

## **Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe**

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## Introduction

An active substance can rarely be administered as such. In the great majority of cases, compounding is required in order to obtain a final product suitable for administration, taking into consideration the characteristics of the active substance, the route of administration, the best pharmacokinetic profile and the patients' compliance.

Traditionally, compounding was the main activity of the pharmacist of the past, being about 80% of all the prescriptions until 1950s. In the second half of 19th century, drug manufacturing, the mass production of drug products, began to dominate the supply of the mainstream market [1], moving pharmaceutical preparation from a pharmacy context to a manufacturing one. Today more than 90% of medicinal products are of industrial origin. Simultaneously with the industrial and technological development, the framework of applicable technical standards has also been developed (see GMP evolution), to guarantee a level of quality, efficacy and safety of the medicinal products consistent with the current development.

The loss of importance in compounding activity both for the pharmacy and the society ensued an impoverishment of the pharmacist's culture and training and a reduced normative attention as legislation not always evolved and stayed in line with the public protection requirements [2]. However, pharmacy compounding is still a key component of pharmacy practice and a relevant therapeutic service, other than an integral part of the modern health care system. Through this practice, patients with particular needs may obtain tailored medicaments. Many patients, whose needs are not met by industrial products, depend on the skills of the compounding pharmacist to prepare a medicament in a dosage or in a dosage form, tailored for their specific situation. Certainly, it is undeniable that pharmacy compounding is not as rigidly monitored as industrial production. Compounding of extemporaneous preparations (magistral formula) in pharmacy is completely different in terms of risk analysis compared to the batch production in the pharmaceutical industry. Pharmacy compounds cannot be tested with the same methods as for manufactured medicinal products and there are several reasons to believe that it is even not necessary, namely a trusted physician – pharmacist – patient relationship, a short-term consumption of the product, the compounding activity reserved only to pharmacist or well-trained technician, and the use of simple equipment for the compounding. In any case, all medicinal treatments bear a certain level of risk; in literature some cases of toxicity caused by the ingestion of bad-quality products, like some deaths and damage in children, or by administration of sterile products are also reported for medicine compounded in pharmacy [3-6]. Safety risks can be minimized through pharmacist knowledge, training, skill and care but also through appropriate regulation of this activity. In any case, we have to accept a different regulation for the pharmacy-prepared

medicinal products respect to regulation applied to industrial products or we have to consider the possibility to renounce to this practice. Nevertheless, considering that there are still many unmet needs, we are convinced that it is not possible to quit this opportunity, so much so that both USA and Europe recognize the need of medicinal products prepared in pharmacies through their norms. In particular, chapters <795> and <797> of US Pharmacopoeia provide general information to enhance the pharmacist's ability in compounding and validate procedures and requirements [7, 8]. Moreover, international organizations like the World Health Organization (WHO) and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) process standards to lead the international development, implementation and maintenance of harmonized procedures. Then finally, many European countries have already applied similar guidelines to guarantee the quality, efficacy and safety of the medicinal products, such as the national or the European Pharmacopoeia monographs. Nevertheless, it seems further necessary to develop a suitable regulation to allow pharmacies to compound an adequately safe medicinal product for the patients.

Aim of this work is to analyze the evolution of the compounding rules and to make proposals about new regulations to warrant the patients the possibility to obtain the proper drug with the adequate quality.

## **Definition and Regulation of Pharmaceutical Compounding**

### **Europe**

The preparation of medicinal products in pharmacies are not harmonized all over Europe; there are only some common definitions. Compounding activity rather falls under the national competencies of individual European countries.

The first European directive of medicinal product was introduced in the 1965 [9], but the compounding activity of the pharmacies was not considered. This concept was introduced with the Directive 89/341/CE [10] that amended Directives 65/65/CE.

Here was defined:

- magistral formula: any medicinal product prepared in a pharmacy in accordance with a prescription for an individual patient;
- official formula: any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question.

These definitions are repeated in the Directive 2001/83/CE [11], which is still in force. This directive exempts “pharmaceutical preparations” from the industrial procedures, such as manufacturing and marketing authorizations. This approach has been recently confirmed by the European Pharmacopoeia monograph on “pharmaceutical preparations” [12]: they are defined as medicinal products generally consisting of active substances that may be combined with excipients, formulated into a dosage form suitable for the intended use, where necessary after reconstitution, presented in a suitable and appropriately labelled container.

Pharmaceutical preparations may be licensed by the competent authority or unlicensed and compounded to meet the specific need of a patient according to current legislation. They are distinguished in two categories:

- extemporaneous preparations (according to Directives 65/65/CE: magistral formula), i.e. pharmaceutical preparations individually prepared for a specific patient or patient group, supplied after preparation;
- stock preparations, i.e. pharmaceutical preparations prepared in advance and stored until a request for a supply is received [12].

Following this definition, in some European countries it is allowed to prepare in stock other than official formulas also magistral formulas, in order to have an immediate availability of the product for the next dispensation.

## **USA**

In the USA, compounding is currently defined by the National Association of Boards of Pharmacy (NABP) as preparation of components into a drug product as the result of a practitioner’s prescription drug order or initiative based on the practitioner/patient/pharmacist relationship in the course of professional practice. Compounding includes the preparation of drugs or devices before receiving prescription drug orders based on routine, regularly observed prescribing patterns [13].

In chapter <795>, “Pharmaceutical Compounding – Nonsterile Preparations” [7], the US Pharmacopoeia defines compounding as the preparation, mixing, assembling, altering, packaging and labelling of a drug, drug-delivery device, or device in accordance with a licensed practitioner’s prescription, medication order, or initiative based on the practitioner-patient-pharmacist-compounder relationship in the course of professional practice. Therefore, the US legislation aims to highlight the importance of the application field of pharmacy preparations and to make distinction from the industrial products.

Traditionally, the boards of pharmacy of each State, supported by the NABP in creating uniform regulations to protect public health, regulate the activity of pharmacy compounding through their general rules and regulations that are not always uniform among States [14].

In 1938 Federal Food, Drug, and Cosmetic Act (FD&C), the FDA's primary source of regulatory authority, passed by Congress to protect the public from unsafe prescription drugs. After Congress in 1938, the FDA did not regulate compounded medications as new drugs. The FDA considered compounding a part of pharmacy practice, which was not a part of its regulatory jurisdiction. The regulation of pharmaceutical compounding, consequently, was left in the hands of the States in their capacity to license and regulate professional practices. FDA's deference to State regulation of pharmacy compounding continued for over fifty years. In the 90's, however, safety concerns triggered attention to the regulation of compounded drug products and the FDA chose to reinterpret its regulatory authority on new drugs. Finally, in 1997, the Congress passed the Food and Drug Administration Modernization Act ("FDAMA"), with a provision meant to regulate and protect the practice of pharmaceutical compounding [14]. The Act exempted compounded products from the new drug provisions of the FD&C, thereby creating a compounding exception to the lengthy and costly drug-approval process to protect the practice of pharmaceutical compounding. The FDA has unsuccessfully attempted at length to restrict compounding pharmacies and has tried to have its authority over the subject matter recognized, but its intervention has been so far marginal and only in rare cases [15].

On September 25, 2013 Senate and House committees of the USA overseeing health policy announced that they had reached an agreement on legislation to ensure the safety of compounded drugs and the national pharmaceutical supply chain [16]. The Pharmaceutical Quality, Security and Accountability Act [17] was prompted by the 2012 meningitis outbreak tied to the New England Compounding Center (NECC) in Massachusetts which killed at least 64 people and sickened more than 750. The inspections subsequent the outbreak at the company's facility found unsanitary conditions. The legislation (title I of the bill) attempted to draw a distinction between traditional compounding pharmacies and outsourcing facilities shipping sterile products across state borders, such as NECC [16]. The FDA would have regulated these larger organizations but exempts from the full spectrum of regulations that are applied to traditional pharmaceutical companies remained, and traditional compounding pharmacies have still regulated by the State boards of pharmacy. Thus, the bill represents a compromise between the need to regulate the large-scale compounding activity and the maintenance of traditional compounding pharmacy. The bill also sets up a tracking drug system: the legislation aims to improve the safety of the US drug supply by requiring enhanced monitoring of the chain of transactions from the manufacturer of a drug to the party that ultimately dispenses the drug to the consumer. It includes serial numbers for drugs and an electronic drug-tracing mechanisms.

### **The aim of compounding**

We have to consider that the exemption of the pharmaceutical preparations from several procedures is justified only by the requirement to meet the special needs of individual patients that cannot be met by the pharmaceutical industry [18].

Among the main therapeutic needs to meet by a compounded product, there are:

- allergies due to excipients contained in medicinal products manufactured by the pharmaceutical industry: the compounder can reformulate the medicament with another excipient that does not compromise the technical properties of the product [19, 20];
- medicines for paediatric patients since the pharmaceutical industry does not often develop paediatric dose and dosage forms [21-23]. For the relevance of this activity it has to consider that some authors estimate that up to forty percent of all paediatric prescriptions in the USA are to be compounded;
- association of active principles: to improve the patients' compliance or to obtain an additional or synergic effect [24];
- orphan drug: an active ingredient that has been developed specifically to treat a rare medical condition [25, 26]. Despite subsidy for the industrial development, compounding has the main role for these medicines;
- medicines for clinical trials and placebo prepared in the hospital pharmacy [27];
- customize therapy like the pain management therapy [28];
- medicines with stability issues: in this cases the extemporaneous preparation is essential [29, 30];
- medicines awaiting authorization: compounders may prepare a medicinal product that has not yet obtained the market authorization, if the active is already known and commercialized.

### **Regulation for the quality, safety and efficacy of preparations**

The Good Manufacturing Practices (GMP) are applied to medicinal products manufactured by the pharmaceutical industry. GMP is a system for ensuring that products are consistently produced and controlled according to quality standards. This guideline is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product [31]. The European Medicines Agency (EMA) has established that pharmaceutical companies must follow GMP procedures in all EU territory, having as main objectives safeguarding the health of the patient as well as producing good quality medicine.

GMP cannot be applied to the pharmaceutical preparations and there are several reasons to believe that this is even not necessary:

- compounded products are prepared for the immediate use;
- compounded products cannot await the long and severe trials that the manufactured ones have to follow;
- preparation of compounded products is directly carried out by the pharmacist or a technician under the pharmacist's supervision, while in industries production is made only by technical staff;
- compounding is mainly based on a trusted physician – pharmacist – patient relationship;
- pharmacies have less automated equipment than the industries, where batches are larger and a major risk must be considered.

Because of these considerations, in 2008 the “PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments” (Ref.: PE 010-3) was proposed by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC/S are two international instruments among countries and pharmaceutical inspection authorities, whose mission is to lead the international development, implementation and maintenance of harmonized standard practices of production and quality systems of inspectorates in the field of medicinal products. Among the participating authorities, there are worldwide agencies, like FDA, and institutions of many countries in Europe and beyond.

Whereas PIC/S Guide PE 009 applies to industrial manufacture of medicinal products, the basic requirements presented in Guide PE 010-3 are referred to the preparation of medicinal products normally performed by healthcare establishments for direct supply to patients [32]. The PIC/S guide follows the structure of the GMP Guide for industry and recognizes that other methods than those described in the Guide are acceptable and desired. The PIC/S guide is not intended to place any restraint upon the development of alternative systems, new concepts or new technologies, which provide a level of quality assurance at least equivalent to those set in this Guide.

Underlining the need to apply, whether possible, relevant international standards, such as those developed by the WHO and the PIC/S, in 2011 the Committee of Ministers of the Council of Europe adopted a Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients [33].

This Resolution aims to harmonize quality and safety assurance and standards for pharmacy-prepared medicinal products among the European countries and to fill the gap in quality and safety assurance between preparation in pharmacies and medicinal produced by the pharmaceutical industry. This Resolution recommends that the governments of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia adapt their regulations in accordance with the principles set out in this document, applied to both extemporaneous and stock preparations. The Resolution has raised some interesting issues. It

underlines that all health care professionals are their own responsibility in the pharmacy preparations. Moreover, these preparations are of added value if, due to medical, pharmaceutical or personal reasons, they are needed by a specific patient or by specific group of patients with particular needs. In our opinion, the prescriber should be responsible for evaluating the added value of an extemporaneous preparation, while the pharmacist should consider if it is more risky to supply that extemporaneous product to the patient, or to leave the patient without this medicine. Finally, added value and risk assessment of preparations are to be evaluated and documented in a suitable product dossier by the dispensing pharmacy. These ethical considerations are already present in the European Pharmacopoeia [12] where is considered the possibility to prepare an unlicensed pharmaceutical preparation if a suitable level of risk assessment is undertaken. The risk assessment is based on some considerations such as the dosage form and administration route, the amount prepared, the pharmacological effect, the therapeutic window, the type of preparation process and if the pharmacy makes preparations for internal or external supply.

The Resolution establishes that pharmacy-prepared medicinal products can be distinguished between two risk levels (i.e. “high-risk preparations” and “low-risk preparations”), and between two different levels of quality assurance system. GMP Guide is recommended as a reference for an appropriate quality control system for “high-risk preparations” and the PIC/S Good Preparation Practices Guide for “low-risk preparations”.

Briefly, upon receiving the prescription, the pharmacist first evaluate the added value of the extemporaneous product, thus establishing if the preparation can take place. Then, the compounder undertakes an appropriate risk assessment in order to determine the level of quality control system which should be applied to the pharmaceutical preparation. Before beginning to compound the preparation, a product dossier must be developed on the basis of the risk assessed. Therefore, after evaluating the added value of the compounded preparation along with the related risk assessment and considering the risk linked to the unavailability of that medicinal product, the dispensing pharmacist can decide whether the preparation has to be compounded.

Authorization by the competent authorities or bodies is a prerequisite for a pharmacy to carry out operations. If considered appropriate to guarantee the quality and safety of pharmacy preparations, the authorities should provide for an additional authorization, that can be granted or suspended, depending on compliance with its conditions, or an appropriate notification for high-risk preparation. These procedures could improve the safety assurance and the quality of preparations. In the USA is already present a sort of voluntary accreditation by the Pharmacy Compounding Accreditation Board (PCAB), so patients may have a direct demonstration of the pharmacy certification. Certainly, the basis for a quality preparation must be a clear and complete documentation of all activities and raw materials, procedures, and responsibilities. This point is well explained both in the ResAP(2011)1 [33] and in the US Pharmacopoeia [7, 8].



The Resolution requires the draft of a “product dossier” for stock preparations by the pharmacist-compounder.

For extemporaneous preparations, it is not possible to compile a complete product dossier, because it could lead to a delay in the supply of necessary medicines, but a batch record must be created. Also the US Pharmacopoeia affirms that a Master Formulation Record should be created before compounding a preparation for the first time. This document helps the compounder to characterize critical processes and establish the risk associated with the preparation. In addition, a Compounding Record should be completed each time a preparation is compounded.

A pharmaceutical preparation is considered safe also if it is correctly labelled. The label should contain complete information, such as reference of the dispensing pharmacy, reference of the preparing pharmacy (if it is not the same), full qualitative composition and the quantity of the active substance, expiring date, special storage conditions or handling precautions, route of administration. Even if the leaflet containing product-specific information to patients, is not required for pharmacy preparations, general information to patients concerning the therapy and the use should be given and this is recommended by the Resolution. A complete label is synonymous with transparency and safety.

The Resolution proposes an appropriate system for reporting quality and safety issues to the competent national authority as, at this moment, pharmacovigilance and inspections by the competent authorities are well defined only for industrial manufacturing.

## **Conclusion**

All national authorities agree that the risk associated with pharmacy-prepared medicinal products is considered acceptable, because of their added value, even if they are not prepared with the industrial rigor. After all, until today the legislator neglected the compounding activity, focusing its attention on industrial products that are the greatest part of the drug market.

If the attention to pharmacy-prepared medicinal products increases, the requests to the pharmacies would increase and, accordingly, the associated costs; so we may need a greater specialization of compounding pharmacies. This way would allow some pharmacies to invest in technological development to produce high-quality and safe medicinal products. A possible solution could be to allow pharmacies to prepare medicinal products on behalf of other pharmacies: this situation is already noticeable in some European countries. Another way to ensure the competence of a compounding pharmacy to patients could be an additional

license or accreditation for high-risk preparations (e.g. sterile products). Moreover, a leaflet with essential information, such product-specific information based on the product dossier and literature, could be given to the patient. This could ensure more transparency and safety for the patient. Also universities may make a propulsive development of this activity, educating pharmacists and prescriptors of the future on the importance of compounding and the necessity to comply with regulations and standards to prepare medicinal product of suitable quality and safety.

Moreover, in a more harmonized European context, it is the time for a modernization of the regulation of medicinal products prepared in pharmacy, even if it must be recognized that they have a traditional history linked to the national territory. Although compounded products are not likely to be in international commerce, it is no longer acceptable to have different quality standards among European countries, because the safety of patients must be considered as a common good and, therefore, cannot exist differences among European patients. Organizations such as International Conference on Harmonization (ICH) and PIC should be further involved to improve regulatory harmonization.

Therefore, an improved quality in medicinal products prepared in pharmacy can be achieved, or at least approached, from several fronts: the legislation on medicinal products prepared in pharmacies has to be modernized and adapted to the needs of the present days, a new regulation for the pharmacovigilance should be introduced; the technical regulation, i.e. the European Pharmacopoeia and the national pharmacopoeias for European countries, has to provide specific Good Compounding Practice to be followed during the compounding activity and specify the importance of the risk assessment and the added value of each preparation.

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