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Replacement Compounding: A Major Threat to the Marketing Authorization System

Maarten Meulenbelt and Andreas Balsiger Betts

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EU and International Rules Provide Only for *Complementary* Compounding

Pharmaceutical laws in the EU, as well as in Switzerland, provide that no medicinal product may be put on the market before a marketing authorization (MA) has been granted. Such MA requirements do not necessarily apply to products exceptionally prepared in a pharmacy. In EU law, these exceptions are referred to, in Article 3 of Directive 2001/83/EC, as *formula magistralis* ("prepared in a pharmacy in accordance with a medical prescription for an individual patient") and *formula officinalis* ("prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia" and "intended to be supplied directly to the patients served by the pharmacy in question"). For Switzerland, the Swiss Act on Therapeutic Products (TPA) contains corresponding provisions (Art. 9, para. 2, lit. a and b).

These provisions must of course be interpreted narrowly, like all EU and Swiss rules that provide an exception to a main rule that is established to protect public health. Moreover, the scope of these provisions is often misunderstood. Article 3 of Directive 2001/83/EC only determines whether a particular product is regulated by Directive 2001/83/EC (and therefore whether it must have a MA before being placed on the market). Thus, Article 3 cannot provide a definitive answer to the question of whether compounding is legitimate or not. The same goes for the Swiss pharmaceutical regulation.

To answer the question of whether the activity of the pharmacy (or pharmacist) engaging in compounding is legitimate, we must look at national rules, which must moreover be consistent with the rules issued under the Convention on the Elaboration of a European Pharmacopoeia (the Convention). The Convention provides for "monographs" to be adopted, which "shall become the official standards applicable" within the respective countries. There are currently 38 signatory countries, including Switzerland. The EU is also bound by the Convention, and dozens of countries and organizations follow the Pharmacopoiea proceedings as an "observer" (including the United States and the World Health Organization). A network of over 700 experts has contributed to the publications of nearly 3,000 monographs and general texts.

The key European Pharmacopoeia (Ph.Eur.) Monograph is No. 04/2019:2619 entitled "Pharmaceutical Preparations." This monograph provides that (complementary) pharmacy compounding is permitted because it serves to "allow the supply of unlicensed products to meet the special needs of individual patients" (e.g., an authorized product might not be available on the market at all, or the patient might be intolerant to excipients, or might not be able to swallow, etc.). The Convention's Committee of Ministers has also adopted "Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients (succeeding Resolution CM/ResAP(2011)1)." This Resolution calls upon all 38 Ph.Eur. countries to provide that

pharmacy preparations are of added value only if "due to medical, pharmaceutical or personal reasons they are needed by a specific patient or by specific population groups with particular needs," and that "Pharmacy preparations are not advisable if a suitable pharmaceutical equivalent with a marketing authorisation is available."

Clearly, all of these rules envisage compounding to be complementary to authorized medicinal products and not as a replacement for authorized products.

A Fundamental Shift

The Ph.Eur. rules sustain the general principle that authorized medicinal products, manufactured within clearly defined and controlled processes and assessed by national competent authorities before being put on the market, are safer than products prepared on a small scale in public or hospital pharmacies. Furthermore, the Ph.Eur. rules confirmed pharmaceutical companies' decades-old trust that if they succeeded in obtaining an MA (and reimbursement), their products would not be copied in pharmacies unless in exceptional circumstances where an individual patient could not use their authorized product for personal, medical reasons.

That trust has been eroded by a trend that started in the Netherlands last year. In April 2018, the Amsterdam Medical Center hospital, in cooperation with the main national insurance companies, put a "replacement compounding" product on the national market on such a large scale that the entire national population of an orphan disease (cerebrotendinous xanthomatosis, or CTX) was switched to the compounded product, purely for cost reasons. As a result, the sales of the authorized orphan drug dropped to a level close to zero. The contractual structure used for this "replacement compounding" was condoned by a decision of the Dutch Health and Youth Care Inspectorate (IGJ) of November 19, 2018, and confirmed by a decision of the Minister for Medical Care of August 13, 2019, permitting all orphan patients in the country to be "loaned" to a single, central pharmacy. These decisions are being appealed, but they currently represent state policy.

The replacement compounding of CTX products was temporarily halted in August 2018, but only because the IGJ found that the active pharmaceutical ingredient (API) — sourced from China and manufactured according to a Chinese monograph from 1995 — had not been manufactured in accordance with the European Pharmacopoeia, was unstable and had eight to 10 times the level of unknown impurities.[1] The IGJ stated that patients' health was put at risk by the pharmacy's use of this API. However, this did not stop the Dutch government from expressing strong support for compounding. In Belgium, which also saw compounding on a national scale, efforts are reportedly being made to "adapt the requirements a raw material must comply with — to allow versions of drugs with minor impurities" (see

[1] See https://www.igj.nl/actueel/nieuws/2018/11/28/igj-publiceert-besluit-op-handhavingsverzoek-eigen-bereiding-cdca-door-amsterdam-umc, click on "Uitgeschreven tekst" (written text).

https://www.theguardian.com/science/2019/oct/15/diy-drugs-should-hospitals-make-their-own-medicine).[2]

More compounding is expected: Changes in government policies have created openings, and more Member States are expected to follow. Moreover, several lists of "targets" for replacement have already been published.

Swiss Exception?

In October 2010, to ensure a better quality of compounded drugs, the Swiss TPA was amended to allow the manufacturing of *formula magistralis* and *formula officinalis* products in small batches. Furthermore, the Swiss legislature, reacting to requests by hospitals, introduced a *formula hospitalis* (Art. 9, para. 2, lit. c^{bis} TPA) allowing hospital pharmacies to manufacture certain medicinal products for their own patients. However, this possibility is explicitly restricted to products for which there is no authorized alternative on the Swiss market.

On this background, it seems clear that *formula hospitalis* products cannot be used to replace authorized products. However, one could argue, a contrario, that the TPA contains no analogue restriction for products manufactured within the *formula magistralis* and *formula officinalis* concept. This view is supported by the fact that a public draft of the recently revised Ordinance on Medicinal Products (OMP) contained a prohibition to manufacture *formula magistralis* and *formula officinalis* products – a prohibition that did not find its way into the definitive OMP. Notwithstanding these arguments, the Ph.Eur. — as expressly stated in Article 8 TPA — is an integral part of the Swiss regulation of medicinal products. Therefore, the Ph.Eur.'s restrictions regarding the replacement of authorized medicinal products through compounding are as valid in Switzerland as they are in the EU.

[2] See also the background article published in NZZ am Sonntag: https://nzzas.nzz.ch/wirtschaft/gefaehrliche-medikamente-marke-eigenbau-ld.1508747?reduced=true.