professionals with technical and scientific information on the quality of medicines to solve special needs. (52)

In Costa Rica there are also some private laboratories that offer physicochemical and microbiological analysis of medicines with assays accredited by ECA under ISO 17025, they do analysis to pharmaceutical products following all the quality standards and assays of the pharmacopoeias monographs such as the United States (USP) and the European (EU). (47)

Currently, two national laboratories are a reference in quality control: The Laboratory of Standards and Quality of Medicines of the Caja Costarricense del Seguro Social (CCSS) and the Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA). (45) As for the Official Drug Control Laboratories, they play a fundamental role in ensuring the quality of medicines. The assurance of that quality as part of the global evaluation process that ends with the efficacy, effectiveness and safety of the drug, is extremely important in public health. (48)

5. Harmonization of technical requirements related to the quality control of medicines in the Central American and Caribbean region

In 1991, the Central American Integration System (SICA, by its acronym in Spanish) was formed, which constitutes the institutional framework for Central American Regional Integration, originally created by the States of Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, with Belize joining as a full member in 2000 and the Dominican Republic in 2013. (53) In the XVII meeting, held in March 2002 in El Salvador, the need to harmonize the standardization measures among the different countries became evident, so it was agreed to carry out evaluations to the official laboratories of the area.

One of the purposes of the Integration System is to have a uniform trade regulation among the States Parties that strengthens the commercial exchange in the region. For

this purpose, several working groups were structured, formed by representatives of the academic, consumer, private enterprise and government sectors, among them the subgroup of Drugs and Related Products. In the field of medicines, six technical regulations were developed and put into effect to support the issues of evaluation and verification of conformity, table 1 presents the names of the regulations, their purpose and the date on which they became effective. (54)

Table 1. List of technical regulations put into effect as harmonization measures between the countries of Central America and the Dominican Republic. (55-59)

Regulation Name	Purpose	Effective Date
Quality Verification	To establish the analytical tests that must be performed to check the quality of the medicines by the regulatory authority.	2008
Regulations for the Validation of Analytical Methods for Drug Quality Assessment	To establish guidelines for the validation of physicochemical and microbiological analytical methods used in drug quality control.	2009
Human drug stability studies for human use	To establish the guidelines for conducting stability studies to determine the validity period of medicines.	2011
Labelling of pharmaceutical products for human use	To establish the minimum requirements to be met by the labelling of pharmaceutical products for human use, both for products from the territory of the countries in the Central American region, and for foreign products.	2012
Health registration requirements	To establish the conditions and requirements under which the sanitary registration of medicines for human use will be granted.	2014
Good manufacturing practices for the pharmaceutical industry	To establish good manufacturing practices for the pharmaceutical industry.	2016

6. Discussion

Throughout history, there has been a growing necessity to ensure the quality and efficacy of medicines and natural products. Today more than ever, their quality and safety must be evidenced. The pharmaceutical revolution has allowed medicines to be produced in large quantities and in many cases accessible to patients who require them, but it also determines the responsibility of ensuring their quality. (32)

The quality and accuracy requirements established by international organizations means control tests are increasing and likewise the requirements of quality assurance of the test results by the laboratories. (48)

In Costa Rica there are several laboratories that analyse the quality of the drugs consumed in the country, both in the state and private security systems. Two laboratories recognized as official before PAHO. (55) These laboratories must have assays accredited by ECA under ISO 17025. (45) It is allowed by the improvement in the quality of drugs consumed in the country, whether imported or nationally produced.

7. Conclusions

Thousands of years ago, humans began to use and prepare natural medicinal products and, along with this, they began to establish measures to ensure the quality and safety of the preparations. Over the years the methods and regulations to ensure the quality of medicines have been improving and becoming more rigorous, this because of unfortunate events in the past that have endangered public health on several occasions. The countries currently have official laboratories specialized in quality control of pharmaceutical and cosmetic products to evaluate their composition and safety. In Costa Rica, the Laboratory of Analysis and Pharmaceutical Consulting (LAYAFA) is responsible for analysing the quality of medicines and cosmetics that are marketed in the country. The differences between the regulations and quality standards of the countries and the effect that this has on the commercialization of medicines in the different regions of the world, has promoted at present the creation of regulations that seek to harmonize the requirements related to different processes and activities of the manufacture, registration and quality control of medicines, this is the case of the Central American Technical Regulations for the countries of Central America and the Dominican Republic.

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Conflict of Interest

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