Falsified medicinal products in the EU: legislating in isolation?

Jackie Mulryne, *Christine Bendall* and *Christopher Stothers* analyse the potential impact of the proposed EU legislation on the industry.

The European Commission's proposal to amend Directive 2001/83/EC on medicinal products to include specific provisions in relation to falsified medicinal products is tentatively scheduled for first reading in the European Parliament on 15 February[1,2]. The aims and objectives of the proposal have been generally welcomed, but the scope and rigour of the provisions it contained have received a mixed reception, and a large number of amendments have been made to the original text of the proposal. As such, the outcome of parliamentary proceedings is awaited with interest.

The proposal, part of the 2008 "pharmaceutical package" of EU legislation, was introduced because of the "alarming increase" in the number of medicinal products in the EU that are illegal because they are "falsified in relation to their identity, history or source" and therefore, do not comply with EU requirements. It addresses the commission's particular concerns that falsified products are being channelled through the lawful supply chain and not only through illegal supply routes.

Although the precise numbers are not clear, the commission referred to "many thousands" of such products being undetected in the supply chain during 2007. The Report on EU Customs Enforcement of Intellectual Property Rights published in July 2010 shows that EU customs registered over 43,500 detentions of goods suspected of infringing IP rights during 2009, at least 10% of which were medicines, comprising almost 12 million pharmaceutical articles[3]. These products may contain contaminated or sub-standard ingredients, the wrong ingredients, the wrong amount of ingredients or no ingredients at all. At best, they are useless, and at worst, potentially fatal. They all pose a threat both to human health and to trust in the legal supply chain.

Much of the current legal framework in place to deal with these products is based upon the protection of IP rights through civil actions (eg for trademark infringement) taken by the owner of the rights in question. There are also measures in place to assist in the identification of counterfeit goods to stop them from entering the EU. However, these are distinct from regulatory measures specifically designed to prevent falsified products entering the legal supply chain, and imposing sanctions to penalise failures to comply.

The proposal

The proposal sought to introduce specific regulatory provisions to deal with the problem of falsified medicinal products. However, it did not include a defined term for "falsified medicinal products" to be introduced into Directive 2001/83/EC (although a definition is included in the current draft, see below).

The European Parliament and the Council of the EU must now agree on the wording of the text of the proposal, amended as they consider necessary, before it can become law. (The "ordinary legislative procedure" – formerly the co-decision procedure – is complex. A procedural flow chart is available on the commission's website[4]).

The proposal was based on the commission's view that the causes of falsified products entering and remaining undetected in the legal distribution chain "can be reduced to four aspects", which the current legislation does not properly address:

- falsified products cannot always be easily distinguished from originals;
- the distribution chain is complex and is only as strong as its weakest link;
- there are legal uncertainties surrounding goods in transit through the EU, but which are not placed on the market; and
- active substances entering the manufacturing process may be falsified.

Therefore, it set out measures to assist with the identification, authentication and traceability of medicines. The main elements were as follows.

Safety features relating to packaging

The proposal provided a legal basis for the commission to make obligatory certain safety features (such as bar-coding and seals), which can be used to ensure the identification, authentication and traceability of prescription-only products.

It envisaged a risk-based approach to the implementation of such features, taking account of the "peculiarities" of different product types. The risks of falsification in view of the price, past incidence of falsification, the conditions that the products are designed to treat and the potential public health consequences of falsification would all be factors taken into account in determining what measures are appropriate. The requirements could be waived for certain products in certain situations.

In drafting the proposal, the commission did not intend to prevent the legitimate repackaging of medicinal products, a practice that has been the subject of extensive litigation in the context of parallel importation throughout Europe. However, the basic principle was that there should be a prohibition on the "manipulation" of safety features by persons operating between the original manufacturer and the last "actor" in the distribution chain. "Manipulation" would include removing (in whole or in part), tampering with or over-labelling a safety feature, and strict conditions would be applied to any such manipulation. In particular, any safety feature would need to be replaced by one that is equivalent in assuring the identification, authentication and traceability of the product, under the supervision of a competent authority.

Manufacturing/distribution chain control

The proposal aimed to address the roles and responsibilities of participants throughout the supply chain and was based upon the expectation that, at each level, there are checks and balances that can and should be applied in order to limit the potential for falsified products to enter.

Manufacturers

Title IV of Directive 2001/83/EC (on manufacturing and importation) would be amended to apply to intermediate products and to active substances used as starting materials.

Manufacturers would be required to use as starting materials only those active substances that had been manufactured in accordance with good manufacturing practice guidelines applicable to those materials. Manufacturers would have to verify compliance with GMP by manufacturers of starting materials, either themselves, or by using an accredited body to conduct relevant checks. Manufacturers would be required to inform the competent authorities of products that are, or are suspected to be, falsified.

Manufacturers of active substances would be required to notify their addresses to the member states in which they are established. The Qualified Person (manufacturing) would be responsible for ensuring that any safety features mandated had been applied to product packaging.

Wholesale distributors

Wholesale distributors would be expected (either themselves or through an accredited body) to verify that their wholesale suppliers comply with good distribution practice. If a product was obtained from a manufacturer or importer, they would need to verify that the supplier held the relevant manufacturing authorisation.

Wholesale distributors would also be subject to an obligation to inform the authorities (and trademark owner or marketing authorisation holder) of products that may be in breach of requirements or trade mark rights.

"Others"

There are other parties that may "trade in", "broker" or negotiate sales of products without taking physical possession of them, but whose activities do not fall within the definition of wholesale distribution. These parties are currently unregulated. The proposal, therefore, recommended that they be subject to "proportionate rules".

Imports and exports

The proposal aimed to clarify the requirements in relation to products that are not intended to be placed on the EU market, but which are for export only, and sought to apply the provisions of Title IV of Directive 2001/83/EC to export-only products. To that end, the proposal included a provision to the effect that member states would need to take steps to prevent products not intended for the EU market from being introduced into the EU, if there was reason to believe them to be falsified.

Importers of active substances would be required to notify their addresses to the member states in which they are established. Active substances could only be imported into the EU if it could be shown that they had been manufactured in accordance with GMP or equivalent standards. Written confirmation of compliance would be required from the exporting third country, unless an EU mutual recognition designation applied.

Inspections

The proposal included strengthened provisions with regard to manufacturer and wholesale distributor inspections, including greater transparency of the results of inspections through publication in the EudraGMP database.

After each inspection, a competent authority would be required to report on whether a manufacturer, wholesale distributor or importer was compliant with the relevant good practice guidance. All certificates of compliance issued would be recorded in the database and a list of compliant wholesale distributors would be available. These provisions sit alongside provisions for greater transparency and sharing of information between authorities in the EU.

The publication (and presumably ongoing review) of harmonised principles and guidelines for inspections, including for active substance manufacturers, was also envisaged.

Sanctions

The proposal required that proper provision be made for "effective, proportionate and dissuasive" penalties in relation to activities involving falsified products.

Responses to the proposal

The key report on the proposal was drafted by Member of the European Parliament Marisa Matias for the parliament's Committee on the Environment, Public Health and Food Safety (ENVI), which has adopted a robust approach to framing amendments to the proposal[5]. The amendments (over a hundred), adopted by the committee in April 2010, are wide-ranging and are intended to strengthen the provisions of the original proposal.

Overall, the various parliamentary and non-parliamentary advisory committees have not been convinced that the text of the proposal goes far enough. The rapporteurs' reports for these bodies propose stronger language and requirements that are wider and more specific in scope, particularly as to what should be expected of the "other" participants in the distribution chain. Although the exact wording may vary between committees, it is possible to identify areas of common ground:

- the proposal must address the "internet issue". The World Health Organization has estimated that 50% of counterfeit medicines are derived from illegal internet sites. ENVI suggests registration of legitimate internet pharmacies, use of an EU-logo and publication of details;
- there needs to be substantial effort made to inform the public about falsified products, illegal supply and the risks that may be associated with mail order purchase of medicines. ENVI also proposed public education campaigns about safety features and other measures that may be introduced to prevent falsified products entering the supply chain;
- efforts in the EU must be directed at gathering and studying data on the causes, sources and extent of trade in falsified products, and the resulting data should be applied in developing effective legal measures;
- all participants of the supply and distribution chain, including "traders", "brokers" and parallel importers, should be "authorised" or "certified" (with relevant details retained in an accessible database), and made subject to good practice standards, "verification" and inspection. Reference was also made to the fact that the relevance and application of requirements to parallel importers, particularly as to repackaging, were unclear;
- excipients should be addressed in the same way as active substances;
- more should be done to harmonise names and brands in use in the EU, and the methods of coding and identifying products;
- considerable care and consideration should be exercised in determining (subject to prior consultation) what "safety features" should be imposed and in what circumstances they would not be required. Various concerns were raised, including that generic entry to the market should not be inhibited and that the costs should be proportionate;
- penalties must be severe: the non-parliamentary advisory committee, the European Economic and Social Committee (ECOSOC or EESC) referred to "draconian" penalties and suggested the closure of businesses that contravene the rules; ENVI referred to action against the relevant regulatory authorisation (suspension, revocation, etc) for non-compliance with good practice standards and to sanctions similar to those applied for narcotics offences;
- all mentioned to some degree concerns with regard to terminology and, in particular, the lack of clear definitions in the proposal. Not everyone was comfortable with "falsified" products and preferred the internationally recognised term "counterfeit". ENVI in particular listed terms that required proper definition, including falsified medicinal product, excipient, active substance and brokering; and
- concern was expressed with regard to the timescale (potentially lengthy) over which the provisions might come into operation across the EU.

Moreover, all parties considered that the problem of falsified products is a "multifaceted" and international issue and that EU efforts must not be looked at in isolation. ECOSOC noted: "On its own, this Directive will not be effective. It forms one part of a multifaceted effort involving criminal law, law enforcement, IP protection, customs surveillance and international co-operation."

The WHO, for example, set up the International Medical Products Anti-counterfeiting Task Force (IMPACT) in 2006. IMPACT developed Principles and Elements for National Legislation against Counterfeit Medicinal Products endorsed in 2007. In addition, the Council of Europe is moving forward with its MEDICRIME convention; adopted in December 2010. This is the first international criminal law instrument that criminalises the counterfeiting of medicines and medical devices and also the manufacture

and supply of medical products that are unauthorised or do not comply with security requirements[6]. ENVI considered it important that the EU support these initiatives.

There are concerns that amendments to Directive 2001/83/EC in isolation will not effectively complement and relate to the other relevant initiatives and frameworks. This could ultimately lead to confusion and duplication of various inspection and enforcement efforts.

The ENVI amendments went beyond those matters summarised above, many of which are contained within the most recently published text of the proposal. These included:

- amendments to distinguish manufacturing "defects", which can arise in the course of normal manufacturing activities and which are already subject to regulatory provision, from falsified medicines;
- the proposal that any person who makes changes to packaging should owe a duty of care to the original manufacturer/marketing authorisation holder and be held strictly liable for the adverse consequences of changes made;
- the application of the requirements in relation to active substances to "distributors", ie notification of activities and address to competent authorities, as well as inspections;
- the view that inspection of third-country production sites needed to be better addressed and that certification by the local authority was insufficient, and instead proposing amendments that EU authority inspection is required;
- stronger provisions were inserted to prevent products not intended for the EU market being introduced onto it, including setting up an EU network for the exchange of relevant information between authorities; and
- stronger provisions were inserted for products intended for export to third countries with a view to building EU credibility and facilitating co-operation at an international level.

Next steps

On 6 December 2010, a progress report on the proposal was provided by the council[7]. It referred to the various opinions produced in committee and described efforts made by the Council Working Party on Pharmaceuticals and Medical Devices during informal "trialogues" in 2009 and 2010 to respond to/reconcile the various views and opinions that had been expressed, with the aim of reaching agreement at the first reading in parliament.

During the trialogues between the commission, council and parliament, three issues have comprised the main focus of the discussions: (i) safety features; (ii) sales on the internet; and (iii) sanctions. Since this report, there have been more meetings between the European institutions, and it appears that they have been able to reach agreement on the majority of issues; the most recent text of the proposal was published on 17 December 2010[8].

Though the parliament's plenary sitting is provisionally forecast to take place on 15 February, this sitting has been postponed a number of times due to the continued attempts by the Council Working Party on Pharmaceuticals and Medical Devices to find agreement between the institutions.

The amended text adopted by the parliament will be transmitted to the council in due course. If the council accepts the parliament's amendments, which should be the case if the Working Party has been able to find agreement, the text can proceed to become law. However, if there is no agreement between the parliament and the council, the proposal will go for a second reading, which will result in further delays.

When the amending directive is finally adopted by the council, it will be published in the *Official Journal* and will come into force 20 days after publication. The proposal envisages an 18-month transition period for member states to implement it into national law.

However, the implementation period, and the possibility of interim provisions allowing certain clauses to be brought into force sooner, has been a matter for discussion. It is, therefore, unclear exactly when the proposal (as amended) may be adopted into law and take effect in member states. On current progress, it seems that implementation could not take place before the first half of 2012 – at the earliest.

Implications for industry

Despite its limitations, the proposal does represent a step forward in co-ordinated efforts at a regulatory level to control the circulation of falsified medicinal products and improve consumer health and confidence in the pharmaceutical industry. The most likely implications for industry are described below.

Potentially, more participants in the supply chain will have to hold and maintain an appropriate authorisation and will be subject to good practice standards, compliance checks and audits. This will mean more resources will need to be dedicated to compliance and regulatory functions by both industry and regulators.

Manufacturers and wholesale distributors will need to take steps to ensure they know who is supplying/buying/brokering their products and whether those parties are legitimate, compliant players of the supply chain. Concern has been raised regarding the burden that could be placed on manufacturers to investigate suppliers and to audit those above them in the chain. One of the proposed amendments by the Parliamentary Committee on Industry, Research and Energy also seeks to place liability on manufacturing authorisation holders for the accuracy of the checks they carry out. The extent and cost of the burden of carrying out such checks is likely to vary according to where suppliers are located.

It seems possible that a consequence of the proposal will be a reduction in the number of participants in the supply chain. This would make the position of manufacturers and wholesale distributors easier in terms of the checks that might be needed as to the reliability of business "partners", and might be seen as a way of improving confidence. Exclusive and direct-to-pharmacy distribution may be a practical way of complying with obligations and minimising the risk of someone infiltrating the distribution chain. ENVI's amendments to the proposal included a definition of "managed distribution chain" where the manufacturer delivers a medicinal product directly to a pharmacy. The explanatory note to this amendment stated: "As the risk of a counterfeit product entering this chain [with this method of distribution] is very low, there is a case for these products to be exempted from having to carry safety features." This definition is not within the current draft of the amendments. However, the "particular characteristics of the supply chain" should be taken into account when deciding if safety features are necessary for a particular product.

The commission's pharmaceutical sector enquiry[9] concluded that although it has no particular concerns over direct-to-pharmacy or exclusive distribution models, it would continue to monitor them. There is a risk that if more companies seek to adopt these models, the commission might re-visit its review of them.

Safety features

The current text of the proposal would require safety features to be added to all prescription-only medicines, unless they had been deemed not to be at risk of falsification. In addition, non-prescription medicines deemed to be at risk would also have to bear a safety feature. It is not known at this point what type of features might be mandated by the commission, as this is being left to comitology, ie the commission and representatives from each member state will discuss the implementation of this provision, and it seems likely that industry will have the

opportunity to make representations on any proposals. Examples were mentioned in the proposal's explanatory memorandum and various committees commented upon possible options including tamper-proof packaging, use of serial numbers and other technologies allowing individual product identification.

The nature and time frame that will apply to incorporating these features will clearly affect the cost and practical measures that companies will need to take in order to comply. The Parliamentary Committee on the Internal Market and Consumer Protection expressed concern that the cost of applying safety features might affect the ability to keep downward pressure on prices. It was particularly concerned that whatever measures were chosen, they must be cost effective and that the costs should be distributed across the supply chain. Exactly how the latter might be achieved was not addressed and it might not be unduly pessimistic to assume that they will fall upon manufacturers and marketing authorisation holders.

The commission's impact assessment[10] looked at the possible impact of safety features on parallel trade and repackaging. It stated that it had not taken "a final stance" on whether there might be a consequential reduction in parallel trade with redistribution to wholesale distributors and the research-based industry. However, it set out the arguments that might be made and there is clearly a possibility that there will be an impact on parallel trade where safety features are mandated, depending upon the nature of those features and the costs that replacing them with equivalents might introduce at the point of repackaging.

Cost

It is clear that cost is a matter that requires consideration at all levels. In its Explanatory Memorandum, the commission said that it had weighed the cost of inaction against the costs of its proposed policy and emphasised that it had chosen an approach designed to: keep the administrative and compliance costs to a minimum; allow flexibility in the regulatory framework so that it could be adapted to changes in circumstance and risk; and spread the responsibility across the distribution chain so that wholesalers, active substance suppliers and importers would have a role to play, as well as the pharmaceutical industry. In terms of cost, the Impact Assessment estimated that the costs of the changes proposed would be approximately divided as set out in Table 1.

It seems likely that the actual costs experienced by industry will be higher. In addition, even if accredited bodies can be used to carry out inspections and letters of "confirmation" from third-country competent authorities can be used rather than formal inspections of suppliers (as in the most recent draft), it seems likely that there will be an increase in the costs for audits and inspections. More inspections require manpower and resources. Authorisation holders usually pay fees towards the conduct of inspections related to their authorisations and it would be realistic to expect the costs associated with inspections to fall upon authorisation holders. Regulatory authorities will need to review the resources they are able to apply to inspections, especially in third countries which are known to be the most costly.

Table 1. Proposed directive on falsified medicines: estimated costs

Manufacturers & importers	€6.8 - €11 billion
Pharmacies	€157 million
Wholesale distributors	€280 million
Export-only wholesalers	€403 million
Other traders	€5 million
Active substance manufacturers	€320 million (bulk of costs falling on third-country manufacturers)

Transparency and records

Consistent with the approach across the regulatory field, industry can expect that details of authorisations, certifications, audits, inspections and activities will be collected, collated, stored and shared between regulatory authorities.

The proposal (and suggested amendments) will involve the keeping of more extensive records consistent with the obligations upon participants in the supply chain to verify and make checks in relation to business partners/suppliers, etc, all of which will be open to inspection by regulatory authorities.

Penalties and liabilities

Evidently, the intent is that the obligations introduced by the proposal will be matched by appropriate penalties for non-compliance, ranging from regulatory action against authorisations to criminal sanctions. These will be largely determined at member state level and so might vary, despite the appetite expressed by the various committees for stringent sanctions.

The most recently published text of the proposal also states that manufacturing authorisation holders, and those which manipulate a safety feature that has been attached to a product, will be regarded as "producers" for the purposes of the Product Liability Directive (85/374/EEC). These parties will, therefore, face strict liability for any damages due to falsification of their products.

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