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

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ABSTRACT

Pharmaceutical preparations are medicines that the pharmacist makes for the special needs of the patients that the pharmaceutical industry cannot comply for economic and logistic reasons. Pharmacy compounding is still an important component of pharmacy practice and a valuable therapeutical service that is an integrant part of the modern health care system, but its legislation is not harmonized among European and US countries.

In 2011 the Committee of Ministers of the Council of Europe has adopted a Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. Aim of this resolution is to harmonize quality assurance and standards for pharmacy-made medicinal products among European countries and to pass the gap in quality assurance and standards between preparation in pharmacies and medicines prepared by the pharmaceutical industry. This article will analyze the actual rules and technical norms that regulate compounding activity and the expectations resultants from the new European and US laws.

1. Introduction

An active substance can rarely be administrated 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 lost 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

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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.

2. Definition and regulation of pharmaceutical compounding

2.1. 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.

2.2. 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