The Council of the European Union is expected shortly to formally adopt a directive on falsified medicines.

The legislation, which was approved by the European Parliament on 16 February, aims to improve the safety of drugs by preventing falsified medicines from entering the legal supply chain. Measures in the directive intend to ensure easier identification of falsified medicines and improved checks and controls at EU borders and within the EU. However, each measure will have its own specific impact on costs for the entire pharmaceutical supply chain, which will in turn have serious implications for patients.

The prevalence of falsified medicines in the EU is low. The directive is unlikely to improve the already safe supply of drugs from GMP-authorised manufacturers. The increased production costs that its measures will entail will place more pressure on company profits. Generics companies, particularly, are likely to be affected. In a bid to offset the extra costs, they might be forced to raise their prices or stop manufacturing drugs that become unprofitable altogether. Ultimately, it will be the end users of medicines who will suffer.

The legal manufacturing process

The distribution chain as we know it today is a closed system. The starting point of the distribution chain for medicinal products in the EU is the batch release by the qualified person of either the manufacturer established within the EU or the importer importing the medicinal product from a third country. The responsibilities of manufacturers and importers are identical. All manufacturers and importers must be authorised for their activities by the European Economic Area member state in which they have their seat and they are subject to strict good manufacturing practice supervision by the competent authorities.

Manufacturers and importers are responsible for all the manufacturing steps before them. The qualified person signs off the protocol for the entire production process. This process begins with the purchase of starting materials: the active pharmaceutical ingredient and the excipients. Each batch of any starting material cannot be used without formal action: the manufacturer of the finished product must check that the starting materials fall within the specifications of the dossier in the marketing authorisation and comply with applicable monographs in the European Pharmacopoeia. Furthermore, since the adoption of Directive 2004/27/EC, manufacturers are required to audit the source of all APIs as well as certain excipients that will be listed by the European Commission in a commission directive. This commission directive has not yet been adopted. The holder of the manufacturing authorisation is bound to the manufacturing process as it is laid down in the marketing authorisation. Furthermore, the manufacturer must comply with EU GMP.

Following the batch release, the finished product may only be delivered to the holder of another manufacturing authorisation or a wholesale distribution authorisation or to a pharmacist.

Is there a problem?

Falsified medicinal products present a huge problem around the world. They occur mostly in two types of situations: in internet sales of lifestyle drugs by criminal organisations and in countries that cannot afford, or are unable to run, adequate competent authorities. The World Health Organization estimates that 50% of internet sales from websites that conceal their physical address involve counterfeits.

The presence of falsified medicines in regular supply chains varies greatly between industrialised countries, on the one hand, and developing countries and countries in transition, on the other: The WHO estimates that the presence of counterfeits in well-regulated markets such as the EU is extremely low – less than 1% of the market value. Within the normal EU distribution chain, there appear to be few problems with falsified medicinal products showing up in regular pharmacies. The system of authorisations and enforcement that governs the supply chain largely seems to work.

The new directive

The falsified medicines directive is one of three legislative proposals of the EU "pharmaceutical package", which the European Commission presented on 10 December 2008 to improve the safety and accessibility of medicines and to foster innovation in the pharmaceutical sector. The term "falsified" has been chosen over "counterfeit" so as to focus on the public health impact of fake drugs rather than intellectual property issues.

The legislation addresses four different areas. Firstly, it is designed to ensure that the identity of medicinal products travelling through the supply chain is secure. Packages would be sealed in such a way as to enable the detection of tampering, and each pack would carry a unique identifier that would reveal its identity when dispensed. Such a system would make the supply chain more watertight.

Secondly, an authorisation or registration would be required for traders and brokers dealing with medicinal products. This means that it will not only be the physical distribution chain that will contain authorised entities – parties that buy and sell medicinal products but do not actually handle the products will also be placed under regulatory supervision. The authorisation of traders and brokers might improve the prevention of falsified medicinal products from entering the legal supply chain because authorities can take a closer look at their business records and their background. However, it can be argued that traders and brokers that do not actually handle medicinal products are unable to physically tamper with medicinal products in the supply chain anyway.

Thirdly, the rules for the manufacturing and import of starting materials, especially APIs, are to become stricter. Since the manufacturing of more than 90% of starting materials takes place outside the EU, mostly in India and China, the falsified medicines directive will have external effects, which are discussed below.

Finally, the new directive addresses pharmacies on the internet. A completely new chapter has been introduced to Directive 2001/83/EC on medicinal products for human use by the European Parliament in an attempt to regulate internet pharmacies. Internet pharmacies must, according to the provisions, receive national authorisation and display a special logo on their websites.

Is it the solution?

The new directive will be applied within the legal supply chain. This means that the already quite safe regular supply of medicinal products from GMP-authorised manufacturers, purchasing their starting materials under GMP conditions, will not be improved. The new measures might improve the safety in the pharmaceutical supply chain by further discouraging illegal entities to tamper with medicinal products. But since the prevalence of falsified medicines is low, the impact of the new measures will remain limited. The new legislation does not address the supply of substandard medicines to (often...
developing) countries that cannot afford to purchase starting materials or finished medicinal products through the EU. In addition, it does not strengthen the regulatory authorities in those countries that would benefit from a reduction of counterfeit and falsified medicines.

**At what cost?**

The directive contains, as already mentioned, three main sets of measures to improve drug safety. Each measure will have a specific impact on costs. As far as the safety features are concerned, the added costs can be easily specified: the cost will add up to a fixed amount per pack, which will depend on the specifications to be set by the commission in the implementing measures. I would argue that the specifications of the safety feature should be related to the resources that possible pirates or counterfeiters obtain to bypass the safety features. Once the falsification techniques parallel the protection techniques, standards will have to be raised. The situation is comparable to developments in the battle against money counterfeiting.

A particularly difficult problem relates to enabling parallel traders to continue doing their business. Substitution of safety features might be the weakest link in the effectiveness of the system. Therefore, supervision of the premises of these entrepreneurs needs to guarantee that they are able to function properly.

Less predictable are the costs that will be imposed by establishing a “pedigree” or tracking system for each individual pack. It can be expected that building a system that contains the necessary safeguards for uninterrupted functioning will be a huge undertaking. In essence, the tracking system should allow even a pharmacy in a village on a small island in Greece to read a (one or two dimensional) barcode and check it in the database before a specific pack could be supplied to the client. However, if the system failed, the prohibition on dispensing without verification would lead to acute problems of availability of medicines for treating the patients. Failure is not, therefore, acceptable. Setting up this tracking system for billions of boxes of medicines that have 100% availability and cannot be tampered with may prove to be a very expensive enterprise.

Last but not least are the costs caused directly or indirectly by the new provisions in respect of the manufacturing of starting materials in third countries. An important new provision of the legislation is Article 46b(2), which is to be included in Directive 2001/83/EC. This provision is paraphrased as follows:

**Active substances shall only be imported if the following conditions are fulfilled:**

(a) the active substances have been manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the Union pursuant to Article 47; and
(b) the active substances are accompanied by a written confirmation from the competent authority of the exporting third country of the following:

i) the standards of good manufacturing practice applicable to the plant manufacturing the exported active substance are at least equivalent to those laid down by the Union pursuant to Article 47;

ii) the plant concerned is subject to regular, strict and transparent controls and to the efficient enforcement of good manufacturing practice, including repeated and unannounced inspections, ensuring a protection of public health at least equivalent to that in the Union; and

iii) in the event of findings relating to non-compliance, that information is supplied by the exporting third country to the Union without any delay.

The consequences of this new provision are far-reaching. In fact, EU manufacturers of finished products will depend on the policies of countries like China and India – which, as already noted, supply 90% of starting materials for medicinal products – to be able to continue to conduct business as usual. If these countries will not adhere to EU standards in respect of GMP for starting materials and, more importantly, will not set up an inspection system at the same level as it should be functioning in the EU, they will not be able to supply any starting material for medicinal products to the EU.

EU manufacturers would have to purchase their active pharmaceutical ingredients, as well as certain excipients, elsewhere. This would of course be a disaster for China and India, which would lose a major market. It would also be an outright disaster for the EU industry. New suppliers would have to be sought; the number of countries able to meet the requirements of Article 46b(2), however, appears to be limited. This could lead to a steep rise in costs for manufacturers.

**Who will bear the extra costs?**

The extra costs will be borne by the entire pharmaceutical supply chain. This includes both the innovative pharmaceutical industry and the generic pharmaceutical sector, as well as pharmacists.

In many – if not all – EU member states, healthcare spending is under pressure and this is reflected in pharmaceutical cost-containment policies. The measures taken by both the generic and the innovative industries have led to a decreasing price level. The increase of production costs that would result as a consequence of the directive on falsified medicines will put further pressure on the profits of the industry. This pressure will not be divided evenly between the innovative and generic industries, as manufacturing costs form a large percentage of total costs for a generic manufacturer. For innovators, manufacturing costs are a small percentage of total costs.

I expect, therefore, that the impact of the new legislation will be felt strongly in the generic industry. In the Netherlands, for example, the average price of generic medicinal products has decreased to an all-time-low level of just over €2 for one package. This means that these products are priced at less than half the cost of a pack of cigarettes.

In order to be able to continue manufacturing generic products, the extra costs that will be incurred because of the new directive will have to be compensated by a rise in prices. At the end of the day, these price rises will have to be paid for by the end user of the products, ie either the patient out of his or her own pocket or the tax payer, who pays the healthcare insurers.

If the end user – or the government of the concerned member state – is not prepared to cover the extra costs, generics companies will have to stop manufacturing medicinal products that become unprofitable. Many medicines that are based on older active substances are only manufactured as a generic service product. If costs rise cause these products to become unprofitable, the industry will stop producing them. The absence of some of these older medicines would present a real threat to public health, with the loss of essential medicinal products causing more harm than falsified medicines.

**References**

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