AESGP
Association Européenne des Spécialités Pharmaceutiques Grand Public
Association of the European Self-Medication Industry
Europäischer Verband der Arzneimittel-Hersteller

AESGP COMMENTS ON:
THE PUBLIC CONSULTATION IN PREPARATION OF A LEGAL PROPOSAL TO COMBAT COUNTERFEIT MEDICINE FOR HUMAN USE

- KEY IDEAS FOR BETTER PROTECTION OF PATIENTS AGAINST THE RISK OF COUNTERFEIT MEDICINES -

AESGP represents the manufacturers of non-prescription medicines in Europe.

AESGP appreciates the opportunity to participate in the public consultation on key policy measures proposed by the European Commission and aiming at a better protection of patients against the risk of counterfeit medicines.

Counterfeiting of medicines is a scourge for society as a whole and AESGP supports appropriate, well-targeted initiatives designed to combat counterfeiting of medicines. However, respecting the spirit of better regulation, measures should take into account the characteristics of non-prescription medicines and be proportionate to the risk of the product being counterfeited. To date, there are no documented cases of counterfeit non-prescription medicines in the EU known to AESGP, which may be explained by the relatively low price of these products but also by the effective regulatory system in place in the EU. Therefore, AESGP fears that some additional measures proposed may lead to additional costs for manufacturers of non-prescription medicines – which may especially be difficult to bear for the many small and medium-sized companies in this sector – without in the end bringing tangible benefits. Some of the envisaged measures should therefore not apply to medicines classified as non-prescription according to Article 72 of Directive 2001/83/EC as amended.

It is noted that “the Commission is aware that the question of counterfeiting encompasses a vast range of aspects, ranging from internet trade to [...] criminal law”. The pharmaceutical sector is today already highly regulated, and AESGP doubts that the proposed measures specifically addressing pharmaceuticals will have the desired impact without the EU at the same time strengthening penal instruments and other collateral measures.

Although the consequences of taking counterfeit medicinal product for humans can be very severe or even fatal, the penalties for perpetrators of counterfeiting generally fall under the heading trademark-infringement or other even less punitive legislation, and therefore probably do not act as a major disincentive on criminal circles. The result is that “dealing” in counterfeit medicines may be an equally lucrative but much less risky business as dealing in illicit drugs. Therefore, it is imperative that the penal instruments be strengthened and that the act of producing and the trade in counterfeit medicines be considered as criminal activities.

In addition, the Commission should consider how it could use its influence to support third countries (especially China and India) in setting up and enforcing an effective control system. If countries refuse to cooperate or if they adopt a lenient approach to counterfeiters, punitive measures should be envisaged.

7, avenue de Tervuren · B-1040 Brussels · Belgium · Tel.: + 32 (0)2 735 51 30 · Fax: + 32 (0)2 735 52 22
E-mail: info@aesgp.be · http://www.aesgp.be

As reported by the World Health Organization (WHO), medicines purchased over the Internet from sites that conceal their actual physical address are counterfeit in over 50% of cases. AESGP would therefore encourage the Commission to look into potential solutions such as, for example, a certification system of licit online vendors. Such a measure should be accompanied by tools to educate and raise the awareness of patients and consumers with regard to purchasing medicines via the Internet.

The current proposals from DG Enterprise must also be seen in connection with the activities of the Commission's Directorate General Taxation and Customs Union (TAXUD). The cooperation of customs with stakeholders and international counterparts has been acknowledged as one of the most effective weapons to combat counterfeits and as such must be strengthened.

Finally, the current system, and the way the legislation is applied, brings confusion as to who is liable for the product in case of product repackaging, product damage or recall. Wholesalers and retailers of medicines should be under an unambiguous no-fault liability for the sale of counterfeit or corrupted products. This would provide an appropriate incentive to safeguard the integrity of the supply chain. The burden on retailers and distributors would be minimal due to the possibility of insurance coverage.

In greater detail, our comments on the Commission's key proposals are as follows:

4.1 TIGHTENING REQUIREMENTS FOR MANUFACTURE, PLACING ON THE MARKET OF MEDICINAL PRODUCTS AND INSPECTIONS

4.1.1 Subject all actors of the distribution chain to pharmaceutical legislation

Key ideas for changes to EC legislation submitted for public consultation

a) Clarify that the obligations for wholesalers apply to all parties in the distribution chain, except for those directly distributing or administering to the patient. Brokers, traders and agents would be considered as wholesalers, with the respective obligations stemming from the pharmaceutical legislation

b) Make regular audits of GMP/GDP compliance mandatory by qualified auditors
- of (contract) manufacturers by manufacturers;
- between suppliers (wholesalers, manufacturers) at least in cases of suspicion of ……non-compliance with GMP and/or GDP.

a) AESGP agrees that brokers, traders and agents should be considered as wholesalers and be subjected to wholesaler requirements. However, in a very first step, the notion 'wholesalers' should be defined unambiguously in the pharmaceutical legislation. Alternatively, following the example of the "WHO principles and elements for national legislation to combat counterfeit medical products", 'wholesalers', 'brokers', 'traders', 'importers', 'exporters' and 'distributors' could all be grouped together under the term 'operator of the distribution chain', with a clear definition of their roles and responsibilities.

b) As far as API suppliers are concerned, such audits are already commonly taking place. AESGP does not have an issue with codifying such audits in principle but the decision on whether to audit, and on the moment and frequency of auditing

should remain with the manufacturer following a risk-based approach (i.e. cases of suspicion of non-compliance, recent new contract manufacturer, etc.). Otherwise, if systematic auditing of all suppliers is required (e.g. obligation for all manufacturers to audit all their suppliers including those supplying excipients, solvents, etc.), such a measure would be counterproductive as the time and resources which would have to be invested would be without any proportion to the risk-benefit gained. Therefore, manufacturers should have the discretionary right to audit their suppliers (e.g. based on doubt of non-compliance) when they choose to do so. It should be made clear that suppliers should be unable to refuse an audit to be performed by a manufacturer.

In addition, companies should have the option of using their own personnel or accredited auditors.

4.1.2 Tightening rules on inspections

Key ideas for changes to EC legislation submitted for public consultation

• Strengthen provisions on inspections and supervisions, in particular regarding inspections in third countries. For example, make application of the Community procedures on inspections and supervision ("Compilation of Community Procedures on Inspections and Exchange of Information") mandatory.

• Include specific harmonised provisions for inspections by competent authorities of parties in the distribution chain (e.g. wholesalers, brokers, traders, agents, business-to-business platforms).

- AESGP sees the merit of strengthening provisions on inspections and supervisions. In practice, the limiting factor will actually be the number of inspectors capable of performing inspections, especially in third countries. Effective cooperation between countries as well as memoranda of understanding (MOU) or confidentiality agreements to enable the exchange of inspection reports will be necessary to achieve this goal (e.g. through the PIC/S forum) in a cost-effective way, while guaranteeing the confidential handling of such information. In addition, inspections should take place following a risk-based approach.

  The Italian situation provides a perfect example of the lack of resources preventing the system put in place to function in practice. The Italian legislation requires manufacturers to obtain GMP certificates from all their APIs suppliers. However, the Italian inspectorate could not enforce this measure because of an insufficient number of inspectors, and the whole system is reportedly stalled.

  The Compilation of Procedures is a collection of GMP inspection-related procedures and forms agreed by the GMP inspectorates of all Member States and designed to facilitate administrative collaboration, harmonisation of inspections and exchange of inspection-related information. Article 3 of the GMP Directive (2003/94/EC) already obliges Member States to take account of these procedures, and they are used as the basis for the standard operating procedures of the quality systems established within the inspectorates themselves.

  It is also important to note that the contents of the Compilation of Procedures are constantly updated, developed and agreed, under the co-ordination of the European Medicines Agency, by representatives of the GMP Inspectorates of each Member State, including those supervising the manufacture and import of veterinary medicinal

products only. Once agreed, they are adopted by the European Commission and then published on its behalf by the European Medicines Agency. While AESGP fully supports consistency in the inspection procedures, it fears that making these texts mandatory would rigidify them and would defeat the purpose of having constantly improved documents reflecting best practices.

- AESGP supports the proposal to include specific harmonised provisions for inspection by competent authorities of parties in the distribution chain (wholesalers, brokers, traders, agents, business-to-business platforms).

- This measure will have to be complemented by cooperation at international level to ensure that third countries are also inspecting facilities on their territory. As inspectorate resources are generally scarce, duplicate inspections will have to be avoided through the confidential sharing of inspection reports.

4.1.3 Improving product integrity through a unique seal from the manufacturer to the retailer or wholesaler, using a risk-based approach, supported by a ban on repackaging.

Key ideas for changes to EC legislation submitted for public consultation

Require the outer packaging of medicinal products to be sealed. This would reveal any subsequent opening of the packs.

Such a requirement could be applied to certain categories of products chosen on a risk-based approach, i.e. by taking into account the public health impact of the appearance of a counterfeit product and the profit strategies of counterfeiters.

The right to opening the outer packaging would be restricted to the market authorisation holder and end-user (hospital, health care professional, or patient)

Non-prescription medicines can be characterised by their low price and high volume. Such a measure should not apply to medicines classified as non-prescription according to Article 72 of Directive 2001/83/EC as amended as its cost would overwhelmingly outweigh its benefits. Apposing a seal alone would not deter counterfeiters. It can easily be anticipated that counterfeiters would immediately copy this and seal their products in the same manner. In the end, this would give patients a false feeling of security and bear a cost for the self-care industry of €0.02 to €0.04 per sticker, €200,000 per production line and €50,000 of additional labour per year and per production line without much added benefit.

4.1.4 Centrally accessible record to facilitate traceability of batches through the distribution chain

Key ideas for changes to EC legislation submitted for public consultation

Require the possibility of tracing ownership and transactions of a specific batch. This should be achieved by making a specific record (pedigree) obligatory.

The record should be accessible by all actors in the distribution chain.

Although AESGP does not deny the value of such a proposal in theory, it is not immediately clear how the implementation of such a system would work in practice. Who would be responsible for the maintenance of the 'unique and centrally accessible database' and how would the associated costs be covered?

4.1.5 Mass serialisation for pack-tracing and authenticity checks on a case-by-case basis

Key ideas for changes to EC legislation submitted for public consultation
Require the possibility to trace each pack and perform authenticity checks. This could be attained by a mass serialisation feature on the outer packaging. Technical details would be further defined in implementing legislation and/or by standardisation organisations.

Non-prescription medicines have a distinct distribution system from that of prescription medicines.

Non-prescription medicines are not exclusively sold in pharmacies. Countries such as the United Kingdom, the Netherlands and Germany and, more recently, the Czech Republic, Denmark, Hungary, Italy, Portugal and Poland, allow certain or all categories of non-prescription medicines to be sold outside pharmacies. This is currently also being considered in Sweden.

If there were to be one coding system for medicines and another identification system (e.g. bar coding) for other goods sold in general outlets, manufacturers of some non-prescription medicines would have to comply with two different coding requirements (for example, 2 different codes would have to be printed on their packs). For these reasons alone, AESGP thinks that medicines classified as 'not subject to prescription' according to Article 72 of Directive 2001/83/EC as amended should be exempted from such a measure.

In addition, the cost of new equipment would be high: an estimated circa €50,000 per packaging line. On average non-prescription medicines manufacturers have 3 lines; the cost would therefore amount to €150,000 per manufacturer. Line speed would also be affected, particularly for high-speed lines producing over 150 packs /minute. On such lines, between 10% and 25% of line efficiency would be lost, translating into a potential cost increase of about 5% per pack. Given that these highly automated, high-speed lines are the norm in Europe, total productivity losses could be significant.

The cost of the database/network allowing the input and retrieval of data/codes should not be forgotten either. It is expected to be highly significant given the number of possible users and the many security features which will need to be built in, on the one hand to ensure confidentiality of sensitive data entered by the pharmaceutical companies and on the other hand to guaranty real-time access by all actors of the supply chain.

Currently there is no evidence of counterfeit non-prescription medicines in the EU.

In summary, in light of the specific distribution chain of non-prescription medicines, the high costs and the reduced benefits expected in return, AESGP strongly believes that mass serialisation requirements should not apply to the non-prescription sector.

AESGP would like to note that this is in line with the situation in the United States where the scope of the proposals on track & trace recently released for comments solely addresses prescription medicines:

- Standards for Standardized Numerical Identifier, Validation, Track and Trace, and Authentication for Prescription Drugs; Request for Comments[1].

- Technologies for Prescription Drug Identification, Validation, Track and Trace, or Authentication; Request for Information[2].

4.1.6 Increasing transparency concerning authorised wholesalers through a Community database

Key ideas for changes to EC legislation submitted for public consultation

• Require GDP certificates to be issued after each inspection of a wholesaler.

• Establish a Community database of wholesalers (including distributing manufacturers25) documenting GDP compliance. This could be achieved via extension of the EudraGMP database.

AESGP does not have any particular comments on this proposal.

4.2 Tightening requirements for the import/export/transit (transhipment) of medicinal products

Key ideas for changes to EC legislation submitted for public consultation

Directive 2001/83/EC would be clarified to the effect that imported medicinal products intended for export (i.e. not necessarily subject to marketing authorisation) are subject to the rules for imports of medicinal products. The following provisions would apply:

• the obligatory importation authorisation under the conditions set out under Article 41 Directive 2001/83/EC, e.g. relating to premises and the qualified person;

• the relevant obligations for the importation authorisation holders set out under Articles 46 and 48 Directive 2001/83/EC, e.g. relating to staff and access for inspection;

• the obligations stemming from Article 51(1)(b) and (2) Directive 2001/83/EC, relating to qualitative and quantitative analysis of the imported medicinal product; and

• the relevant obligations stemming from Directive 2003/94/EC on good manufacturing practice.

The corresponding rules on inspections would apply.

AESGP supports these measures aiming at tightening the requirements for the import, export and transit of medicines.

[1] http://www.fda.gov/OHRMS/DOCKETS/98fr/oc0841.pd
[2] http://www.fda.gov/OHRMS/DOCKETS/98fr/oc0842.pdf

4.3 TIGHTENING REQUIREMENTS FOR MANUFACTURE, PLACING ON THE MARKET OF ACTIVE SUBSTANCES AND INSPECTIONS

AESGP would like to note that herbal substances and preparations are addressed in a specific annex (Annex 7) to the GMP guide. Herbal substances and preparations cannot be considered as standard 'APIs'. They are therefore considered out of the scope of the proposed measures concerning APIs.

4.3.1 Requirement of a mandatory notification procedure for manufacturers/importers of active substances

Key ideas for changes to EC legislation submitted for public consultation

Submit the manufacturing/import of active ingredients to a mandatory notification procedure.

• Render information on notified parties available in a Community database. This could be achieved via extension of the EudraGMP database.

The implementation of such a measure would need to be carefully crafted so as not to entail administrative delays, additional fees, etc. AESGP would generally support one general notification but not a notification for each and every import. In addition, roles and responsibilities for an API notification procedure need to be clearly defined for the different actors in the supply chain.

Details about the source of the active substance have to be provided already today in the application file.

4.3.2 Enhancing audit and enforceability of GMP

Key ideas for changes to EC legislation submitted for public consultation

• Make regular audits of active substance suppliers on GMP compliance by manufacturers and importers of medicinal products mandatory. Auditors should be sufficiently qualified.

• Require, where scientifically feasible, control of active substances via sufficiently discriminating analytical techniques, such as fingerprint technologies, Near Infrared Spectroscopy (NIR), as a mandatory method for identification by the manufacturer of the medicinal product. Such a testing is meant to identify deviations of the manufacturing process and manufacturing site for each batch.

• Turn principles of good manufacturing practice for active substances placed on the Community market into a legal act of Community law (e.g. a Commission Directive) in order to enhance enforceability.

Currently the system is based on the liability of manufacturers to ensure that their active supplier/manufacturer complies with GMP. AESGP thinks that the current system works well and fails to see how a further increase of GMP audits would add to product safety.

The European Commission's Consultation document fails to address the important role and responsibilities of the qualified person (QP) in the current system. The QP needs to

abide by very specific requirements, and his/her personal responsibility is engaged as defined in Article 48 of Directive 2001/83/EC as amended. The QP signs a declaration that the API is manufactured according to GMP. AESGP thinks that this system, unique to Europe, is adequate and has proved its superiority in comparison to other systems. AESGP therefore does not believe that additional legislative requirements concerning audits are the right way forward. To what extent an audit is appropriate should be left in the responsibility of the marketing authorisation holder, who at the end has to guarantee the safety, quality and efficacy of his/her products.

A survey of AESGP members has shown that a direct audit by a company's auditors is the type of audit most commonly used. Third-party audits are currently used to a lesser extent. Third-party audits would allow a saving of resources on travel and on the audit itself, but the cost involved in preparation, follow-up, etc. would remain unchanged.

Manufacturers test active substances for impurities and other components which can reasonably be expected to be found. At the time of submission of the marketing authorisation application, the authority can check whether the tests carried out are sufficient and appropriate.

The use of Near Infra-red technology should be left to the discretion of manufacturers as the high cost of this technology (the starting price is around €100,000) may be difficult to bear for smaller-sized companies.

In summary, AESGP objects to a change of the current system. In addition to the above, an increase of GMP enforceability on pharmaceutical companies will not address the counterfeit issue. The aim of GMPs is to ensure that medicinal products put on the market are consistently produced in accordance with the manufacturing methods defined in the marketing authorisation. Lack of compliance with GMP requirements does not make the producer a counterfeiter. The two issues should therefore be clearly separated.

4.3.3 Enhancing GMP inspections

Key ideas for changes to EC legislation submitted for public consultation

The competent authority may carry out announced or unannounced inspections of active substance manufacturers in order to verify compliance with the principles of good manufacturing practice for active substances placed on the Community market.

According to AESGP, this is already the case. The Compilation of Community procedures on inspections and exchange of information[3] states that "where it has grounds for suspecting non-compliance, the competent authority may carry out announced or unannounced inspections at the manufacturer or distributor of the active substances".

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[3] http://www.emea.europa.eu/Inspections/docs/CoCP/CoCP_APIGMPInspTriggers.pdf