EUCOPE
European Confederation of
Pharmaceutical Entrepreneurs AISBL

Position Paper: Compounding Drugs to Lower Costs Puts Patients at Risk

Compounding – a practice whereby a licensed pharmacist combines, mixes or alters pharmaceutical ingredients in order to prepare a medicinal product tailored to the specific needs of an individual patient – can **play an important role for patients who have unique medical needs**. For example, an elderly patient who cannot swallow a pill would greatly benefit from receiving a compounded medication in liquid form.

Compounded drugs, also known as pharmacy or magistral preparation, can also be beneficial in areas **where authorised medicinal products are not available**. In these cases, following the prescription of the treating physician, the pharmacist prepares a medication in a manner that aims to address the unmet medical need of a patient. This practice is quite common in certain therapeutic areas, such as in child care or for the treatment of rare diseases.

Despite their importance in addressing the unique needs of some patients, **pharmacy preparations are to be classified as unlicensed medicines**, as they do not undergo the scrutiny process licensed products are subjected to by the appropriate regulatory body in terms of quality, safety and efficacy.

There are a number of health risks associated with compounding:

- pharmacy preparations **do not go through the robust clinical trial process** which authorised medicines have to go through – thus they have not demonstrated their efficacy or safety profile as per authorised medicines;
- the **active ingredient may come from a questionable source** and the licensed pharmacist is not obliged to disclose the source of the API used;
- pharmacy preparations are **not subject to Good Manufacturing Practice (GMP)** requirements and this may pose risks to patients in terms of stability and quality of the product;
- by its very nature, the act of compounding increases the **risk of contamination**; and
- compounded products are **not subject to pharmacovigilance practice** in contrast to commercial drugs.

In disregard of its special nature, over the past few years, European patients have witnessed a concerning trend of **compounded products being used in hospitals instead of available licensed medicines without any medical rationale but purely to save costs**. In this context, some pharmacies have started large-scale compounding to replicate existing authorised products, using the same active substance and the same mode of administration. This is known as **economic compounding**. It **contradicts EU legislation and jurisprudence** in this area and carries significant risks for patients.[1] In some cases, economic compounding has even been encouraged by national authorities in an

[1] Resolution CM/ResAP(2011) on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients.

attempt to achieve savings in the healthcare budget to the detriment of patients' health outcomes and safety.

In order to protect patients and high-standard of care in Europe, EU legislation and jurisprudence clearly states that a decision to prescribe a patient with a compounded product should always be made on the basis of the **specific medical need of the patient**.[2] However, as soon as pharmacists are encouraged to dispense compounded products as a way to reduce costs, the medical needs of the patient is not the primary concern anymore and the patient can be exposed to unnecessary risks.

Drug Compounding and the Risks to Patients

Pharmaceutical drugs undergo a robust clinical trial process before they appear on the market. They are also manufactured under the highest standards, so called GMPs, which greatly reduces the risk of quality deficiencies or contamination. After the drug is licenced, companies are obliged to have pharmacovigilance and medical information systems in place and bear liability for the effects of their products used by patients under the terms of the marketing authorisation. Prescribers and dispensers should be obliged to report all adverse events to the appropriate authorities. As the European Medicines Agency explains, "*only industrially prepared products which undergo a rigorous assessment process and are finally granted a Marketing Authorisation can be said to* ***have a demonstrated quality, safety and efficacy***".[3]

On the other hand, **compounded drugs are not subjected to such a rigorous process**: there is no assessment of the efficacy or safety by the competent health authorities, or any vetting of the process used to make the finished drug product; the active ingredient may come from questionable sources and the licensed pharmacist is not obliged to disclose the source of the API used. Compounding pharmacies are not controlled for production of their preparations according to GMP practice. Moreover, product information is frequently lacking in compounded products and there is no obligation in terms of pharmacovigilance and medical information. In these cases, all product liability rests with the prescriber and dispensers.

This opens patients up to increased risks, including due to unreliable manufacturing processes (where the active ingredient is concerned), formulation failures (resulting in sub-therapeutic or overdose being administered) and contamination. In 2012, the New England Compounding Center (NECC), a pharmacy located in Massachusetts, infected more than 800 people with fungal meningitis through compounded medications. Sixty five of those people died. [4]

The 2015 incident at the Careggi Hospital in Florence, Italy, where five patients risked losing their sight after being treated with a contaminated compounded medication despite a licensed alternative being available, was a reminder of the unnecessary risks implied in economic compounding.[5] Despite the risk, patients are often not informed by physicians or pharmacists of the licensed status of the medication they are prescribed.

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[2] Ibid.

[3] https://ec.europa.eu/health//sites/health/files/files/orphanmp/2015_11_pc_orphanmp/replies/2015_11_pc_orphans_ema.pdf

[4] https://www.cdc.gov/hai/outbreaks/meningitis.html

[5] http://www.regione.toscana.it/sl/web/toscana-notizie/-/infezioni-oculari-a-careggi-concluso-l-audit-della-regione

To minimise the risk, the **Council of Europe in its 2016 Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients** made a number of relevant recommendations, including that pharmacy preparations should not be used if a suitable pharmaceutical equivalent with marketing authorisation is available.[6] However, these recommendations are increasingly disregarded by countries in Europe.

Law on Compounding Drugs is Not Harmonised across Europe

Article 3(1) and (2) of Directive 2001/83, which outlines the provisions concerning the marketing, manufacturing and sale of medicines in the EU, provides an exemption from the requirement to obtain marketing authorisation for the sale of compounded drugs. This was recently interpreted by the Court of Justice of the European Union ("CJEU") in a strict manner. The CJEU stated that the **prescription for a compounded drug must be for a particular named patient and that the patient must be identified before the medicinal product is prod**uced. In other words, any product which is prepared in advance in a pharmacy, prior to a prescription for an individual, identifiable patient is not covered by the exemption.

However, national practice is sometimes in contradiction with this court ruling. The exception to the marketing authorisation rule contained in Article 5(1) of the Directive has been used by Member States to accommodate historically existing preparation practices in their legislation, leading to a wide variety of fundamentally different local legal situations. While the CJEU has made clear that **Article 5 exemptions cannot be applied for economic reasons**, the application of the article largely depends on the individual Member State's transposition and the situation remains fragmented throughout Europe.

Economic Compounding Stifles Innovation

The decreased requirements for pharmaceutical quality, development control and pharmacovigilance lead to dramatically reduced costs for preparations, especially when compared to high-priced medicinal products or small-scale industrial production of approved orphan medicinal products. However, these **requirements are in place for approved medicinal products to protect the safety of patients, and ensure the effectiveness of a patients' treatment**; this should not be undermined by the use of compounded preparations.

Allowing or promoting the use of compounded alternatives in place of approved medicines for any reason other than the health and well-being of the patient would also have a **detrimental effect on innovation**. Knowing that compounded preparation could be widely used instead, companies will be less ready to undergo the costly and time-consuming research and development process needed to bring a safe, efficacious, and approved drugs to market.

The consequence of this practice in the medium to long-term is likely to be a reduced access to safe, effective, innovative medicines for patients, especially for fragile groups such as patients with rare diseases, children and the elderly.

[6] https://search.coe.int/cm/Pages/result_details.aspx?ObjectID=090000168065c132

EUCOPE Policy Recommendations

We call the national and European competent authorities to:

- Recognise that prescribing compounded products in place of equivalent licensed products for reasons other than the medical need of a patient **exposes patients to unnecessary risk, creates double standards for patients in Europe and has a negative effect on innovation** and long-term access to safe and innovative medicines.

- Limit pharmacy compounding operations to situations where a **suitable medicinal product with a marketing authorisation is unavailable** and in order to meet the special medical needs of individual patients.

- Ensure that healthcare professionals **educate and inform patients** about the rationale behind the prescription of a compounded product as well as its potential risks, and put in place the tools needed to monitor the effect of the medication on patient and report any potential adverse event.