Introduction

The Pharmaceutical Manufacturing Sector Group of the Malta Federation of Industry concurs fully with the concerns of the European Commission concerning increasing counterfeiting activity in the field of medicinal products. Many of the suggestions proposed by the Commission are well-meaning and would undoubtedly result in a decrease in counterfeit penetration. However, the Federation is of the opinion that careful consideration should be given to the practical implications of the proposed measures, in order to avoid negative socioeconomic impacts.

1. Licensing of brokers, traders and agents

The Malta Federation of Industry is in agreement with the Commission's proposal that brokers, traders and agents should be considered as wholesalers, and hence subject to the respective legal obligations. Indeed, it would not be amiss to take the position that all actors in the distribution chain should be either holders of a manufacturing authorization[1] - and hence distributing the manufactured products by virtue of said authorisation[2] - or a holders of an authorization to engage in activity as a wholesaler[3]. In the latter case, this requirement should be enforced irrespective of whether the actor physically distributes the product as part of the activities or is merely acting as a broker, trader or agent. Failure to do has the potential to result in problems at the wholesale dealing level downstream of the broker, trader or agent, particularly when the authorized wholesaler needs to rely on the broker, trader or agent for the maintenance of a quality documentation system consonant with principles of good distribution practice, especially in matters relating to regulatory affairs.

Another issue of particular concern is that of on-line traders in pharmaceutical medicinal products. The problem is particularly acute in Member States either when individuals do not find medicinal products authorized in the Member State or the market prices in the Member State are elevated, and revert to obtaining directly the medicine for personal use over the internet, thus obtaining medicine which may be counterfeited.[4] It is readily discernible that all efforts to stem entry of counterfeit medicinal products into the European Union will prove futile unless this method of obtaining medicinal products is also regulated. Whilst one does not wish to inhibit the progress of technology, the provision of medicinal products must continue to be carried out within the appropriate regulated environment, and under the supervision of licensed health care professionals. It is therefore imperative that some means of regulating on-line pharmacies is developed in the near future.

2. Responsibilities

Audit responsibility is more complex than is indicated in the Commission document. It should be appreciated that whilst the Qualified Person is responsible for ensuring the quality of every batch of medicinal product released within the European Union, it is the marketing authorization holder who answers to the Medicines Authority on all issues regarding the marketing of the product. Marketing authorization holders may sub-contract the manufacture

[1] Art. 40 Directive 2001/83/EC.
[2] Art. 77(3) Directive 2001/83/EC
[3] Art. 77(1) Directive 2001/83/EC
[4] Availability of Human Medicinal Products, Report of Task Force of HMA MG, 2007

of their product to a company in one member state, and then shipped to a sub-contracted wholesale dealer in a second member state. Since the technical agreements of the manufacturer and wholesale distributor are signed separately with the marketing authorization holder, the obligation to demonstrate to both manufacturer and wholesaler that product movement is occurring between licensed players in the chain belongs to the market authorisation holder. Since the product is the legal property of the marketing authorization holder and no contract exists between the manufacturer and wholesale dealer, it is a point of debate as to whether the manufacturer has the responsibility or even the right to audit the wholesale dealer for compliance with GDP. Given these types of complexities, the Malta Federation of Industry believes that it would be ill-advised to attempt to make provisions for such restrictions within the Directive. It would be more suitable for possible scenarios to be outlined, together with appropriate guidance, in a document similar to Annex 16 (*Certification by a Qualified Person and Batch Release*) to Volume 4 (*Good Manufacturing Practices*) of EudraLex: The Rules Governing Medicinal Products in the European Union.

The Malta Federation of Industry also believes that the lack of stipulation of qualification requirements, responsibilities and professional accountability for the qualified person designated as responsible[5] for wholesale dealing activities, is a major shortcoming of the Directive. Malta is well placed in this regard since local legislation[6] indicates that such a person must be a pharmacist, stipulates the knowledge required of such a person, and provides for professional regulation by the Pharmacy Council. However, this is not the case for all EU Member States. A recent recommendation by the European Industrial Pharmacists Group has in fact called for an amendment of the Directive in this regard, and the FOI believes it is high time for the Commission to act upon this suggestion.

Furthermore, the Federation of Industry also believes that the current guidelines on Good Distribution Practive (GDP) issued by the Community[7] are somewhat outdated and do not provide sufficient guidelines to wholesale dealers, whose GDP activities, particularly where documentation requirements and validation procedures are concerned, are becoming more akin to those observed in Good Manufacturing Practices. More detailed guidelines, similar to those found in Volume 4 (*Good Manufacturing Practices*) of EudraLex: The Rules Governing Medicinal Products in the European Union would be recommended. The WHO has recently published its own guidelines for Good Distribution Practices for Pharmaceutical Products, which should form the basis for a similar document issued by the Commission[8].

3. Repackaging

Most pharmaceutical manufacturers operate on a minimum order quantity principle, where such minimum orders frequently exceed even the annual consumption of small-sized markets. This leads to problems, particularly where specific requirements exist in terms of the language of the packaging and patient information leaflet, and the addition of the authorisation number. A ban on repackaging will probably encourage marketing authorisation holders either to increase their supply prices to provide small orders, or to withdraw their products from the market. Such actions will only serve to have a negative impact on the

[5] Art. 79(b) Directive 2001/83/EC
[6] Art. 2 Legal Notice 386 of 2005
[7] Commission Guidelines 94/C 63/03
[8] Annex 5, 40th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series 937, 2006

availability and accessibility of medicines in small Member States. The repackaging of medicinal products to serve the needs of a specific market, when carried out under strict compliance with the principles of Good Manufacturing Practices, constitute no more risk to counterfeit penetration than sub-contracted final stage manufacturing of bulk product.

The problems that these economies of scale engender have been typically illustrated by events in Malta, where limited availability of GMP-accredited repackaging facilities and human resources, particularly Qualified Persons, resulted in the suggestion by certain stakeholders that relabeling activities should be carried out under non-GMP conditions – a suggestion that was, and remains, unacceptable since it would only exacerbate current problems with respect to penetration of counterfeit medicinal products. Moreover, these problems have led to a lack of enforcement in the packaging requirements of medicinal products, particularly with regards to the requirement for the presence on the outer packaging of the number of the authorization for placing the medicinal product on the market.[9] Indeed, it is high time for this legislation to be enforced, since the availability of both in-house and sub-contractable repackaging companies is now established. Moreover, it would also be appropriate to eliminate loopholes in current legislation that only require holders of parallel import licences to place the number of authorization on the problem when repackaging is required for other purposes[10]; the guarantees in ensuring the integrity of the chain of supply that are afforded in the process of a Qualified Person release of repackaged medicinal products cannot be overemphasised. Failure to tighten observance of the legislation in these regards constitutes a greater risk to counterfeit penetration than allowing repackaging to continue – an activity that is required in order to deal with the specific requirements of small markets.

The risks inherent in repackaging, as outlined by the Commission, can be diminished if a number of proposals are taken on board by the Commission, namely:

a. the requirement for repackagers to introduce repackager-specific mass serialization features at the repackaging stage. The use of two-dimensional barcodes (data matrices) is increasing, as individual Member States, such as France, require an ever-increasing amount of information to be present in the barcode, and represents a technology that can be fairly readily implemented at the point of sale particularly since the standards implemented in the use of barcodes are fairly uniform internationally. However, having said this, the costs involved in implementing these features are not minimal, and could necessitate a substantial capital investment by pharmaceutical manufacturers. This would undoubtedly impact the market price of certain medicinal products, disrupting the market balance between generics and originator medicinal products, and hence having negative impacts on pricing strategies currently in place.
b. repackagers could be encouraged to introduce repackager-specific security features. However, a word of caution must be added here. The pharmaceutical manufacturing market contains a plethora of safety features. Once again, whilst the most basic safety feature, namely, that of a seal, is fairly easily implemented, other more advanced overt, semi-covert and covert features are more expensive to implement, and will undoubtedly disrupt the socio-economic balance of current pricing systems and the economic viability of small and medium-sized players in the pharmaceutical supply chain. Furthermore, unless global harmonization in the use of these safety features is

[9] Art. 54(c) Directive 2001/83/EC
[10] Art. 7(d) Legal Notice 437 of 2004

encouraged, points of sale (i.e. pharmacies) are unlikely to invest in all the necessary paraphernalia required to detect a variety of safety features.

c. the need to regularize the process of secure disposal of the original packet or patient leaflets, to the same level and standards applied when medicinal products are disposed of, in other words, repackaging materials should be disposed of by incineration or shredding and, when subcontracted, covered by a technical agreement. This recommendation, however, may result in problems when considering the obligations of authorisation holders under the Directive on Packaging and Packaging Waste[11], and consequently it continues to be recommendable that the Commission recognizes that medicinal products constitute a unique class of products even with respect to this Directive, and exempt authorization holders from requirements on the recycling of packaging materials of medicinal products.

4. Harmonised Databases

The concept of a centrally accessible database records is indeed an attractive one, particularly with regards to the extension of the EudraGMP database to cover wholesale dealers. However, with regards to the database of the medicinal products there are at least two concerns that need to be addressed.

a. establishing and monitoring a database requires funds. These, together with the increased costs inherent in more stringent security features will possibly result in increased market prices, complicating the already delicate balances that exist in medicinal products' pricing systems in Europe
b. the further away one moves from the manufacturing source, the more one will have to rely on reliable reporting of product movement by wholesale dealers. The very real possibility exists that some wholesale dealers may be suppliers of parallel importers and/or, in a more recent development, applicants for Article 126a authorisations[12] without the knowledge of the original MA holder. The reliability of data supplied by such wholesale dealers may therefore be questionable as these will not wish to have their activities exposed.

Thus, the Federation of Industry feels that, even under the most ambitious circumstances, it , it is unlikely that attempts to create a trackable database for each and every unit will meet with much success. A more realistic goal would be to create a registry of unique mass serialization numbers, which would allow end-users to ensure that a particular unit serial number has been released by a Qualified Person in the European Union, and agrees with the information present on the outer packaging. The end-users should be restricted to Qualified Persons, Responsible Persons and health care professionals in order to prevent leakage of these mass serial numbers to the counterfeit industry.

Apart from the databases proposed, the concept of a central database would be also be usefully applied in the process of harmonization of SPC's and PIL's across the European Union. One currently observes a certain degree of variation in the contents of SPC's and/or PIL's in various Member States. It is a matter of no small concern that certain information dependent on the nature and concentration of the active ingredient in the blood stream, typically included in Sections 4 and 5 of the SmPC, may vary from one country to another. One causative factor appears to lie in problems in synchronizing the time periods required for

[11] Directive 94/62/EC
[12] Art. 126a, Directive 2001/83/EC

different member states to approve variations to PIL's and/or SmPC's. This is quite likely to be the case for competent authorities with limited human resources in smaller member states. Such variations in the PIL and SmPC of what should otherwise be identical medicinal products can only facilitate the penetration of counterfeits into the market. Thus, the Commission's recent efforts to hamonise SmPC's across the European Union will probably contribute in this regard. However, it would be advisable for guidelines to ensure that when Article 24(3) of the Directive concerning the validity of the market authorization for an unlimited period[13] comes into practical effect, the competent authorities should continue to be informed of the outcome of the regular review of SmPC's and/or PIL's by the marketing authorization holder.

Thus, with these principles in mind, it is proposed that:

a. a central database of PIL's and SmPC's accessible only to holders of marketing authorisations, Qualified Persons, Responsible Persons, and registered health care professionals should be set up
b. SmPC's should have enforced harmonization across Europe, particularly with respect to Sections 4 and 5. Country-specific differences necessitated by legal issues (e.g. the use of hormonal preparations for abortion) should be highlighted in a single SmPC. Furthermore, more rigorous controls should be in place to ensure that authorized patient information leaflets do indeed contain information which complies with the SmPC.[14]
c. Good Practice guidelines should require that PIL's or SmPC's are reviewed at least every 5 years and the authorities informed of the outcome, irrespective of whether any changes have been effected. PIL's and SmPC's should always bear the most recent review date. Furthermore, the review date of a PIL in a medicinal product should not be excessively older than the manufacturing date.

The Federation also feels that the concept of a "lifetime database" is more readily applicable to pharmaceutical manufacturing and analytical equipment. Second-hand, ex-demo and decommissioned equipment is frequently available on-line and consequently available to counterfeit manufacturers. The use of such a database, in combination with the EudraGMP database, would serve to ensure that every piece of equipment has a dossier associated with it, throughout its useful life thus ensuring legal tracing of the equipment together with buyer certification.

Conclusion

Finally, it must be stated that all measures to combat penetration of counterfeit medicinal products will only be as strong as the level of enforcement that the Medicines Authority can implement. Small member states have limited resources, human and otherwise, and it is critical that the authority is supported by the necessary financial investment that will permit the necessary structures to be in place to ensure compliance with local and European legislation. It is only through this cooperation that any concerted efforts to limit counterfeit medicinal products can yield the best results.

[13] Art. 24(3), Directive 2001/83/EC
[14] Art. 59, Directive 2001/83/EC