



Brussels, 11.03.2008

**PUBLIC CONSULTATION  
IN PREPARATION OF A LEGAL PROPOSAL  
TO COMBAT COUNTERFEIT MEDICINES FOR HUMAN USE**

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

**1. INTRODUCTION**

Counterfeiting of medicinal products is an increasing concern for the patients, industry, EU and national policy-makers. The European Parliament has called for action and, on 6 September 2006, adopted a resolution on counterfeit medicines.<sup>1</sup> In addition, the European Parliament raised concerns regarding the source and quality of active substances<sup>2</sup> in a written declaration on 4 September 2006.<sup>3</sup>

The European Commission has launched a study to assess various policy options to prevent the counterfeiting of medicinal products in the EU.

In addition to this, the Directorate-General for Enterprise and Industry is using this document to consult all stakeholders and interested parties on key ideas for amending the regulatory framework for medicinal products in an effort to combat the counterfeiting of medicinal products.

Both the study and the feedback to this public consultation will be fed into the ongoing impact assessment of the legal proposal.

**2. COUNTERFEITING OF MEDICINAL PRODUCTS — AN INCREASING THREAT TO  
PUBLIC HEALTH AND SAFETY**

A recent analysis of the present situation has revealed that counterfeit medicines have become an increasing threat to public health over the past few years.

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<sup>1</sup> <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+MOTION+P6-RC-2006-0467+0+DOC+PDF+V0//EN&language=EN>

<sup>2</sup> "Active principles" as phrased in the declaration are meant to be understood as "active substances" or "active pharmaceutical ingredients".

<sup>3</sup> <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+WDECL+P6-DCL-2006-0061+0+DOC+PDF+V0//EN&language=EN>

The Commission has observed the following worrying trends in particular:

- A sharp increase in seized counterfeit medicines: EU Statistics report the seizure of a total of 2 711 410 medicinal products (articles) at EU customs borders in 2006. This is an increase of 384% compared to 2005.<sup>4</sup>
- A trend towards counterfeiting of life-saving drugs: Counterfeit medicines in the EU originally focused on ‘lifestyle’ medicines, including erectile dysfunction and weight loss medicines. Now, criminals increasingly target life-saving medicines, including medicines to treat cancer and heart disease, psychiatric disorders, and infections. For example, there are indications that, in 2007, counterfeit medicines have reached the legal supply chain towards patients. These medicines were used for treatments of diseases such as heart diseases and psychiatric disorders. They had a significantly lower quantity of the active ingredient than declared. Treatment with such medicines could have fatal consequences. This trend may increase as the main driving factor is high value, high turnover and total disrespect for patient health.
- A trend towards targeting the classical supply chain: Recently, there has been alarming evidence that, besides the internet, the licensed distribution chain, including authorised wholesalers, parallel traders and pharmacies are being increasingly targeted by counterfeiters, as they allow distribution of high volumes of medicines. The UK MHRA reported that incidents affecting the regular distribution chain have steadily increased since 2004, with counterfeit medicine reaching patients on 9 occasions, necessitating batch recalls, and discovered at wholesale level on a further 5 occasions.<sup>5</sup>
- A blurred line between counterfeit and sub-standard active substances in medicinal products: The risk of counterfeit or sub-standard active substances entering the supply chain towards a medicinal product poses additional risks to patients. For example, in the early 2000s, numerous deaths and side effects were connected with antibiotics containing gentamicin as an active substance. These effects are assumed to be related to faulty manufacture and impurities of the active substance.<sup>6</sup>

The following factors may have facilitated the rise of counterfeiting:

- Certain deficiencies in supply chain integrity, as there is uncertainty as to whether certain participants in the distribution chain are subject to pharmaceutical legislation (e.g. brokers, traders, business-to-business platforms). This is closely linked to the lack of specific requirements for supplier qualification.

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[http://ec.europa.eu/taxation\\_customs/resources/documents/customs/customs\\_controls/counterfeit\\_piracy/statistics/counterf\\_comm\\_2006\\_en.pdf](http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/counterf_comm_2006_en.pdf)

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MHRA Anti-Counterfeiting Strategy 2007-2010  
<http://www.mhra.gov.uk/home/groups/ei/documents/websiteresources/con2033156.pdf>

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Wiener, Deubner, Holzgrabe: Composition and Impurity Profile of Multisource Raw Material of Gentamicin – a Comparison; Pharmeuropa Vol 15, No. 2, April 2003.

- Lack of transparency for economic operators as to whether wholesalers and other actors in the distribution chain comply with Good Distribution Practice (“GDP”).
- Certain shortcomings in product integrity, especially when packs are opened for repackaging and changed for relabelling purposes.
- Difficulties in conducting targeted recalls, in particular in the case of counterfeit products.
- Legal uncertainty and differing practices between Member States concerning the application of pharmaceutical legislation to imports for the purpose of export.
- Active substances may not be manufactured in compliance with GMP standards, in declared sites or in accordance with declared procedures.

In addition, there is evidence that Member States are starting to consider taking unilateral action to address the problem of counterfeit medicines. These measures — admittedly motivated by justified concerns — may raise concerns as regards their compatibility with the rules for medicinal products in the internal market. Different approaches may also lead to different levels of protection of public health and safety. Indirectly, this kind of way forward could encourage counterfeiters to target Member States with lower levels of protection of the legal distribution chain.

Finally, the Community has committed itself internationally to addressing these new risks to public health. In this respect the European Commission has actively contributed to and supported the WHO International Medical Products Anti-Counterfeiting Task Force (IMPACT). The recently published “Principles and Elements for National Legislation against Counterfeit Medical Products”<sup>7</sup> have been developed with funding through the Commission’s Competitiveness and Innovation Framework Programme.<sup>8</sup> The agreed principles emphasise the need to regulate the activities of all operators in the distribution chain. Vice-President Verheugen had previously announced that any anti-counterfeiting strategy of the European Commission will build on the results of IMPACT.<sup>9</sup>

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<sup>7</sup> <http://www.who.int/impact/events/FinalPrinciplesforLegislation.pdf>

<sup>8</sup> [http://ec.europa.eu/cip/docs/eip\\_wp2007.pdf](http://ec.europa.eu/cip/docs/eip_wp2007.pdf); [http://ec.europa.eu/cip/docs/eip\\_wp2007\\_measures.pdf](http://ec.europa.eu/cip/docs/eip_wp2007_measures.pdf)

<sup>9</sup> Speech by Vice-President Verheugen at the 1st European Parliamentary Symposium “Putting an end to Drug Counterfeiting”, Brussels, 14 May 2007; [http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc\\_id=248&userservice\\_id=1](http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc_id=248&userservice_id=1)

**There is clear evidence that the risks to public health in the EU are set to increase still further if the Community does not act firmly. The Directorate-General for Enterprise and Industry is committed to taking every step necessary to address this important health threat.**

### **3. LEGISLATIVE STRATEGY AND IMPACT ASSESSMENT**

Tightening requirements for the manufacturing, trading and distribution of medicines for human use and active substances may include:

- amendments to Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use;<sup>10</sup>
- amendments to Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice.<sup>11</sup>

Changes to the above legislation might have further implications on technical guidelines, such as

- Good Manufacturing Practice (“GMP”) guidelines, as published by the European Commission;<sup>12</sup>
- Good Distribution Practice (“GDP”) guidelines (94/C 63/03), as published by the European Commission;<sup>13</sup>
- Compilation of Community Procedures on Inspections and Exchange of Information, as published by the European Medicines Agency (EMA).<sup>14</sup>

Moreover, it is evident that any legislative measure needs to be complemented by appropriate supervision and enforcement. Any legislation can only be fully effective if it is thoroughly enforced by the competent authorities of the Member States.

Any changes to this regulatory framework for medicinal products are going to be carefully considered by the Commission. Different policy options are going to be developed. An impact assessment is going to be carried out addressing the social, economic and environmental impacts of these options. A special focus will be on impacts in terms of regulatory burden, including administrative costs, for all actors in this sector. In particular, impacts on actors in the supply chain, which may be particularly affected by measures against counterfeit in the legitimate distribution

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<sup>10</sup> OJ L 311, 28.11.2001, p. 67, as last amended.

<sup>11</sup> OJ L 262, 14.10.2003, p. 22.

<sup>12</sup> <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm>

<sup>13</sup> <http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2001/may/gdpguidelines1.pdf>

<sup>14</sup> <http://www.emea.europa.eu/Inspections/GMPCompmpoc.html>

chain, are going to be carefully assessed and weighted against the benefits of the various policy options.

With view to this public consultation, the responses to it are going to be carefully studied in the framework of the impact assessment process.

#### **4. KEY IDEAS FOR BETTER PROTECTION OF PATIENTS AGAINST COUNTERFEIT MEDICINES**

The Commission is aware that the question of counterfeiting encompasses a vast range of aspects, ranging from internet trade to product-related legislation and even criminal law. Several of these aspects may fall outside the competences of the Community or may require further in-depth analysis.

It is equally clear that only a concert of various measures designed to change and improve the current regulatory framework can help to minimise the risk of counterfeit medicines entering the legal supply chain.

Against this background, the Commission has identified **three areas of regulation of medicinal products** where improvements to the regulatory framework can make a real contribution to protecting against counterfeit medicinal products. These relate to:

- medicinal products placed on the market (i.e. issues of traceability, product integrity, and distribution chain, 4.1. below);
- medicinal products brought into the Community without being placed on the market (i.e. issues of import/export and transit, 4.2. below); and
- active ingredients supplied to the manufacturer of medicinal products placed on the market (i.e. regulation of active substances, 4.3. below).

While these are three separate areas of medicinal products legislation, it needs to be stressed that they complement and support each other thus contributing as a whole to a better protection from counterfeit medicinal products in the EU.

##### **4.1. Tightening requirements for manufacture, placing on the market of medicinal products and inspections**

It is crucial to protect the legal supply chain from an influx of counterfeit medicinal products. Therefore, the Commission is considering:

- subjecting all parties in the distribution chain to pharmaceutical legislation;
- improving product integrity and traceability;
- sharpening the technical requirements for GMP and GDP;
- tightening inspections and supervision; and
- increasing transparency.

#### *4.1.1. Subject all actors of the distribution chain to pharmaceutical legislation*

The distribution chain of medicinal products involves a number of parties. Apart from the wholesaler,<sup>15</sup> suppliers may be brokers and agents, i.e. persons who do not actually handle products but merely act via, for example, business-to-business platforms. The responsibility of these players should be similar to those of wholesalers.

Moreover, audits (i.e. verification of compliance with standards of an economic operator by another economic operator under the responsibility of the industry) are an important means of ensuring that economic operators act with reliable partners. These audits should be mandatory. This holds not only for the “manufacturer-(contract) manufacturer” relationship but also for the “manufacturer/supplying wholesaler-purchasing wholesaler” relationship if there are grounds to suspect non-compliance with GMP and/or GDP. In general, quality risk management principles should be pursued for performing audits.

To rationalise, acceptance of third-party audits by accredited companies could be considered. Minimum professional qualifications for auditors should be established taking into account those defined for the qualified person<sup>16</sup>. Finally, there are currently no requirements for the qualification of the qualified person to be designated by the wholesaler.<sup>17</sup>

#### **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.

#### *4.1.2. Tightening rules on inspections*

Effective enforcement through inspection and supervision – not only within the EU but also in third countries - is crucial, while continuous cooperation with third countries on the basis of bilateral arrangements should ensure international synergies in performing inspections.

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<sup>15</sup> Art. 1(17) Directive 2001/83/EC.

<sup>16</sup> as defined in Arts.49, 50 Directive 2001/83/EC

<sup>17</sup> Art. 79 (b) Directive 2001/83/EC

While there are guidelines on inspection procedures in the EU (“Compilation of Community Procedures on Inspections and Exchange of Information”), these have merely “to be taken into account” by Member States.<sup>18</sup> Moreover, regarding third countries, inspections of manufacturers are discretionary.<sup>19</sup>

In addition, very few procedures exist which address aspects of inspection of parties in the distribution chain (e.g. inspections of wholesalers).

Recently, specific consideration has been given to quality risk management principles for the planning of inspections and this concept should be pursued further in the future.

**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).

*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*

Generally speaking, in order to successfully infiltrate the legal distribution chain, counterfeiters seem to veil the source of the product by selecting highly complicated distribution concepts. At the end of this “journey” counterfeiters tend to target traders who accommodate the packaging for the market of destination.

Maintaining the integrity of the outer packaging with the medicinal product contained in it is crucial to making it more difficult for counterfeit medicinal products to infiltrate the legal supply chain.

This integrity should be secured by an obligatory product sealing. The right to open the seal would be restricted to the market authorisation holder and the end user (hospital, health care professional, or patient).

This would address the practice of exchanging and/or opening of the outer packaging of a medicinal product in the distribution chain which could lead to the following situation:

- Safety features relating to the original product and attached to the outer packaging (in particular, mass serialisation - cf. 4.1.5. below) disappear. Indeed, these safety features are only efficient if they remain firmly linked

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<sup>18</sup> Art. 3 Directive 2003/94/EC.

<sup>19</sup> Art. 111(4) Directive 2001/83/EC, Art. 8(1), (2) Regulation 726/2004.

with the original medicinal product contained in the packaging throughout the distribution chain; and

- There is a potential for misuse of original packs, especially when discarded after repackaging. Counterfeit products could be packaged into an outer packaging bearing safety features.

**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).<sup>20</sup>

*4.1.4. Centrally accessible record to facilitate traceability of batches throughout the distribution chain*

An efficient traceability system for medicinal products is crucial to combating counterfeit products.

At present, Directive 2001/83/EC refers to the batch number as the obligatory identification tool on the packaging.<sup>21</sup> Manufacturers<sup>22</sup> and wholesalers<sup>23</sup> are to keep records of their transactions relating to batches.

However, in order to trace a product, each player in the supply chain has to be consulted. The information is fragmented.

To address this fragmentation, there should be a unique and centrally accessible record of all past ownerships and transactions (so-called pedigree). This pedigree would include the transaction between manufacturer, the wholesaler(s) and the supplied retailer/pharmacist. The supplied retailer/pharmacy would be the final traceable point in the distribution chain.

A centrally accessible pedigree should help greatly to trace back products when there is a suspicion of counterfeit medicines, as well as quality defects or relevant pharmacovigilance reports. As thus, the system would

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<sup>20</sup> This may impact on the possibility to exchange package leaflets and inner packaging by actors in the distribution chain. Consequences and possibilities to address this issue are going to be considered by the Commission in the impact assessment (cf. 3 above).

<sup>21</sup> Art. 54(m) Directive 2001/83/EC.

<sup>22</sup> Art. 80(e)(g) Directive 2001/83/EC.

<sup>23</sup> GDP Guidelines, points 7, 8.

- act as deterrent for producers/traders of counterfeit medicinal products to supply their products through the legal distribution chain; and
- assure participants in the distribution chain (e.g. wholesalers, traders, brokers) about the source and quality of their products.

Note, that such a pedigree is currently being discussed for recommendation by the WHO in the revised Good Distribution Practices.

**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.

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

Apart from the fragmentation of information (4.1.4. above), the present system for traceability only allows products to be traced on the basis of their batch number. It is not possible to trace a specific *pack* back to a specific distributor.

In order to trace counterfeit products, however, it may be crucial to identify who has handled *a specific pack* in the supply chain.

Pack-specific tracing requires mass serialisation. Mass serialisation is based on a code on the outer packaging which “individualises” the pack. The code is read with a reading device. Currently, various tamper-proof technologies to implement such a concept are under discussion by the industry (e.g. datamatrix/2D barcoding).

This mass serialisation, combined with a pedigree (4.1.4. above) would thus allow, when necessary and on an ad-hoc basis, the distribution chain of a specific pack to be traced.<sup>24</sup> Moreover, as each pack would bear a different individualisation code, the authenticity of a product could be verified on an ad-hoc basis at the point of wholesale or retail.

The requirement for mass-serialisation could be restricted to certain categories of products in view of a cost-benefit analysis.

**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.

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<sup>24</sup> Access to specific databases and possibilities to read information may be required at various levels in the distribution chain up to the retail/ pharmacy level. Policy options to address in particular economic impacts are going to be considered by the Commission in the impact assessment (cf. above 3 above).

#### 4.1.6. *Increasing transparency concerning authorised wholesalers through a Community database*

In practice, wholesalers currently verify the reliability of their (wholesale) suppliers by requesting a copy of the wholesale authorisation. A database with public access and containing information on authorisations and GDP/GMP certificates of wholesalers or manufacturers engaged in wholesale would provide a better and safer tool for assessing the GDP compliance. At the same time, the obligation of the customer to verify GDP compliance of the wholesaler would remain unchanged.

##### **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 manufacturers<sup>25</sup>) documenting GDP compliance. This could be achieved via extension of the EudraGMP database.

#### **4.2. Tightening requirements for the import/export/transit (transshipment) of medicinal products**

The scope of EU legislation on medicinal products is far-reaching and includes:

- medicinal products intended to be placed on the Community market,<sup>26</sup> regardless of whether the product has been manufactured in the EU or in a third country;
- the manufacturing of medicinal products in the EU, regardless of whether the product is exported<sup>27</sup> or not;
- the wholesale distribution of medicinal products;<sup>28</sup> and
- the importation (including re-importation) of medicinal products into the EU.<sup>29</sup>

With regard to the last point, it is important to stress that **the physical introduction of the medicinal product into the Community is sufficient for the rules on importation to apply**. The intention to place the product on the Community market is not required.<sup>30</sup>

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<sup>25</sup> Art. 77(3) Directive 2001/83/EC.

<sup>26</sup> Art. 2(1) Directive 2001/83/EC.

<sup>27</sup> Art. 2(3), Title IV Directive 2001/83/EC.

<sup>28</sup> Title VII, Art. 1(17) Directive 2001/83/EC.

<sup>29</sup> Art. 2(3), 40(3) Directive 2001/83/EC.

<sup>30</sup> Art. 2(3), 40(1) and (3) Directive 2001/83/EC.

However, there is some uncertainty as to the precise extent of the rules for products imported for the purpose for exportation. For example, some provisions on imports seem to address only products imported to be placed on the Community market.<sup>31</sup>

These uncertainties have led to divergent enforcement practices amongst the Member States and thus to “blind spots” in the supervision of medicinal products entering the EU. This has facilitated breaches of legal requirements (e.g. storage conditions, relabelling with respect to origin). Moreover, there is a risk that these “blind spots” are being used to channel counterfeit products into the legal supply chain.

**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.

#### **4.3. Tightening requirements for manufacture, placing on the market of active substances and inspections**

A comprehensive strategy to combat counterfeit medicinal products also requires a reassessment of the rules for active ingredients of medicinal products.

Indeed, the “traditional” focus in pharmaceutical legislation is placed more on the manufacturing/importation/marketing of the final medicinal product than on the manufacturing/supply of active ingredients. This possibility that risks to patient health and safety may originate at the early stage of the production chain was highlighted in a declaration of the European Parliament.<sup>32</sup> A survey

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<sup>31</sup> Cf. Art. 51(1)(b) Directive 2001/83/EC.

<sup>32</sup> Written declaration of 4 September 2006 (<http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+WDECL+P6-DCL-2006-0061+0+DOC+PDF+V0//EN&language=EN>)

launched by the Commission amongst Member States authorities confirmed the need for action.

To address existing shortcomings, the Commission envisages a combination of notification requirements, tightened GMP standards and enhanced inspections in an effort to improve the legal framework for active substances.

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

The legal framework for active substances used as ingredients in medicinal products addresses only the manufacturing stage. The activities of distributors, traders, agents and brokers are currently outside the scope of Community legislation.

Moreover, even with regard to manufacturing, there is a lack of transparency of the players involved.

A notification regime for manufacturers as well as importers of active substances placed on the EU market either on their own or in preparations would improve transparency and facilitate supervision of the parties involved in the supply chain.

In addition, distributors, traders and brokers involved in such a placing of active substances on the EU market should be subject to the relevant GMP.

#### **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.

#### *4.3.2. Enhancing audit and enforceability of GMP*

At present, the manufacturing and importation of active substances is regulated via the obligation of the manufacturing authorisation holder to use active substances manufactured in compliance with GMP.<sup>33</sup> This is supervised in practice by means of auditing by the manufacturing authorisation holder. To rationalise, acceptance of third-party audits by accredited companies could be considered. Minimum professional qualifications for auditors should be established taking into account those defined for the qualified person.<sup>34</sup>

Moreover, manufacturers of medicinal products are currently obliged to test active substances supplied to them. This should help to identify counterfeit active substances not containing any ingredient or a lower quantity. However, such a testing does not address residues of inappropriate use of toxic solvents

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<sup>33</sup> Arts 46(f) and 46a Directive 2001/83/EC.

<sup>34</sup> as defined in Arts. 49, 50 Directive 2001/83/EC

and impurities. This problem could arise if active substances have been manufactured in other sites and with other manufacturing processes as declared.

These shortcomings have been exploited in the past: low-quality active substances were channelled into the production chain towards a medicinal product.

Finally, GMP for active substances are currently only established as a guideline. Enshrining the major principles of GMP for active substances in a Directive would increase the legally binding nature. This kind of approach would also be in line with GMP for finished medicinal products.<sup>35</sup>

**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.

*4.3.3. Enhancing GMP inspections*

Official inspections are crucial for effective enforcement.

Today, inspections by competent authorities are restricted to cases of suspected non-compliance with GMP.<sup>36</sup> This limitation raises particular concerns with regard to the manufacturing of active substances in third countries where GMP are not equivalent to those laid down in the Community or where inspection and control mechanisms are insufficient. Inspections of the premises of manufacturers should be enhanced in these third countries. At the same time, continuous cooperation with third countries on the basis of bilateral arrangements should ensure international synergies in performing 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.

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<sup>35</sup> Art. 47 Directive 2001/83/EC.

<sup>36</sup> Art. 111(1)(4) Directive 2001/83/EC.

The competent authority shall carry out these inspections if there is suspected non-compliance with GMP.

The competent authority shall carry out repeated inspections in the exporting country if the third country applies standards of good manufacturing practice not at least equivalent to those laid down by the Community or if mechanisms for supervision and inspections are not at least equivalent to those applied in the Community. To this end, a Member State, the Commission or the Agency shall require a manufacturer established in a third country to undergo an inspection.

### **WHO IS CONSULTED?**

Contributions from all stakeholders and interested parties are welcome. This includes, for example, associations representing patients, health care professionals, the industry, as well as academic bodies. Citizens are also welcome to contribute to this consultation.

### **HOW CAN I CONTRIBUTE?**

Contributions should be sent by e-mail to **entr-pharmaceuticals-counterfeit@ec.europa.eu** by **09 May 2008**. Contributions will be made publicly available on the "Pharmaceuticals" website of Directorate General Enterprise and Industry [http://ec.europa.eu/enterprise/pharmaceuticals/index\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm) once the consultation period is over. Upon specific request for confidentiality, only an indication of the contributor will be disclosed.

Respondents should indicate whether they are a company, consumer, academic association or other. If they are a company, the approximate size (turnover, employees) and the main market (product and geographical market) should be indicated.

### **WHAT WILL HAPPEN NEXT?**

All contributions will be carefully analysed. A summary of the outcome of the consultation will be published on the "Pharmaceuticals" website of the Directorate-General Enterprise and Industry.

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