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Preparation of compounded products in pharmacies and compounding-magistral pharmacy, personalized medicine in Türkiye and Spain

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ABSTRACT: The pharmacist is the only individual authorised to prepare medicines as a result of the training they have received. The pharmacy profession is one of the few that will not accept mistakes in terms of human life and health. Even the smallest mistake can lead to irreversible consequences such as non-recovery, disability and death. In the event of such a situation, every sensitive pharmacist will undoubtedly face a great deal of conscientious responsibility. In order to avoid such a situation, it is necessary to be aware of the developments in the profession and to exercise caution when providing services. It is also important to avoid leaving work to others and to strive to avoid making any mistakes. Personalised medicines prepared by a pharmacist in a pharmacy laboratory according to a doctor's prescription, packaged and labelled, and presented to the patient are known as magistral products. These are formulations that are prescribed and prepared individually, with the doses of the active substance determined by the physician in terms of volume or weight according to the degree of the disease present in the patient. In the context of personalised therapies globally, the importance of compounding products is increasing daily, and the rules and regulations governing the preparation of compounding products vary from country to country.

This review study examines the laws, regulations, and rules applicable in Türkiye and Spain for the preparation of compounding products. It also considers the future of compounding pharmacy.

KEYWORDS: Compounded Products; Compounding Pharmacy; Magistral; i.v. Nutrition; Hormon Replacement Therapy; Personalized Medicine; Pharmacies in Türkiye; Spain

1. INTRODUCTION

It is widely acknowledged that rare diseases are chronic conditions that affect relatively small numbers of patients. The research and development (R&D) processes for drugs used to treat these diseases are inherently challenging, requiring significant time and resources. Furthermore, the market supply of such drugs is often limited, leading to low demand for R&D and production. Consequently, these drugs are often referred to as "orphan drugs" [1-4].

Nevertheless, a number of pharmaceutical companies are engaged in research on rare diseases and the development of innovative treatments, motivated by a sense of social responsibility, with the aim of enhancing the quality of life of patients and prolonging their lifespan. Nevertheless, these endeavours are not yet sufficient.

In a world where even our fingerprints are different from each other, it is unreasonable to expect that all individuals will react to the same drug in the same way. A multitude of factors, including age, gender, race and weight, can influence the bioavailability of drugs. Consequently, the preparation of personalised medicines and the development of individualised treatment protocols are of paramount importance [5]. In light of the potential risks associated with the preparation of bespoke medicines in pharmacies, there have been numerous reports of patient safety concerns [6,7,8,9].

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Nevertheless, the potential for significant side effect risks associated with industrial production of medicines when they reach large masses, coupled with the fact that 'big pharma' is unable to prepare and license every tailor-made formulation and prescription in every dosage, necessitates the preparation of the magistral products required for individualised medicines in pharmacies.

A plethora of preparations are available for acquisition from pharmacies that have obtained the requisite licence [10]. A plethora of "bioidentical" hormones, including progesterone [11], testosterone [12], estradiol [13] and estriol, are commercially available [10]. These hormones can be administered in a variety of pharmaceutical dosage forms in hormone replacement therapies for menopause and andropause. A variety of dosage forms are available, including tablets, syrups, and transdermal gels for topical application [14]. It is established that orally administered hormones are subject to the first-pass effect in the liver. Furthermore, the conversion of estradiol to estrone when metabolised can result in adverse effects in women when taking estradiol as a hormone replacement therapy [15]. In addition, conventional transdermal gels have been observed to exhibit slightly toxic effects due to the high quantity of alcohol utilised as the solvent for the hormones [16]. In the event that there is a requirement for a special drug carrier system that does not contain alcohol [17] and is capable of transporting herbal raw materials into the body with high and controlled release efficiency [18], it is observed that such carrier systems, including liposomes and lipogelosomes, are not currently available on the market [16,19].

The COVID 19 pandemic has taken an important place in our lives by affecting a wide range of areas from education [20] to health, from changes in food consumption habits [21] to the use of artificial intelligence [22]. One of the most important effects has been the supply problem that occurred in some of the industrially produced drugs during the pandemic period. In periods of pandemic, when issues may arise in the supply chain, pharmacists who are able to prepare magistral preparations to meet the prescriptions requested for personalised treatments have played a pioneering role in the prevention of such crises. In the aftermath of the 6 February 2023 earthquake in Kahramanmaraş, Türkiye, which affected a vast area, pharmacists capable of preparing pharmaceutical preparations have been working through their associations since the day after the disaster. Despite a disruption in the drug supply chain in the earthquake region, pharmacists affiliated with the Association of Pharmacists of Pharmaceutical Pharmacists (Majistral Eczacıları Derneği) demonstrated remarkable efficiency and precision in fulfilling their responsibilities.

In the context of the preparation of magistral products, the focus naturally turns to aromatic and aromatherapy oils. These oils, which have a multitude of benefits when prepared as magistral, have recently been combined with probiotics and included in magistral formulas in pharmacy science [23], both internally and externally. Moreover, postbiotics, which are metabolites, have begun to be incorporated into cosmetic products for various applications [24,25]. It is anticipated that some cosmetic products will be prepared as magistral in the near future. The role of excipients in zinc oxide nappy rash creams used in infants is of significant importance, despite the products' categorisation as cosmetics. To ensure safety, physicians may prescribe these creams on an individual and magistral basis [26]. In the context of dermatological diseases, there is a continued need for individualised treatments, magistral drugs and cosmetic formulas in numerous areas, including alopecia and even nodular alopecic lesions [27,28], herpes zoster infection (shingles) [29], seborrheic dermatitis [30], the negative effects of rosacea [31] and sun exposure problems [32]. Despite the recognition of madecassol and antioxidants such as resveratrol [33,34] and some herbal extracts [35]-essential oil [36] in the literature as beneficial for wound healing [33-35] and antifungal activity [36], these products have not yet been prescribed by physicians or prepared by pharmacists.

In light of the aforementioned developments, this review is a systematic examination of the regulations pertaining to the preparation of pharmaceuticals and pharmaceutical preparations in Spain, a member state of the EU, and in Türkiye within the context of the European Union Harmonisation Laws. In recent years, the funding provided by the Spanish Foundation for Hospital Pharmacy has facilitated an increase in research projects and the production of compounding units for the manufacture of magistral and, in particular, ophthalmic preparations [37,38] and pediatric magistral formulations [39]. While the legal regulations require updating, the review includes both similar and divergent sections from both countries.

The pharmaceutical quality system tailored for personalized preparations exhibits key distinctions from that intended for mass-produced pharmaceuticals. This is due to the variations in the scale, complexity, and operational features of the production laboratory, as well as the specific applications and purposes of the medications created. It is essential for legislation to evolve and align with the demands of personalized preparations, addressing existing deficiencies in this domain. An analysis of the constraints faced by personalized preparations within the pharmaceutical quality system has been conducted, resulting in the proposal of a methodology centered on a specially crafted proficiency testing program: the Personalised Preparation Quality Assurance Programme (PACMI) [40].

On March 2022, the Spanish Agency for Medicines and Health Products, in conjunction with the Ministry of Health, released a proposed Royal Decree aimed at replacing the existing legislation [41]. This initiative presents a significant opportunity to improve and modernize the current legal framework. Key areas identified for advancement include the following: The proposed regulations would allow for the storage of pharmaceutical preparations in anticipation of urgent patient requirements [42]. This practice is already prevalent in several European nations, where the European Pharmacopoeia characterizes such preparations as those "prepared in advance and stored until a supply request is received." Additionally, the regulations should include provisions for sterile forms, thereby ensuring the fulfillment of all prescriptions while adhering to necessary quality standards. It is essential to recognize the differences in quality between industrially produced and personalized medicinal products.

The Turkish Pharmaceutical Sector Strategy Document Action Plan (2015-2018) outlines the objectives related to rare diseases as follows: "A detailed current situation and needs analysis will be conducted on rare diseases in our country." The orphan drug policy will be established in accordance with the results determined.

In accordance with this objective, a priority inventory registration system for rare diseases and centres where these rare diseases can be diagnosed will be established in our country. It is essential to ensure the communication of the national reference system established with the existing network systems on rare diseases. The Ministry of Industry (2015) has indicated that special policies will be developed for the development and production of drugs to be used in rare diseases in our country [43]. Nevertheless, it is evident that tangible progress has not been made in this regard.

In the present era, orphan drugs, which are medications utilized by rare patient populations, are imported from abroad by the Turkish Pharmacists Association on behalf of patients who have applied for them. In Türkiye, the majority of generic drugs are manufactured by domestic pharmaceutical companies. It has been observed that rare patients in Türkiye are dependent on foreign countries for access to orphan drugs. In conclusion, rare diseases represent a significant public health concern in Türkiye, as well as in other countries around the globe.

The limited number of drugs available for the treatment of these patients, the difficulties encountered in obtaining these drugs and the high cost of drugs present a significant challenge for both patients and scientists engaged in research into these diseases.

2. THE LEGAL FRAMEWORK REGULATING THE PREPARATION OF PHARMACEUTICAL PRODUCTS IN TÜRKIYE

The Law on Pharmacists and Pharmacies, published on Saturday 12 April 2014 in the Official Gazette (No: 28970), defines a medicinal product, the characteristics of the laboratory section for medicinal products, the labelling and packaging of medicinal products and the prescription characteristics of medicinal products. In accordance with Article 50 of the regulation, the Turkish Medicines and Medical Devices Agency has prepared the "Good Pharmacy Practices Guideline." This guideline encompasses a multitude of topics, including the definition of major pharmaceuticals, substances utilized in the preparation of major pharmaceuticals, the preparation of major pharmaceuticals, supply, storage, presentation to the patient, and the disposal of drugs.

The legislative framework pertaining to medicinal products is delineated in the following sections of the Law on Pharmacists and Pharmacies and the Regulation on Pharmacists and Pharmacies [44].

3.LAWS RELATED TO PHARMACY in TÜRKİYE;

3.1- Law No. 1262 on Pharmaceutical and Medical Preparations (1928)

The term "Ispenciyari" is derived from the Old Turkish language and translates to "pharmacist." The adjectival form, "Ispençiyari," is used to describe a preparation of pharmaceuticals. The term "Müstahzar" is also encountered frequently in Turkish and is of Arabic origin. According to the Turkish Dictionary of Contemporary Turkish Language (TDK), "Müstahzar" means a commercial medicine, a preparation prepared in advance and kept in the pharmacy.

Article 19 of the relevant legislation states that those who manufacture preparations without a licence or those who knowingly sell, offer for sale or cause to be sold preparations so manufactured shall be sentenced to imprisonment for a period of between one and five years. If it is understood that these preparations do not possess the therapeutic qualities attributed to them or are manufactured in such a way as to reduce or lose these qualities or from impure substances, the penalty shall be increased by one-third [45].

3.2- Law No. 6197 on Pharmacısts and Pharmacies (1953)

As in other countries, the regulation of the pharmacy profession in Türkiye is determined by laws and regulations. The definition of the pharmacy profession was established in the Law No. 6197 on Pharmacists and Pharmacies, which was adopted on 18/12/1953 and published in the Official Gazette dated 24/12/1953 and numbered 8591.

Pharmacy is a health service that carries out activities related to the preparation of different pharmaceutical types of drugs from natural and synthetic drug raw materials. These are used in the diagnosis and treatment of diseases and prevention of diseases; analysis of the drug, monitoring in terms of the continuity of its pharmacological effect, safety, effectiveness and cost; ensuring standardisation and quality assurance related to the drug; informing patients about problems related to drug use and reporting the problems that arise. In order to open and operate a pharmacy and to be the responsible manager of a pharmaceutical warehouse, it is essential to be a pharmacist. A pharmacist may establish and operate pharmaceutical production facilities, cosmetics manufacturing plants, pharmaceutical research and development centres, or act as managing director in public or private establishments.

Furthermore, the third section of the legislation provides an explanation of the terminology used in relation to pharmaceuticals and chemicals.

Article 21 - The pharmaceuticals and chemical substances included in the Turkish Codex that are kept in the establishments shall have the qualifications and conditions written in the Turkish Codex.

Article 22 - The owners and managers of pharmacies, pharmaceutical warehouses and laboratories shall be responsible for the contamination and improper storage of unpackaged medicines and chemical substances.
Article 23 - The storage and sale of poisonous and potent drugs to consumers shall be carried out in accordance with the laws and regulations in this field.
Article 24 - (Amended: 2/1/2014-6514/36 Art.) Pharmacies may not sell poisonous and potent substances and medicines in bulk, and pharmacies may not participate in tenders. The sale of medicines, their return to the pharmaceutical warehouse from which they were purchased or to other warehouses in case of force majeure, their exchange between pharmacies and the destruction of expired or spoiled medicines must be reported to the drug tracking system. Medicines may not be sold via the Internet or any other electronic medium. No website may be opened in the name of pharmacists and pharmacies. Pharmacists may not cooperate in any way, overtly or covertly, with institutions, doctors, other healthcare institutions and organisations or third parties for the purpose of sending prescriptions to them, nor may they employ brokers, couriers or similar intermediaries, collect or direct prescriptions or accept prescriptions received in this way. In case of detection of these acts, the pharmacist and the intermediary person or organisation shall be fined between 5,000 and 50,000 Turkish Liras. In case of a repetition of the acts, the administrative fine to be imposed shall be double the amount of the previous fine.
Article 25 - It is obligatory that the prescriptions given to the pharmacy to be manufactured shall be made without any changes or alterations, and the delivery of the medicines and prescriptions (by writing the prices on them) to the buyer shall be made according to the principles to be determined and announced by the Ministry of Health and Social Welfare. The responsible manager of the pharmacy is directly responsible for errors and other mistakes in the medicines of the prescriptions prepared in the pharmacy. Pharmacists may not prepare prescriptions that they suspect to be incorrect in content, or prescriptions that contain more medicines than the amounts specified in the codex and that are not underlined in two lines and signed separately, without contacting the doctor. However, in cases where it is not possible to contact the doctor, they must issue the prescription in accordance with the maximum amounts indicated in the code and inform the highest health authority in the district [46].

3.3- Law No. 6643 on the Union of Turkish Pharmacists (1956)

As in other countries, the practice of pharmacy in our country is regulated by laws and regulations. In the relevant articles of these laws, in addition to the criminal provisions, disciplinary offences are also mentioned which are related to acting contrary to the matters and rules specified in the "Turkish Pharmacists Deontology Regulation", the decisions of the General Assembly and the Board of Directors [47].

3.4- Regulation on Pharmacists and Pharmacies (2014)

On Saturday, 2 April 2014, the Turkish Pharmaceutical and Medical Devices Agency published in the Official Gazette the Regulation on Pharmacists and Pharmacies under the number 28970 in Section FOUR of the Regulation on Pharmacies and Pharmacies, which contains explanations on the locations and departments of pharmacies.
(3) The laboratory parts of pharmacies shall be separated in such a way that there is no contact with customers or patients. Pharmacists who had a pharmacy licence before natural disasters such as earthquakes, floods and fires, but who certify that the workplace used as a pharmacy has been significantly damaged and rendered unusable as a result of these disasters, may be granted a licence to operate a pharmacy in places or temporary structures with a minimum area of 20 square metres for a maximum of two years.
(5) A pharmacy may have more than one door, provided that this is specified in the project submitted to the competent authorities. None of these doors shall open into another shop or store. The pharmacy laboratory may not be directly connected to the outside.
Laboratory section
ARTICLE 21 - (1) Chemical substances, galenic preparations and drugs used in the preparation of magistral medicines shall be kept in glass bottles; substances that may deteriorate by exposure to light shall be kept in coloured bottles in a separate cabinet.
(2) In pharmacies, the counter reserved for the preparation of medicines shall be made of heat-resistant glass, marble and materials that do not cause microbiological contamination. Precision, centigram or kilogram scales shall be kept on the counter or on a separate special table so as not to interfere with their settings. It is obligatory to obtain the certificate of control of the scales from the competent institution every two years.
(3) Tap water is mandatory in laboratories.
Toxic substances cabinets
ARTICLE 22 - (1) All poisonous substances shall be sorted according to the pharmacopoeia and kept in separate cabinets. The lid of one of the cabinets shall be coloured red with the words "serious poisons" and the lid of the other shall be coloured green with the words "poisons to be kept separately". These cabinets must be kept locked at all times and the key must be kept by the pharmacy manager. Depending on the type of poison to be placed in these cabinets, the name of the poison is written on red or green labels on the medicine bottles to be placed inside. In addition, labels with the words "serious poison" or "poison to be kept separately" must be affixed. Red prescription medicines must be kept in a steel safe.
Magistral medicines, labelling and packaging

ARTICLE 31 - (1) A label shall be affixed to the packaging of essential medicinal products in such a way that it cannot fall off. These labels shall indicate the name of the pharmacy, the practitioner and the patient and the method of use of the medicinal product.
(2) Labels of medicines for internal use shall be white and labels of medicines for external use shall be red.
(3) Magistral medicinal products to be prepared in pharmacies shall be packed in new and suitable packaging which has never been used.
Prescriptions for essential medicinal products
ARTICLE 32 - (1) It is forbidden to show any prescription, including prescriptions to be prepared in pharmacies, to anyone other than the prescribing doctor and the patient or the patient's relatives, or to give them the original or a copy thereof.
SECTION SIX covers medicines and chemicals and the properties and responsibilities of medicines.
ARTICLE 39 - (1) All medicines in pharmacies must comply with the specifications of the pharmacopoeia. The owner and the responsible manager of the pharmacy are responsible for these matters.
Storage of medicinal products
ARTICLE 40 - (1) All chemical raw materials for medicinal products, finished medicinal products, vaccines and serums must be stored properly, taking into account their characteristics as stated in the pharmacopoeia and the storage conditions indicated on the packaging. For this purpose, the temperature and humidity of the pharmacy environment shall be appropriate to the storage conditions.
(2) Labels on bottles containing substances such as bromine, iodine, acids and alkalis, which cause deterioration of the labels, shall be such as to prevent their removal and deterioration. Deteriorated and contaminated labels must be replaced. The batch number, date of manufacture and expiry date, place of manufacture and storage conditions shall be indicated on the packaging of chemical substances.
(3) Food supplements, pharmaceuticals, chemicals and other health products used in pharmacy and agriculture, medicines, chemicals and other health products used in pharmacy and agriculture, and veterinary medicines, excluding veterinary biological products, manufactured or imported with the approval, licence or price of the competent ministry shall be kept in separate cabinets so as not to affect each other.
Additionally, the date 12.04. In the Good Pharmacy Practices Guide, Article 50 of the Regulation on Pharmacists and Pharmacies, which entered into force after being published in the Official Gazette dated 12 April 2014 and numbered 28970, the objective is to enhance the quality and continuity of services provided in pharmacies, ensuring access to safe, effective and quality medical products. The objective is to enhance the quality and continuity of pharmaceutical services, ensure patient compliance with treatment regimens, and raise awareness among patients regarding potential drug-drug, drug-nutrient, and drug-adverse effect interactions, as well as irrational drug use. This is done in order to address the problems that arise from incorrect drug selection and dosage. Additionally, the guideline aims to foster collaboration with physicians regarding the appropriate selection of drugs and the necessary dosage and duration of treatment. Finally, the guideline seeks to develop and implement Good Pharmacy Practices. The Guideline encompasses pharmacies and pharmacists, as well as other personnel engaged in the aforementioned activities. The underlying philosophy of Good Pharmacy Practices is to provide services related to the products held in the pharmacy, to facilitate the optimal benefit to society from these services, and to implement activities designed to enhance efficiency by evaluating the anticipated benefit and the actual benefit derived from medicines.
In the Guideline, Magistral Drug is defined as "the drug or drugs prescribed by the physician specifically for the patient and prepared in the pharmacy according to this formula" (p. 10). Furthermore, the "Pharmacy laboratory department" is defined in detail in Section 7.
7.1. The laboratory section of pharmacies can be located on the mezzanine or basement floor, but it is separated in such a way that it has no contact with people or patients and no direct connection with the outside (p. 11).
7.2. The counter designated for the storage of medications is constructed from heat-resistant glass, marble, and materials that are not conducive to microbiological contamination.
7.3 The laboratory is designed and equipped in accordance with the principles of aseptic technique, with the objective of minimising the potential for errors and optimising the conditions for the preparation of the medication.
7.4 The laboratory is designed in such a way as to prevent contamination and cross-contamination.
7.5. Precision, centigram, or kilo scales are kept on the counter or on a separate special table so that their settings are not disturbed. A calibration control certificate is obtained from the relevant institution for the scales every two years. The dates of the most recent calibration and the date of the next scheduled calibration are indicated on the device label. All calibration records for devices in the pharmacy are stored in a manner that allows for the inclusion of the most recent calibration record for each device during audits.
7.6. Chemical substances, galenic preparations and drugs utilised in the preparation of magistral drugs are stored in glass bottles and/or in their original packaging. Substances that may deteriorate from light are stored in coloured bottles and labelled in a separate cabinet.
7.7. City water is available in laboratories for use in scientific experiments.
7.8. Laboratories are exclusively dedicated to the storage of chemical substances, and the appropriate humidity and temperature conditions are maintained to prevent deterioration.
Furthermore, section 10 of the Good Pharmacy Practices Guide includes definitions related to the preparation of the Magistral Medication and the Supply, Storage, Presentation to the Patient and Disposal of Medicines.
10.a. Preparation of Magistral Medication

10.a.1. It is the responsibility of the pharmacist to ensure the safe, effective and high-quality preparation and delivery of medicinal products.
10.a.2. The pharmacist shall meticulously peruse the information inscribed on the prescription, and shall promptly contact the physician in the event that any missing, erroneous, or opaque elements are identified.
10.a.3. No more than one major medicinal product may be prepared in the laboratory at the same time.
10.a.4. The necessary cleaning procedures are carried out after the preparation of the drug in the laboratory.
10.a.5. The preparation of magistral drugs is the responsibility of the manager, assistant, or second pharmacist, and the drugs prepared by the assistant and second pharmacists are presented to the patient under the supervision of the responsible pharmacist.
10.a.6. Written standard operating procedures are prepared for all operations, and work and operations are carried out in accordance with these procedures. Should any amendments be made to the information documented, these are duly signed and dated. Such alterations are made in a manner that preserves the original information. Should the necessity arise, the rationale behind the alteration is duly recorded.
10.a.7 Magistral medicine may be prepared in the pharmacy. Furthermore, cosmetics, medicines and medical devices are not manufactured for commercial purposes.
10.a.8. It is not permitted to produce and send bulk medicines to doctors' offices.
10.a.9. It is not permitted to prepare magistral medicine upon the request of patients.
10.a.10. The invoices of the suppliers of the chemicals used in the preparation of magistral drugs are retained for retrospective research and to be presented during audits.
10.b. Magistral Drug Packaging and Labelling
10.b.1. It is imperative that a label be affixed to the packaging of magistral drugs in a manner that ensures its stability and prevents it from becoming detached. The aforementioned labels shall include the name of the pharmacy, the name of the pharmacist who prepared the drug, the names of the doctor and the patient, the method of use of the drug, the date of preparation of the drug, the substance/substances it contains and their amounts, the storage condition of the drug and any warnings. In the event that more than one major drug is provided to the patient simultaneously, distinctive phrases shall be incorporated into the labels.
10.b.2. The labels of drugs intended for internal use shall be white, while those intended for external use shall be red.
10.b.3. Drugs prepared in pharmacies are placed in new and suitable packages that have never been used.
This information is included in the form [48].

Historical, conventional and clean room included pharmacy figures in Türkiye were given in Figure 1, 2, 3, respectively.

Figure 1. Historical pharmacy, raw material and lab equipment pictures in Türkiye.

Figure 2. Conventional, non-steril lab included pharmacy pictures in Türkiye.

Figure 3. Novel, Clean room and laminar air flow Class-II cabinet included pharmacy pictures in Türkiye.

3.5- Turkish Penal Law (2004)

Criminal Responsibilities of Pharmacists; it is necessary to examine the criminal responsibilities of pharmacists according to the new Turkish Criminal Code and their criminal responsibilities according to other laws and regulations in two parts.

-(Criminal Liabılıty According to the Turkish Penal Code Numbered 5237-5271 Numbered Criminal Procedure Law)
- Criminal Liabılıty According to the Turkish Penal Code No. 5237

The manufacture or sale of medicines in a manner that endangers the life and health of individuals.
Article 187 - (1) Any individual who manufactures or sells medicinal products in a manner that endangers the life and health of individuals shall be sentenced to imprisonment for a period of one to five years and shall be subject to a judicial fine.
(2) In the event that this offence is perpetrated by a physician, pharmacist, or individual engaged in the practice of a profession or art for which official authorization has been granted, the penalty to be imposed shall be increased by one-third [49].

3.6- Criminal Liabilities According to Other Laws and Regulations

Article 32 of the Law No. 5326 on Misdemeanours imposes criminal sanctions.
These include instances where pharmacies fail to comply with the days and hours of duty, opening and closing hours, or operate a collusive pharmacy. Additionally, there are cases where pharmacies do not keep secrets, use intermediaries for doctor's prescriptions, sell medical preparations and magistral formulas above the price determined by the Ministry of Health, sell controlled drugs without a prescription, and so forth. Failure to attend general assembly meetings, the sale or keeping of expired or spoilt medicines, the performance of therapeutic applications, the failure to maintain the medicines used in emergency treatment and available on the market in the pharmacy, the failure to maintain an

illuminated on-call chart, the making of advertisements on behalf of the pharmacy, the making of web pages on behalf of the pharmacist and pharmacy.

The disciplinary responsibilities of pharmacists are defined by the 6643 numbered Turkish Pharmacists Association Law, the 6197 numbered Law on Pharmacists and Pharmacies, and the Turkish Pharmacists Deontology Regulation. These laws stipulate that any actions or omissions that contravene the decisions of the General Assembly or Board of Directors constitute disciplinary offences, in addition to the relevant criminal provisions.
Article 30 – The Court of Honour shall impose the following disciplinary penalties on those who fail to enter the chamber or otherwise fail to fulfil the obligations imposed on them by this law, and on members whose documents are submitted to it, according to the nature of their acts and behaviours that are contrary to the professional decency and dignity. These penalties may include:
a) Written warning
b) (Amended: 23/2/1995 – 4078/4 Art.) A fine of between four and fifteen times the annual fee of the chamber on the date the act is committed.
Prohibition from practising one's art for a period of between three and 180 days.
Prohibition from working in a region where one has been banned from practising for a period of between three and three years. The Councils of Honour shall have the discretion to impose these penalties without regard to order. Nevertheless, in the event that the members who have been temporarily banned from practising according to paragraph (c) are banned from practising again due to the repetition of their previous acts and behaviours, the maximum limit of the penalty written in this paragraph shall be imposed. (Addition: 23/2/1995 - 4078/4 Art.) It is the duty of the chambers' councils of honour to conclude the files submitted to them within a period of three months.
The regulations that pharmacists in our country are obliged to comply with are set out in the Turkish Pharmacists' Association Deontological Regulation. Pharmacists registered with the Turkish Pharmacists Association are subject to the provisions of this regulation. Article 7 of the bylaws is concerned with pharmaceutical formulae.
Article 7 stipulates that a pharmacist shall not be subject to disciplinary action for failure to cure pharmaceutical preparations in accordance with established pharmaceutical rules or for failure to administer pharmaceutical preparations.
In evaluating this matter in terms of the Turkish Code of Obligations, it is important to remember that the relationship between pharmacists and patients is one of a purchase-sale relationship. (Related articles of the Code of Obligations No. 6098)
In the event that a damage occurs as a result of the pharmaceuticals and medical assistance provided in the patient-pharmacist relationship, as a result of the pharmacist or his/her employee's negligent act, as a result of the recipient patient's use of them, the pharmacist is obliged to compensate the damage suffered by that person, depending on the location of the damage.
In the event of death, the damage suffered by the relatives of the deceased may include compensation for deprivation of support, non-pecuniary damages, and burial expenses. In the case of disability, the relatives may also claim compensation for loss of the labour force and non-pecuniary damages. In the event of prolongation of the disease, the relatives may claim compensation for loss of wages caused by the loss of work and additional expenses spent for treatment, as well as non-pecuniary damages according to the situation.
The concept of moral compensation is elucidated in Article 56 of the Code of Obligations. In accordance with the aforementioned article, the judge may award moral compensation to the injured person in the event of damage to their physical integrity, and to the family in the case of severe physical damage and death, contingent upon the circumstances and conditions.
In the event of a similar occurrence in a hospital setting, both the pharmacist responsible for the incident and the institution employing them are held liable. The responsibility of the institution is determined according to the principles of "strict liability". The institution has the right of recourse to the pharmacist (Article 66 of the Code of Obligations) [50].

4. LAWS AND REGULATIONS FOR THE PREPARATION OF PHARMACEUTICAL PRODUCTS IN SPAIN;

4.1 The Regulations Needed for the Practice of the art of Pharmaceutical Pharmacy in the Kingdom of Spain;

The regulations presented in detail below have been revised in accordance with the prevailing requirements and are subject to the provisions of the relevant legislation.
In general, these regulations address the licensing of pharmacy laboratories, the procedures and requirements for pharmacies preparing pharmaceutical preparations, as well as the authorization of third parties (raw material suppliers) and personnel (pharmacy technicians, assistant pharmacists) and the registration and registration system.
The relevant Parliamentary Commission Board has issued Decree-Law 65/2009 of 9 July, which sets out the procedures that pharmacists must follow when preparing private and official prescription formulas and office preparations in pharmacy laboratories and making them available to patients.
In accordance with Royal Decree No. 175/2001 of 23 February, the preparation and quality control of magistral formulae and office preparations are governed by a set of regulations that require pharmacy laboratories and pharmacy

services to adhere to specific standards. Furthermore, the aforementioned decree stipulates that the preparation of medicines in pharmacies must be continuously updated in accordance with evolving regulatory requirements.

The current adaptations to be made in accordance with the content of the formulation, the type and volume of the preparation to be made and the technological device infrastructure required are included. Furthermore, the relevant units of the Ministry of Health and the professional organisation are held responsible for the meticulous supervision of these adaptations.

Spanish Royal Decree 175/2001, 23 February 2001

This decree, along with the draft law that provides comprehensive details regarding the competent authorities responsible for approving norms pertaining to the preparation and quality control of pharmaceutical formulae, was approved by the Spanish Parliament, submitted for the King's signature, and subsequently entered into force upon publication in the official gazette on 16 March 2001 (BOE no. 65, Annex).

The decree contains, in general terms, the relevant regulations and related subheadings.

The properties, analyses, certificates and storage conditions of the active substances to be used in medicinal preparations must be considered.

- CTI/FM/149/00/13 16 October 2013 CTI/FM/150/02/16 21 September 2016 CTI/FM/150/02/16 Two legislative acts were published concerning the active ingredients used in the principal formulations employed in medicinal preparations. The legislative provisions were drafted by representatives of the Ministry of Health, the Professional Organisation and the Academic Board and submitted to the Council of Ministers for approval. Once approved and signed, they entered into force.

Furthermore, the decree encompasses the particulars pertaining to the third edition of the National Formulary.

On 23 November 2020, the AEMPS published the third edition of the National Formulary.

This Royal Decree approves the reference norms for the correct production and quality control of the preparations included in the Magistral Formularies, the National Formularies and the internationally recognised Pharmacopoeias.

In applying these norms, it is imperative to adhere to the specific conditions set forth in the National Formulary for the appropriate preparation and quality control of select off-label formulae and preparations included in the National Formulary.

A single additional provision is to be included.

This Royal Decree is adopted in accordance with the Law of 20 December 1990 on Medicinal Products and is therefore considered to be legislation pertaining to pharmaceutical products. This is in accordance with the stipulations set forth in Article 149.1.16 of the Constitution, which establishes this Decree as conclusive.

The initial definitive judgment. The rules are to be updated.

The Ministry of Health is empowered to amend the approved standards in accordance with the guidelines set forth in the pharmaceutical code, as may be necessary to accommodate scientific and technical advancements, and in the interest of the public good.

The second-to-last provision is as follows: The entry into force of this decree shall be as follows:

This Royal Decree shall come into force on the day following its publication in the 'Official State Gazette'.

Signed in Madrid on 23 February 2001 by His Majesty King Juan Carlos and His Excellency Celia Villalobos Talero, Minister of Health [40, 51].

4.2 Standards for the Correct Preparation and Quality Control of Master Formulae and Office Preparations

In order to achieve the goal of 'Superior Quality in the Art of Pharmacy' in a reliable manner, it is necessary to implement a quality assurance system that encompasses the following:

a) The preparation and control of magistral formulae and office preparations must adhere to quality standards, utilising the correct ingredients and techniques.

b) All quality The aforementioned procedures delineate the responsibilities of personnel.

c) The quality procedures shall include provisions for the storage and distribution of each preparation until post-preparation approval and delivery to the end-user, and for informing the end-user so that the quality of the preparation does not deteriorate until the expiry date.

The pharmacist responsible for preparing the magistral formulae and office preparations must conduct periodic self-evaluations to assess the alignment of their procedures with the established quality norms. This evaluation should be documented and accompanied by any necessary corrective actions.

Objectives and Definitions

The objective is to: The objective of this quality standard is to guarantee the quality of pharmacist-produced preparations.

The correct standards for drug preparation and quality control, as well as the personnel, laboratories, devices, raw materials and packaging materials used, quality control and the necessary documentation related to drug preparation and delivery to the patient, define the minimum conditions that these procedures must meet. The aforementioned quality standard encompasses all aspects that may directly or indirectly influence the quality of preparations manufactured in both pharmacy laboratories and pharmaceutical services.

In order to facilitate a comprehensive understanding of the provisions outlined in this regulation, the following definitions are provided:

1. Packaging: All operations, including packaging and labelling, that are necessary for a bulk product to become a finished product.
2. The process of calibration is defined as follows: A series of operations which, under specific conditions, establishes the relationship between the values indicated by a measuring instrument or measuring system, or expressed by a criterion/measure, and the device/system measuring that system, whose values are known by reference.
3. The term "cross-contamination" is used to describe the transfer of substances or particles from one object or substance to another, resulting in the contamination of the latter. The contamination of one raw material or product with another, resulting in the transfer of substances between them.
4. Quarantine is defined as: The status of raw materials, intermediate products, bulk or finished products and packaging materials that have been effectively isolated, whether physically or otherwise, at the time of a decision to approve or reject.
5. The documentation of a given batch is as follows: The data set pertaining to each individual batch at any given point in time, inclusive of whether the requisite criteria have been met and the entirety of the requisite control measures in relation to said criteria.
6. The magistral formula is defined as follows: An individualised medicine is defined as a pharmaceutical preparation intended for a single patient. It is prepared in accordance with the technical and scientific standards of the art of pharmacy, either by the pharmacist or, on the pharmacist's instructions, by an assistant pharmacist or technician. The preparation is made to meet the specifications set out in a detailed prescription, which contains the active substances and their quantities. The finished product is then delivered to the user in the pharmacy, accompanied by appropriate information, by the pharmacist who prepared the medicine.
7. An off-label formulation is defined as a medication that is used for a purpose other than that for which it was originally developed. Medicines prepared by a pharmacist in accordance with the formula set forth in the Pharmacopoeia and subsequently made available.
8. The preparation room is the area of the pharmacy where medications are prepared. This is the area of the laboratory that is dedicated to the production and control procedures.
9. Batch: A defined quantity and specification of a raw material, packaging material, or product manufactured in accordance with a specific process or series of processes under fixed conditions. The fundamental quality of a batch is its homogeneity.
10. In the context of the Medicines Act of 25 December 1990 (art. 8.4), the term 'raw material' refers to any substance, whether active or inactive, employed in the manufacture of a medicinal product. This may remain unaltered, undergo chemical and physical modification, or be lost during the processing stage.
11. The term "packaging material" is defined as follows: The categorisation of packaging materials for medicinal products is dependent on whether the material is in contact with the product. Materials used in the packaging of medicinal products, other than those used for handling or transport, are classified as either primary or secondary packaging material.
12. Batch number: The distinctive combination of numbers, letters, or both that serves to identify a specific lot.
13. The preparation stage is characterised by a series of technical operations that ensure the quality and stability of the pharmaceutical product. A series of technical operations, conducted in accordance with the established norms and standards for quality control and assurance, are employed at each stage of the production process. These operations are designed to ensure the correct and standardised implementation of the production stage, as well as the stability of the pharmaceutical form in question.
14. Magistral preparation is defined as follows: The process of producing and delivering directly to patients in the pharmacy laboratory, in accordance with the appropriate prescriptions written to the patient by the physician, formulations listed and defined in the National Formulary and pharmacopoeias, prepared by or under the direction of a pharmacist and of guaranteed quality.
15. Procedure: A set of actions, measures and procedures to be taken directly or indirectly related to the preparation of a medicinal product.
16. Standard operating procedures: Written and approved procedures in accordance with the correct preparation and quality control standards that specifically describe the activities carried out in the preparation of an office formulation and in the preparation and quality control of an official prescription.
17. Bulk product: a product that has undergone all stages of preparation except final packaging.
18. Finished product: a medicinal product that has undergone all stages of preparation, including final containerisation.
19. Registration: the manual or computerised compilation of all data relating to raw materials, intermediates and finished products, whether office formulations or pharmaceutical preparations.
20. Quality assurance system: the set of operations and activities organised to guarantee the quality of medicines.

4.2.1. Section I

1. Personnel
All personnel engaged in the preparation of medicines in pharmacies or pharmaceutical services must possess the requisite qualifications and experience.

1.1 The responsibilities and qualifications of personnel engaged in the preparation of medicines.
In accordance with the prevailing legislation, the pharmacist bears responsibility for the preparation conducted within their pharmacy or for that undertaken under their direction within the scope of their professional duties.
The preparation of any medicinal product may only be carried out by a pharmacist or by another individual with the requisite qualifications and training, under the direct supervision of the pharmacist.
Operations necessitating specific technical expertise (such as identification and evaluation) may only be conducted by the pharmacist or by personnel under their supervision who have received the requisite training.
1.2 Organisation of work.
In order to optimise the organisation of work, the pharmacist should, on the basis of this assessment, evaluate the competence and experience required for each stage of preparation and control, and set out in writing the qualifications of their staff. The supervision of operations may be delegated to an assistant pharmacist, provided that the pharmacist retains overall responsibility for the activities conducted by the assistant.
1.3 Training and motivation.
It is incumbent upon the pharmacist to promote and update the training of all personnel involved in the manufacturing and control operations.
The objective of this training is twofold: firstly, to ensure that staff attain an adequate scientific and technical level, and secondly, to emphasise the importance of compliance with these standards for precise knowledge and correct preparation and quality control of the pharmaceutical preparation and office formulations.
1.4 Staff hygiene.
The pharmacist should establish and document personal hygiene rules, which should include, at a minimum, the following:
a) Prohibition of eating, smoking, and chewing gum, as well as any practices that are unhygienic or could contaminate preparation facilities.
b) Requirement to use lockers for storing clothes and personal belongings.
c) The utilisation of appropriate attire in accordance with the specific preparation type (apron, hat, footwear, gloves, mask, etc.).
d) The regular cleansing and replacement of this attire when necessary.
e) The temporary exclusion of individuals with dermatological disorders, injuries, or any infectious disease from preparation work.

4.2.2. Section II

Laboratory and equipment
This section comprises a series of general considerations, together with preliminary information and precautions.
In general, the laboratory and the instruments used should be adapted to the following aspects:
a) The pharmaceutical form of the preparations.
b) The type of preparation.
2.1 General characteristics of the laboratory environment.
2.1.1.1 The preparation, packaging, labelling and control of the pharmaceutical form should be conducted in a dedicated area of the laboratory, designated as the 'preparation room', within the pharmacy specifically constructed for these activities. The design should facilitate effective supervision by the pharmacist.
2.1.2 Furthermore, the preparation of other preparations for which the pharmacist is responsible in accordance with current regulations is also feasible in this area. Nevertheless, activities that may result in contamination of the prepared formulae should be conducted in an area separate from this one.
2.1.3 It is imperative that the conditions of the laboratory are conducive to the preparation of the intended pharmaceutical formulations and that the requisite technology is available.
2.1.4 It is of the utmost importance that the environment is adequate to prevent any risks of confusion or contamination during the preparation of drugs. The necessity for an enclosed area entirely dedicated to drug preparation is contingent upon the quantities or nature of the products involved.
In the event that sterile preparations are to be made, the area designated for this purpose must be isolated and equipped with adequate air filtration mechanisms. This enables the floor, ceiling and walls to be cleaned with antiseptic agents, thus ensuring the microbial and particulate contamination requirements for the area are met. These requirements are determined by the pharmacist in charge, based on the specific preparation, manufacturing process and sterilisation technology employed. The objective is to minimise the risk of cross-contamination.
2.1.5 The surfaces of floors, walls and ceilings should be smooth and free of cracks, in order to facilitate the processes of cleaning and disinfection. It is essential that the laboratory is adequately protected against insects and other pests.
2.1.6 The laboratory must be equipped with potable water and the necessary energy sources. The laboratory must be well ventilated and illuminated, and the ambient temperature and relative humidity must be adjusted to suit the nature of the products to be processed.
2.1.7 Maintenance and cleaning operations shall be conducted in accordance with the instructions set forth in the written manual. All waste shall be disposed of on a regular basis in suitable containers. Furthermore, it is essential to maintain optimal organisation within the laboratory to prevent confusion.

2.1.8 At a minimum, the following items shall be available for the production of preparations:
a) A workbench constructed of smooth, inert materials that are easily cleaned and disinfected, resistant to colourants and abrasive substances.
b) A pair of sinks with hot and cold water, constructed of smooth, durable materials.
c) A separate area for containers and equipment awaiting cleaning.
d) A horizontal weighing bench with sufficient space for the balance(s), avoiding vibrations as much as possible. e) An area dedicated to reading and taking notes, with all relevant documents, including the Royal Spanish Pharmacopoeia, the National Formulary and useful reference books for preparations, readily available.
f) Cabinets and shelves with sufficient capacity, protected from dust and light (if any).
g) A refrigerator equipped with a precision thermometer to allow maximum and minimum temperature for storing heat-resistant products, whether raw materials, bulk products or finished products.
2.2 General characteristics of the apparatus and equipment.
2.2.1 The apparatus and instruments should possess the following general characteristics:
a) They should be suitable for the intended use and, where applicable, properly calibrated. Prior to commencing any preparation, it is recommended that an assessment be conducted to ascertain the suitability of the available tools for the intended preparation.
b) The design of the tools should facilitate easy washing, disinfection and, where necessary, sterilisation. It is imperative that no surface in contact with the product affects the quality of the drug or its components.
c) The product used for the operation or maintenance of the equipment (lubricants, inks, etc.) must be manufactured in a way that does not contaminate the manufactured products.
2.2.2 In order to prevent cross-contamination, all parts of the equipment that come into contact with products must be properly cleaned.
2.2.3 It is imperative that instruments be kept in a state of cleanliness and in good working order. The cleaning and maintenance of equipment must be carried out in accordance with standard operating procedures, which must be documented and specific to the tools and products in question. It is recommended that cleaning be carried out as soon as possible after use.
2.2.4 It is recommended that measuring instruments be subjected to periodic verification and calibration in order to guarantee the precision of the data obtained. The results of these periodic assessments should be archived for future reference. It is recommended that the calibration and validation of any measuring instruments, with particular attention to scales, be conducted prior to the commencement of any process.
2.2.5 The minimum apparatus, tools and equipment required for the preparation and control of magistral formulae and off-label preparations.
It is essential to have the appropriate equipment to ensure the requisite quality standards are met during the preparation and control processes.
The aforementioned minimum requirements pertain to the requisite apparatus, tools, and equipment that each pharmacy office or pharmaceutical service must possess for the preparation of pharmaceutical formulae and official preparations. A comprehensive list of these essential items is provided at the conclusion of this regulatory document.
2.3 Adjacent facilities.
The regular maintenance and cleanliness of changing rooms, toilets and washbasins shall be monitored. The toilet shall not have direct access from the preparation area.

4.2.3. Section III

Documents
Documentation plays an indispensable role in the quality assurance system for medicines prepared in the pharmacy. It serves to circumvent errors that might arise from verbal communication or from working with memorised data. Furthermore, it enables the reproduction of each procedure at the conclusion of the process.
It is the responsibility of the pharmacist to prepare, date and sign the relevant documents. In the event that there are multiple pharmacists present in the pharmacy, the document may be prepared by any of them. However, it is then the responsibility of the pharmacist in charge to approve the document, ensure that it is updated on a regular basis and, should the need arise, implement any necessary modifications. Furthermore, the responsible pharmacist will date and sign the document. Documents that are no longer in use should be removed from circulation in order to prevent confusion.
Documents must be clearly titled to indicate their purpose and content, and must be written in a legible manner.
It is imperative that the personnel responsible for preparing the medicinal product have a clear and detailed understanding of the relevant documentation, which must be stored in a readily accessible manner at all times.
All documentation must comply with the rules set out in the relevant regulations and will be archived and stored for a minimum of one year following the expiry date of the medicinal product.
The fundamental documentation will comprise the following:
3.1 General documents
3.2 Documents pertaining to raw materials.
3.3 Documents pertaining to packaging materials.
3.4 Documentation pertaining to majistat formulae and office preparations.

3.1 General documentation.
As a minimum, the following elements shall be included:
3.1.1 Standardised procedures for the cleaning of laboratories and equipment, indicating the recommended frequency and the products to be used.
3.1.2 Standardised maintenance and calibration procedures for materials and equipment, including implementation schedules.
3.1.3 Personnel hygiene standards.
3.1.4 Qualifications of personnel involved in preparation.
3.2 Documents relating to raw materials.
The following documents shall be included:
3.2.1 Registration.
3.2.2 Specifications.
3.2.3 Quality control sheet (mandatory only when the analysis is conducted in the pharmacy laboratory or supplier laboratory, as outlined in section 4.1.3).
3.2.1 Record.
This constitutes the minimum set of data required for the identification of each raw material present in the pharmacy laboratory.
The data set shall include the following:
a) Internal registration number.
b) The name of the raw material specified in the Pharmacopoeia or, in its absence, the IUPAC name.
c) Supplier.
d) Batch number.
e) Quality control number of the pharmacy laboratory, supplier or an accredited laboratory.
f) Date of receipt.
g) Quantity and number of containers.
h) Expiry date or, in its absence, the next analytical control.
i) Decision of acceptance or rejection, dated and signed by the pharmacist.
3.2.2 Specifications
This document provides a comprehensive account of the quality characteristics of the raw materials, including, where applicable (for raw materials included in the Spanish Royal Pharmacopoeia, it will be sufficient to indicate the monograph number), the processing conditions.
a) The requirements that the raw material must meet, as specified in the Royal Spanish Pharmacopoeia or, in its absence, in a recognised and esteemed pharmacopoeia: identification of the raw material, its grade and class, if any, possible impurities and description of the analytical procedures allowing the identification of the aforementioned characteristics.
b) Storage conditions.
c) Any hazardous or toxic characteristics, as well as specific precautions to be taken in the event of contact.
3.2.3 Quality control document
This file contains the controls carried out by the pharmacy when necessary, as well as the documents to be recorded.
The document should include the following information:
a) Internal control number.
b) Name of the raw material.
c) Batch number.
d) Supplier.
e) Amount.
f) Date of expiry or repetition of the validity of the analytical control.
g) Tests performed, methods of analysis and results obtained.
h) A decision regarding acceptance or rejection, dated and signed by the pharmacist.
The aforementioned data are those presented in the supplementary document, which is designated as file 1.
3.3 Documentation on packaging materials.
It is a requirement that the primary packaging complies with the specifications set out in the Royal Spanish Pharmacopoeia. Furthermore, a record shall be maintained that includes, at a minimum, the following information:
a) Internal registration number.
b) Product identification.
c) Supplier.
d) Batch number.
e) Date of receipt.
f) Quantity and number of containers.
g) Expiration date, if applicable.
3.4.1 Standard preparation and control procedure.
The document must contain all the information necessary for the correct preparation of a specific pharmaceutical formula.
As a minimum, the following data should be included:
a) Description of the preparation: name and/or qualitative composition, pharmaceutical form.
b) Method of manufacture and bibliographic reference.

c) Analytical controls to be performed, the methods followed and the limits established and accepted.
d) Necessary packaging material.
e) Information to be provided to the patient.
f) Conditions of protection.
g) Expiry date.
3.4.2 A guide to the preparation, control and recording of pharmaceutical formulas.
It must contain all the information necessary for the preparation of each formula.
The following data must be included at a minimum:
a) The name of the medicinal formula or the off-label preparation.
b) Composition.
c) Modus operandi (working method).
d) Registration/batch number of the magistral formula or office preparation.
e) Pharmaceutical form.
f) Quantity prepared (weight, volume or number of units).
g) Date of preparation.
h) Identifying data of raw materials used: name, quantities, supplier and batch.
(i) A description of the personnel involved in the manufacturing process and the tools used.
(j) Details of the quality control tests performed, including the personnel, equipment and reagents used, as well as the series in which they were conducted.
(k) The expiry date.
(l) Details of the dispensing data, including the date (in the case of medicinal preparations, the date of presentation to the patient must be within the expiry date), the quantity, the prescriber and the patient.
(m) Any observations made.
(n) The decision to accept or reject the product, dated and signed by the responsible individual.
The data presented herein are derived from the sample document, which is designated as file 2.

4.2.4. Section IV

Raw Materials and Packaging Materials
In light of the pivotal role that raw materials and packaging materials play in the quality of pharmaceutical formulations and office preparations, it is imperative that pharmacists exercise meticulous attention to their acceptance, quarantine, labelling, origin and quality control, transfer, storage and preservation.
4.1 Raw Materials
The raw materials employed in the preparation of magistral formulae and office preparations must be active substances that have been legally indicated in Spain in accordance with the provisions set forth in Law 25/1990 of 20 December on Medicines and Royal Decree 294/1995. The aforementioned decree, enacted on 24 February, regulates several key aspects pertaining to the Royal Spanish Pharmacopoeia, the National Formulary, the obligations of the Ministry of Health, the Food and Drug Administration, and the advisory bodies of the Ministry of Consumption.
4.1.1 The provenance of raw materials.
It is the responsibility of the pharmacist in charge to ensure that the raw materials are manufactured and processed in accordance with the requisite production standards, which guarantee their compliance with the defined purity, identity, richness and acute toxicity requirements.
The pharmacist may procure supplies from the following sources:
4.1.1.1.1 Raw materials may be purchased from an authorised centre as defined by Royal Decree 2259/1994 of 25 November, which regulates pharmaceutical stores and the wholesale distribution of medicines for human use and pharmaceutical products.
4.1.1.1.2 Raw materials purchased from other organisations, including hospitals and faculties.
It is incumbent upon the responsible pharmacist to be conversant with the quality system of the raw material manufacturer and to engage in the exchange of information and documentation with the aforementioned parties on matters pertaining to production, control and processing.
4.1.1.1.3 Water.
From both qualitative and quantitative perspectives, water represents one of the most significant raw materials utilized in the preparation of pharmaceutical formulations and office preparations. It thus falls upon the pharmacist to exercise the utmost care in ensuring conformity.
4.1.1.1.4 Centralised procurement by the relevant administrative body (ministry or pharmaceutical association) is to be employed in the case of active and excipient substances for which import is not possible.
In the event of exceptional supply difficulties, an exception may be made.
4.1.2 Reception and Quarantine
It is imperative that raw materials undergo an initial inspection to ascertain their integrity, appearance, and labeling.
Following this preliminary verification (validation), the raw materials received should be immediately recorded and placed in quarantine until their final acceptance or rejection is determined. To obviate any potential for ambiguity between raw materials in 'quarantine' and those that have been accepted or rejected, it is imperative that they are stored

in discrete, distinctly labelled locations. Furthermore, a system must be established whereby quarantined products can be distinguished from accepted products by their labelling, in order to prevent confusion.
4.1.3 Conformity control.
The raw materials used for the preparation of magistral formulae and office preparations must comply with the requirements set forth in the Royal Spanish Pharmacopoeia, or, in the event that the Royal Spanish Pharmacopoeia does not provide guidance on a particular matter, with the standards set forth in a recognised and prestigious pharmacopoeia. The specific conformity checks to be carried out will depend on the origin of the raw material in question and the controls to be carried out. The following checks are to be carried out:
4.1.3.1 In the case of raw materials subject to control by an authorised centre, the control reference number and the certificate of analysis obtained from the aforementioned centre and duly signed by the technical director shall be deemed sufficient to guarantee the quality of the product.
In any case, given that the responsibility for the quality of the pharmaceutical formula or the office preparation rests with the pharmacist, it is considered appropriate to verify, at least by some means, all the criteria to be met by the raw materials supplied (analysis reports).
4.1.3.2 Raw materials that have not undergone analysis at an authorised centre.
It is the responsibility of the pharmacist in charge to conduct a comprehensive analytical control of the raw materials provided, ensuring compliance with the standards set forth by the Royal Spanish Pharmacopoeia. Additionally, they must prepare the quality control form in accordance with section 3.2.3. Furthermore, analytical services may be obtained from a laboratory that has been duly accredited by the relevant health authority, in accordance with the provisions set forth in Royal Decree 2259/1994 of 25 November, which regulates pharmaceutical stores and the wholesale distribution of medicines.
4.1.3.3.3 In either of the aforementioned cases, once the requisite control has been carried out, the pharmacist shall act as follows:
4.1.3.3.1 Accepted raw materials: the pharmacist shall assign an internal registration number specific to the pharmacy or its pharmaceutical service.

4.2.5. Section V

Details

In order to guarantee the quality of the medicinal product in a documented manner, all operations carried out during the preparation process must be accurately detailed in accordance with the standards set forth in the National Formulary or other recognised scientific sources of similar prestige. Furthermore, in line with quality control norms, before a medicinal formula or an office preparation is prepared, all the working procedures for its preparation must be reviewed in detail.
In the context of drug preparation, it is of paramount importance to implement a process that is free from errors, confusion, omissions, and contamination. It is of particular importance to consider all factors that may potentially impact the stability of the preparation.
5.1 Preliminary checks.
Prior to the commencement of production, the individual responsible for the process should evaluate the suitability of the preparation from a pharmaceutical standpoint. Additionally, they should ascertain the following:
5.1.1.1 The absence of any products, materials, or documentation unrelated to the preparation procedure to be carried out in the pharmacy laboratory.
5.1.2 The laboratory must also ensure the availability of all relevant documents, materials and tools, including those that may be hazardous or toxic, and that their condition and expiry date have been verified. All items must be correctly labelled.
5.1.3 The correct functionality of the instruments to be utilised. It is imperative to ascertain whether the last control and calibration dates of measuring and analysing instruments, in particular balances, have been duly updated.
5.1.4 The instruments and laboratory space must be cleaned in an appropriate manner.
5.2 Details are provided below.
5.2.1 It is the responsibility of the pharmacist to oversee the weighing or measuring of raw materials. In the event of toxic substances or high pharmacological activity, the responsibility for checking the weighing or measurement falls upon the pharmacist.
The handling of unstable, dangerous or toxic raw materials (section 3.2.2) must be conducted with the requisite precautions.
In any case, the procedures described in the specific monographs of the National Formulary or other relevant sources must be followed during the preparation stage.
5.2.2 Throughout the processing phase, containers and utensils must be appropriately labelled to facilitate comprehensive identification of the raw materials, intermediate or finished products, and the stage of preparation.
5.2.3 During the production phase, a relevant production and control manual should be compiled in accordance with the data listed in section 3.4.2, which should always allow for the historical reconstruction of each step of production. It is imperative that all processes are meticulously harmonised and duly recorded in this manual.
5.2.4 The packaging material used should be such as to ensure that, depending on the nature, pharmaceutical form and stability of the preparation, it is correctly preserved until the expiry date.

It is of the utmost importance that the labelling is carried out with the utmost care in order to avoid any errors or confusion. Furthermore, it must be in accordance with section 6.1.
5.2.5 The quality control of finished preparations shall be carried out in accordance with the sequential procedures set forth in the National Formulary and in the documentation described in Section III. Additionally, samples shall be analysed in accordance with the established rules. The decision to accept or reject the manufactured product, as set forth in the Royal Spanish Pharmacopoeia and in the data in Section 3.4.2 of the National Formulary, signifies that the pharmacist assumes responsibility for the finished product.
The following minimum controls of the finished product have been established:
a) Magistral formulae: Examination of organoleptic properties.
b) Controls on standard formulae and office preparations shall be as specified in the National Formulary.
It is incumbent upon the pharmacy to maintain a sample of each batch of office preparations that is sufficiently large to permit a comprehensive examination of the product up to one year after the expiry date. In the case of non-official preparations and standardised major formulae, the expiry date will be determined in accordance with the expiry date stated in the relevant monograph of the National Formulary.
In the case of the remaining principal formulations, the date will be established in accordance with the prescribed treatment's duration.
In instances where the legislation in force stipulates that the fulfilment of any stage of the production or analytical control of a preparation is entrusted to another undertaking, the pharmacist in charge shall be held primarily responsible for the quality of that preparation.

4.2.6. Section VI

Distribution (presentation to the patient)
The dispensing of medicinal formulae and off-label preparations shall be regulated in accordance with the provisions of the current legislation.
Magistral formulae and office preparations must be presented in containers appropriate to their nature and intended use in order to guarantee the preservation of their content and quality throughout the period of manufacture and expiry determined by the pharmacist.
It is incumbent upon the dispensing pharmacist to provide the patient with adequate information regarding the correct identification, storage and use of the products in question at the time of presentation.
The aforementioned information shall consist of the data indicated on the label and in the remarks, which must comply with the content of the monographs included in the National Formulary.
6.1 Labelling
1. The labelling of containers of magistral formulae and office preparations must comply with the format set out in the National Formulary. It must be easily legible, clearly understandable and expressed in indelible characters. It must contain the following data on the primary packaging:
a) the name of the designated off-label preparation as set out in the National Formulary or, where appropriate, the name of the standardised prescribing formula;
c) The pharmaceutical form, route of administration and quantity supplied.
d) The registration number of the Pharmacopoeia or supporting documents replacing it in accordance with the prevailing legislation.
e) The batch number in the case of an off-label preparation.
f) The date of preparation and the period of validity or expiry date.
g) The storage conditions, if any.
h) The name and diploma number of the prescribing physician for preparations requiring a prescription.
i) The name of the patient in the case of major formulae.
j) The name, address and telephone number of the pharmacy and pharmacist.
k) It is recommended that this product be kept out of the reach of children.
2. Where the size of the container does not allow all the above information to appear on the label, at least the following information shall appear
(a) the name of the designated off-label preparation as it appears in the National Formulary or, where appropriate, the name of the Standard Prescription Formulary
(b) at least the full qualitative and quantitative composition of the active substance and of the excipients to be used
(c) the route of administration in case of confusion
d) In the case of the master formulae, the registration number of the pharmacopoeia or of the alternative documentary support in accordance with the legislation in force.
e) Batch number in the case of an official preparation.
(f) Date of preparation and period of validity or expiry date.
g) Identification of the pharmacy laboratory or distribution service.
3.º The other information that cannot be included on the labelling, the written information for the patient that must accompany the dispensing of the medicinal product formulation or the office preparation, must be supplied with the package leaflet.

6.2 Information for the patient.
At the time of dispensing the majoristral formula or the officinal preparation, the pharmacist shall provide the patient with the necessary and sufficient verbal and written information to ensure its correct identification, storage and use, as well as adequate monitoring of the treatment.
In the case of officinal preparations and general formularies, this information shall be provided in full compliance with the points contained in the national formulary.
In addition, the written information to be provided when a master formula is dispensed shall include the following data
a) the name, address and telephone number of the pharmacy or dispensing pharmaceutical service
b) Mandatory declaration; at least the complete qualitative and quantitative composition of the active substances and excipients used in the formulation.
(c) pharmaceutical form, unit dose and number of doses
d) Route of administration.
e) Dose and frequency of administration as prescribed.
(f) the rules to be followed for proper treatment.
(g) where appropriate, conditions of protection and storage.
(h) a warning: Medicinal products should be kept out of the reach of children.
2. Where the nature of the medicinal product so requires, special warnings shall also be included, such as
(a) duration of treatment, which should be limited
(b) precautions to be taken in particular population groups (children, pregnant or breastfeeding women, the elderly, sportsmen and women, certain pathologies).
c) possible effects on the ability to drive or to use certain types of machinery.
d) overdose precautions.
6.3 Preparation and presentation to the patient
6.3.1 Presentation of magistral formulations to the patient and official preparations requiring it
7.º If magistral formulations are prepared using readily oxidisable active substances, a biosafety cabinet capable of operating under inert gas should be available.
6.3.2 Prescription and non-prescription preparations containing narcotic or psychotropic substances or substances under special medical control should also be dispensed to the patient in accordance with specific legislation.
6.3.3 After dispensing, the prescription must be kept in the pharmacy for at least three months, without prejudice to the provisions of Article 12.2 of the Royal Decree of 26 September 1910/1984 on prescriptions.
List of minimum equipment for the preparation of main formulae and office preparations (Part II, point 2.2.5).
A. General equipment
(a) balances accurate to 1 mg
(b) Volumetric equipment from 0,5 ml to 500 ml (graduated flasks of various capacities, test tubes, pipettes, etc.).
c) Mortars of glass and/or porcelain.
d) Water bath system. Heating table.
e) Stirrers (mechanical and magnetic).
f) Metal and rubber spatulas.
g) Thermometers.
h) Miscellaneous glassware (beakers, flasks, funnels, watch glasses, etc.).
i) Magnifying lenses.
j) Heat generating equipment.
B. Special equipment.
1. Depending on the galenic form (pharmaceutical form) and the type of preparation, in order to meet the requirements in full;
a) sieves for coarse, fine and ultra-fine powders.
b) pH determination system.
c) Melting point measurement system.
d) If capsules are to be printed, a complete capsule filling and sealing kit shall be available.
e) If ovules or suppositories are to be manufactured, the appropriate moulds must be available.
2.º If tablets and/or dragees are to be manufactured, the following equipment is compulsory
a) a mixer.
b) Compression machine.
c) Dragee drum.
3.º If ophthalmic, injectable or other sterile preparations are to be made, it will be necessary to have
a) Autoclave.
b) Liquid dispersers and phase separators (Soxhlet device, centrifuge, etc.).
c) Devices for sterilising filtration equipment.
d) Laminar air flow hood.
e) Dry heat sterilisation and depyrogenation oven.
f) Homogeniser
g) Equipment for sealing ampoules, vials and bottles.
h) Adequate material washing system.
i) Heater digital table.

j) Petri dishes.
4. If the active substance is freeze-dried, the following features must be available:
a) Freeze dryer (dry freezer).
b) Refrigerator with freezer.
5.º If tablets/capsules are made, there shall be a separate box for each tablet or capsule.
6.º Impregnation and dynamisation systems are required for the preparation of homeopathy granules or globules.
7.º If magistral formulas are prepared with easily oxidisable products, they must have a hood capable of working with inert gas.
8.º To carry out analytical determinations of raw materials and manufactured products, the necessary equipment shall be available for each case in accordance with the provisions of the Royal Spanish Pharmacopoeia and the National Formulary.
Raw material quality control document;
In which the necessary identification data and checks carried out by the pharmacy (preferably using computerised tools) will be recorded.
The raw material quality control document shall contain at least the following
Data on the raw material:
Internal control registration number (which must appear on the master formulation registration form).
Name of the raw material.
Batch number.
Supplier.
Quantity of raw material.
Analytical control expiry date or repeat date.
Controls performed and additional data:
Analytical techniques used.
Description of analytical methods.
Results obtained.
Confirmation of acceptance or rejection.
Responsible pharmacist.
Magistral formulation record form [41,51].

5. DISCUSSION

The relevant articles in the above-mentioned laws and regulations emphasise that the duty of pharmacists is a sacred and honourable duty which, like that of doctors, requires the utmost care and that pharmacists must act with great responsibility in the exercise of their profession. In general, the responsibilities of pharmacists are defined not only in one law, but also in many laws in the form of prohibitions or the assignment of duties.

Medicinal products must be at least as effective, safe and of high quality as preparations and must be produced in appropriate places and under appropriate conditions. The Regulation on the Licensing of Medicinal Products for Human Use, which aims to ensure the efficacy, safety and quality of medicinal products, states that all types of products referred to as magistral are excluded from its scope. Pharmacists are obliged to pay due attention to their laboratories in order not to abuse this privilege, which is recognised as a result of the trust placed in pharmacists in our country and throughout the world.

On the other hand, there is a need to redefine and categorise pharmacy laboratories in order to contribute to the improvement of the quality of Magistral production activities in Türkiye at an internationally competitive level, to increase the safety and quality of formulations in the production of Magistral prescriptions written by doctors in pharmacy laboratories and, if necessary, under aseptic conditions, using technological infrastructure at the standards specified in international sources of formulation and stability.

The Magistral Pharmacists Association was established in Konya in February 2020 with the objective of organising a range of training activities for pharmacists and physicians. These activities were designed to ensure the activation and development of "Magistral Production" activities, which represents the art of the pharmacist. Furthermore, the Association's activities were intended to support pharmacists and pharmacist organisations working on this issue.

The association is a speciality body that contributes to the improvement of the quality of pharmaceutical production activities in our country at an internationally competitive level. It aims to move forward together with

qualified pharmacists who comprehend current and developing technologies, are equipped with research-based knowledge and skills, have ethical principles and attitudes, and have adopted the principle of lifelong learning.
The preparation of pharmaceutical formulas, which is the process of creating medicines, has been a continuous activity in pharmacies since the inception of pharmacy vocational education at the academic level.
The production of drugs that are not currently available, or that are intended for treatment but which manufacturers are reluctant to produce due to the unprofitability of the investment in research and development, is becoming increasingly important in the global pharmaceutical industry.

6. CONCLUSION

In our country, the drugs prescribed by our physicians are manufactured in pharmacy laboratories, namely "Compounded Production". The cost-effectiveness of the drug and the national project are evaluated to prevent unnecessary expenditure in the field of health and improve the quality of treatment of patients.
Furthermore, prescriptions containing the "Compounded Formula" will enhance the reputation of physicians and pharmacists and expand the range of available treatments.

In the current economic climate, it is crucial to rethink the role of pharmacy laboratories in the "Domestic and National Production" project and reconsider the production of magistral within this framework.

Indeed, the hand antiseptics produced by pharmacists in their laboratories during the initial stages of the Covid-19 pandemic have once again demonstrated the crucial role of magistral production in terms of public health. Consequently, the pharmacists of this country possess the requisite knowledge and equipment to contribute to the resolution of extraordinary situations or the production of drugs in short supply. Consequently, pharmacies are not merely distribution points for pharmaceuticals but rather centres to produce medicines. This review study examines the laws, regulations, and rules applicable in Türkiye and Spain for the preparation of compounding products. It also considers the future of compounding pharmacy.

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