



*Making Medicines Affordable*

# **POSITION PAPER**

---

**EUROPEAN COMMISSION 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**

**MAY 2008**



## CONTENTS

|                                                                                                                                                                                  |           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>1. EXECUTIVE SUMMARY</b>                                                                                                                                                      | <b>3</b>  |
| <b>2. Introduction</b>                                                                                                                                                           | <b>5</b>  |
| <b>3. Subject all actors of the distribution chain to pharmaceutical legislation</b>                                                                                             | <b>5</b>  |
| <b>4. Supervision and Enforcement (GMP/GDP)</b>                                                                                                                                  | <b>8</b>  |
| 4.1. Audits.....                                                                                                                                                                 | 8         |
| 4.2. Inspections by Competent Authorities.....                                                                                                                                   | 12        |
| 4.3. Third party Auditors.....                                                                                                                                                   | 15        |
| <b>5. Transparency</b>                                                                                                                                                           | <b>17</b> |
| 5.1. Increasing transparency concerning authorised wholesalers through a Community database.                                                                                     | 17        |
| 5.2. Mandatory notification procedure for manufacturers/importers of active substances.....                                                                                      | 18        |
| <b>6. Tightening requirements for the import/export/transit (transshipment) of medicinal products</b>                                                                            | <b>19</b> |
| <b>7. Traceability</b>                                                                                                                                                           | <b>20</b> |
| 7.1. 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. .... | 20        |
| 7.2. Centrally accessible record to facilitate traceability of batches throughout the distribution chain.....                                                                    | 21        |
| 7.3. Mass serialisation for pack-tracking and authenticity checks on a case-by-case basis.....                                                                                   | 22        |
| <b>8. Annexes</b>                                                                                                                                                                | <b>23</b> |
| 8.1. Additional Explanatory Figures on GMP/GDP .....                                                                                                                             | 23        |
| 8.2. Example of Inspections carried out by the “Raw Materials Inspection Unit” (“Unità Ispettiva Materie Prime”, Italy).....                                                     | 26        |
| 8.3. EC Key Proposal 4.1.4. - “Centrally accessible record to facilitate traceability of batches throughout the distribution chain”.....                                         | 27        |
| 8.4. EC Key Proposal 4.1.4. - Batch Level Model I - Generic medicines Manufacturers costs .....                                                                                  | 28        |
| 8.5. EC Key Proposal 4.1.5. - “Mass serialisation for pack-tracking and authenticity checks on a case-by-case basis”.....                                                        | 30        |

## EGA POSITION PAPER

### EUROPEAN COMMISSION 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. EXECUTIVE SUMMARY

The European Generic medicines Association (EGA) welcomes the European Commission Public Consultation in Preparation of a Legal Proposal to Combat Counterfeit Medicines for Human Use.

The counterfeiting of medicines is a criminal act which puts at jeopardy the health and life of patients. Although generic medicines have not been reported to be subject to counterfeiting in the European Union, the EGA sees this initiative as an encouraging step forward in the fight against the counterfeiting of medicines.

The EGA considers that the most significant results in the effort to combat counterfeiting will be achieved through the following European Commission proposals:

- Subjecting all pharmaceutical business operators in the pharmaceutical supply chain to:
  - The pharmaceutical legislation in force,
  - Tighter and harmonised inspections and supervision measures;
- Enhancing international co-operation (EU and non-EU) and harmonisation, particularly through the mutual recognition of the findings of inspections and audits;

Through the creation of a higher level playing field, the following proposals are also expected to contribute indirectly to the fight against counterfeit medicines:

- Auditing activities,
- Transparency measures for inspection outcome.

The EGA further recommends that, for optimal results, other key aspects be considered:

- The introduction of clear definitions of the roles and responsibilities and the scope of activities of actors or business operators in the medical supply chain,
- The establishment of equal levels of liability for all actors of the pharmaceutical supply chain,
- The introduction of cross-functional interactions and criminal enforcement procedures for alleged counterfeiting,
- The development of common European licensing system and risk assessment criteria,

- The conducting of business within the pharmaceutical supply chain with certified/licensed partners only,
- The optimisation of resource allocation for both the industry and the authorities.

Furthermore, it must be underscored that the use of seals and traceability systems as proposed by the EC are expensive measures that will not stop the counterfeiting of medicines or prevent a fake medicine from reaching patients.

The EGA believes that new technical solutions will not add considerable value to the existing traceability systems in the fight against counterfeiting. Even more, over-reliance on technology will provide a false sense of security.

In addition, there is substantial risk that new rules requiring the use of seals or mass serialisation could substantially increase the manufacturing costs of generic medicines, potentially reducing the generic medicines industry's ability to provide affordable medicines.

In this context, any additional rules and requirements proposed, whether they relate to GMP or traceability should be shown to adequately address the problems at stake (ie, the counterfeiting of medicines or the introduction of substandard active substances or medicines onto the community market) and to lead to the enhanced protection of patients.

Attention should be paid to avoid increasing the administrative and financial burden to the companies and organisations which ALREADY comply with the set requirements.

In this respect, the impact assessment carried by the European Commission in parallel to the public consultation is of paramount importance in that it will allow for a careful evaluation of the implementation costs of the measures put forward. More specifically, consideration should also be given to the resources needed for implementation, both for the industry and for the authorities. Accordingly, effective measures which have been identified should receive priority.

## 2. Introduction

The EGA considers that the European Commission's key proposals effectively target the real problem of counterfeiting through:

- Tightening the requirements for the manufacture, trade and distribution of medicinal products,
- Extending the legal framework to encompass active substance GMP, and
- Enhancing the supervision and means of enforcement ,

New initiatives should take into consideration the systems currently in place in the pharmaceutical industry, bearing in mind the established effectiveness of these existing systems in protecting patients from substandard and counterfeit medicines reaching them through the legitimate supply chain.

The effectiveness of additional new measures in the combat against counterfeit medicines will be tightly linked to their implementation.

The impact assessment carried out by the European Commission in parallel to the public consultation is of paramount importance in that it will allow for a careful evaluation of the implementation costs of the measures put forward.

Therefore, the EGA has prepared this document focusing on three key points:

- The effectiveness of the key proposals for preventing the counterfeiting of medicines,
- Patient safety,
- The impact on the European generic medicines industry.

The EGA's position is presented in detail in the following pages.

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

### Key ideas for changes to EC legislation

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

The EGA welcomes the European Commission proposal aimed at introducing obligations of compliance to the pharmaceutical legislation<sup>1</sup> in force for all parties involved in the production, trade and distribution of medicinal products (ie, “pharmaceutical business operators”).

This measure would effectively combat the counterfeiting of medicines because pharmaceutical business operators at all stages of production, trade and distribution within the businesses under their control would be responsible for ensuring that pharmaceutical products satisfy the requirements of the pharmaceutical legislation relevant to their activities.

Such measures<sup>i</sup> are already applicable in other regulated industries (eg, food industry, Regulation (EC) No 178/2002<sup>2</sup>).

In order to maximise the results sought by the European Commission in enhancing patient safety, the EGA advises that additional points be taken into consideration:

- In addition to brokers, traders and agents, all pharmaceutical business operators from the early<sup>3</sup> to the late<sup>4</sup> stages of the supply chain, whether in direct or indirect contact with the pharmaceutical product (ie, having direct or indirect impact on the medicines safety) should be considered for inclusion in the revised scope of the pharmaceutical legislation;
- Appropriate definitions of all the possible “pharmaceutical business operators” in the supply chain into the pharmaceutical legislation would help clarify their roles, scope of activities, duties and responsibilities, as well as their associated liability throughout the supply chain;
- To maintain the consistency of definitions in the legislation, existing provisions<sup>5</sup> should be taken into consideration when changes are introduced to the pharmaceutical legislation with regards to brokers and traders of active substances;
- Equal levels of liability for all actors<sup>6</sup> involved in the medicines supply chain should be included in the pharmaceutical legislation. This principle is already mentioned in

---

<sup>1</sup> Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, as amended

<sup>2</sup> Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the principles and requirements of food law, establishing the European Food Safety Authority and laying down the procedures in matters of food safety.

<sup>3</sup> Reference is made here to the recent heparin situation whereby early intermediate defects were identified as the root cause of the many adverse reactions observed.

<sup>4</sup> Pharmacists are important ‘integrity keepers’ within the pharmaceutical supply chain due to their direct interaction with the medicinal products (delivery or preparation) and patients. Consideration should be given to national initiatives addressing this and which have led for instance to the establishment of Good Compounding Practices detailing sourcing, operating, traceability, supervision, control and transparency standards (eg, France).

<sup>5</sup> Eg, article 46a of Directive 2001/83/EC as amended

<sup>6</sup> Liability should correlate to the level of handling of the medicinal product and the associated risk for the medicinal product integrity.



*Making Medicines Affordable*

Council Directive 87/374/EEC<sup>7</sup> on product liability and applicable to other regulated industries (eg, food industry<sup>2)ii&iii</sup>;

- As with wholesale distribution<sup>8</sup>, the European provisions setting out the required conditions for granting various existing operating licenses at national level (eg, manufacturing, distributing or trading licenses) should be refined and streamlined. In most EU Member States, the grant of an operating license does not distinguish the exact scope of the concerned business operator's activities (eg, direct handling of the product or business intermediaries).

For a given pharmaceutical business operator, the scope of his activity (eg, physical handling of the medicinal product, re-labelling, storage, trade, etc) should correlate with the appropriate level of licensing requirements. Accordingly, wholesaler's duties and responsibilities might not be fully applicable to all business operators under consideration in the present proposal and might deserve specific provisions.

Based on this, the EGA suggests that a unique European licensing system be created in order to provide Member States with common grounds for implementation.

---

<sup>7</sup> Council Directive of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products (85/374/EEC)

<sup>8</sup> Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use & Guidelines on Good Distribution Practices of medicinal products for human use 94/C63/03

## 4. Supervision and Enforcement (GMP/GDP)

### 4.1. Audits

An audit is defined by the European Commission as the verification of compliance with the standards<sup>9</sup> of an economic operator by another economic operator. Carrying out an audit falls under the responsibility of the industry.

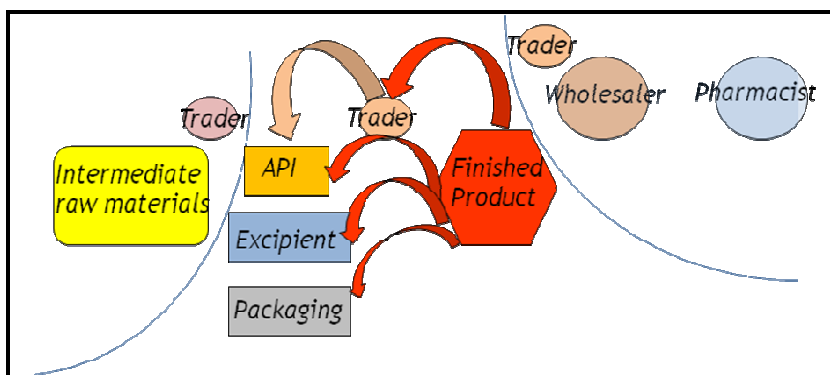


Figure 1: Auditing requirements under the current pharmaceutical legislation (Dir. 2001/83/EC as amended)<sup>10</sup>

#### Key ideas for changes to EC legislation:

- (4.3.2.a) Make regular audits of active substance suppliers with regards to GMP compliance by manufacturers and importers of medicinal products mandatory. Auditors should be sufficiently qualified.
- (4.3.2.c) Turn principles of good manufacturing practice for active substances placed on the Community market into a legal act of Community law (eg, a Commission Directive) in order to enhance enforceability.

The EGA agrees with the European Commission's key ideas regarding audits of active substance manufacturers.

Since the revised pharmaceutical legislation entered into force in October 2005, medicinal product manufacturers are legally required to use, as starting materials, only those active substances which have been manufactured in compliance with good manufacturing practices. The direct consequence of this provision is that the industry is required to perform regular audits of their various active substance suppliers and manufacturing sites

<sup>9</sup> Stemming from the pharmaceutical legislation and guidelines, and other relevant qualification/certification system (eg, ISO)

<sup>10</sup> Key to symbols is provided in 8.1 Additional Explanatory Figures on GMP/GDP



as shown in Figure 1. Accordingly, EGA companies have implemented the necessary changes to ensure compliance with this requirement. Adequate training of auditors is part of a company's quality system which is subject to inspection under the provisions of the current pharmaceutical legislation.

Having good manufacturing practice for active substances turned into a legal act of the Community is seen as a move toward a consistent approach for the entire pharmaceutical chain. A modification in the scope of Commission Directive 2003/94/EC could constitute an effective way of achieving this harmonisation in requirements and enhanced enforceability.

**Key ideas for changes to EC legislation:**

- (4.1.1.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 suspected non-compliance with GMP and/or GDP

The European Commission proposal (above) is represented by dotted arrows in Figure 2 below.

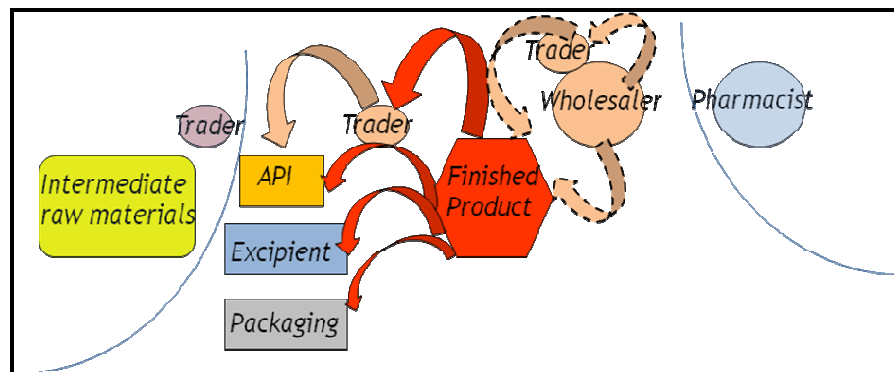


Figure 2: EC Key Proposal on regular audits of GMP/GDP compliance<sup>10</sup>

Although pre-qualification evaluation is routinely carried out prior to engaging in regular business contracts, the EGA concurs with the European Commission that auditing activities clearly represent a reinforced security level when dealing with new business partners or in case of doubt.

EGA member companies have expressed their position in favour of doing business with certified/licensed partners only in an earlier position paper on counterfeit medicines<sup>11</sup>.

It should be clear that auditing has proven to contribute to establishing a relationship of trust along the supply chain; however it does not directly prevent the counterfeiting of medicines which, in highly regulated markets such as Europe, has its roots in the corruption of the staff of business operators. Audits do allow for commercial decisions from the auditor company, but not for any official enforcement measures (eg, non compliance sanction).

The EGA strongly believes that in relation to the relative effectiveness of this proposed measure on enhancing patient protection, it will be necessary to evaluate its impact on the pharmaceutical business operators involved.

In addition to the wholesalers costs of setting up auditing activities, the EGA would like to emphasise the additional inherent costs of being audited (“passive” costs) incurred to the ‘audited pharmaceutical business operator’. With wholesalers foreseen to engage in auditing manufacturers (auditees), the EGA would like to point out that rationalisation measures should be considered to ensure that the additional “passive costs” do not reduce the generic medicines industry’s ability to provide affordable medicines.

Furthermore, in order to maximise the results of combating the counterfeiting of medicinal products sought by the European Commission, the EGA advises that the following additional points be taken into consideration:

- To avoid duplication and redundancy of audits and overall disruption of operations, further considerations (other than third party auditing) should be given to ways of streamlining industry audits and optimising resources by industry. This could be achieved through access to the EudraGMP database and to an industry managed “audit-database”, the modalities of which would have to be defined.
- The establishment of European common risk assessment criteria<sup>12</sup> to define the criticality of a product/business partner as well as the adequate frequency of audit (or inspection) to appropriately manage this criticality would be welcome (eg, in a Guideline)<sup>13&14</sup>.

---

<sup>11</sup> “Business with certified partners only”, EGA Position Paper on anti-counterfeiting policy - [http://www.egagenerics.com/doc/ega-anticounterfeit\\_position.pdf](http://www.egagenerics.com/doc/ega-anticounterfeit_position.pdf)

<sup>12</sup> As an example, Germany has enacted a legal provision for the prioritisation of inspections whereby products of human, animal, fermentation, microbiological or genetically modified origin are given high priority. (§ 72 - German drug law (Deutsches Arzneimittel gesetz)).

<sup>13</sup> An example of ranking can be found in the GMP Guide Part II where increasing GMP requirements are applied depending on the type of manufacturing of an active substance.

<sup>14</sup> Referring to the heparin situation as an example, the crude intermediate used for the production of the active substance could be considered highly critical in that changes to it proved to be impacting dramatically the overall medicinal product safety profile. This further highlights the need to establish the appropriate need and frequency for audit (or inspection) for all business operators (including early and late stages of the supply chain).

### Key ideas for changes to EC legislation:

(4.3.2.b) 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.

EGA companies believe that the current analytical methods for active substances are sufficiently discriminative, and would request that fingerprint technologies or NIR remain as optional approaches. Introduction of such provisions in the pharmaceutical legislation will lengthen the process of updating and to adapt to state-of-the-art technologies.

The requirements for testing medicinal products for their conformity to the required specifications are well defined<sup>15</sup>. The level of testing is decided according to a risk-based approach (ie, level of compliance with EU standards)<sup>iv</sup>.

In today's practice, prior to any finished dosage form manufacturing, for raw materials (active substances and others), the manufacturer of medicinal products should establish a sampling and testing procedure appropriate for the concerned material, regardless whether the raw material is manufactured in the EU or imported from third countries.

The EGA would recommend that for active substances (and other raw materials) re-testing be required in accordance to the scheme applicable to medicinal products (above).<sup>16</sup>

NIR might serve a purpose as far as medicinal products are concerned as it allows for the identification of the presence of a given active substance through a non-destructive test. However, it does not always give a quantitative indication of potential contaminants, nor does it address their presence. To this extent, making this methodology mandatory would not help to detect the presence of counterfeit medicines.

The creation of new mandatory rules should clearly add value to the existing system<sup>17</sup> and not simply constitute a "penalty" for those companies operating under a satisfactory level

---

<sup>15</sup> Volume 4 - Medicinal Products for Human and Veterinary Use : Good Manufacturing Practice; The Rules Governing Medicinal Products in the European Union

<sup>16</sup> In Germany, in October 2006, the AMWHV introduced a revised manufacturing regulation (covering GMP aspects for both finished product and active substance). The new regulation requires the mandatory release of active substances coming from outside the EU prior to their entry on the market. Although the data generated since entry into force are not publicly available, the EGA strongly believes that analysis of this data would provide the European Commission with an accurate overview of the actual standard of active substances currently imported into the European Union. Verordnung zur Ablösung der Betriebsverordnung für pharmazutische Unternehmer Vom 3. November 2006; Bundesgesetzblatt Jahrgang 2006 Teil I Nr. 51, ausgegeben zu Bonn am 9.November 2006.

<sup>17</sup> For marketed medicinal products, analytical methods of all involved materials have been developed and validated by the industry, in some instances according to existing European standards (eg, EP or BP analytical methods), and have in addition been assessed and approved by regulatory authorities for their ability to adequately monitor the quality of the materials concerned.

of compliance with the current system. The costs of implementing such new technology as a mandatory tool should be taken into account.

#### 4.2. Inspections by Competent Authorities

An inspection is defined by the European Commission as the verification of compliance with standards<sup>18</sup> of an economic operator by any competent authority. This falls under the responsibility of the regulatory authorities.

#### Key ideas for changes to EC legislation:

- (4.1.2.a) 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.
- (4.1.2.b) 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).

The EGA particularly welcomes the European Commission’s proposal to tighten the rules on inspections through the introduction of Community procedures as mandatory inspection standards.

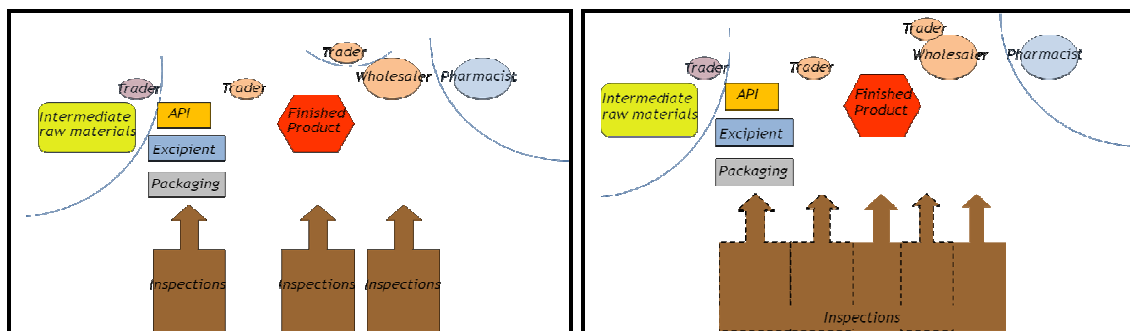
Standardising the operating requirements of the authorities will greatly contribute to the harmonisation of practices throughout Europe and will certainly favour greater synergy through mutual acceptance and recognition of inspection reports and conclusions.

It is indeed desirable that Member States enforce the pharmaceutical legislation, monitoring and verifying that the relevant requirements are fulfilled by pharmaceutical business operators at all stages of production, trade and distribution.

For that purpose, they should maintain a system of official controls and other activities as appropriate to the circumstances, including communication on inspection results and inspections planning (eg, EudraGMP database).

---

<sup>18</sup> Stemming from the pharmaceutical legislation and guidelines, and other relevant qualification/certification system (eg, ISO)



**Figure 3: Current Inspection scheme (left) and new legislative proposal for Inspection scheme (right)<sup>10</sup>**

It would, however, be necessary to evaluate the impact of this additional measure on the pharmaceutical industry business operators involved.

The EGA would again like to emphasise the additional inherent costs (“passive” costs) to the ‘inspected business operator’ of being inspected.

With inspections covering more business operators inside and outside the European Union (eg, traders, logistic providers, suppliers), the EGA would like to highlight that the inspection fees along with the “passive costs” will create a drastic increase in costs to the generic medicines manufacturers (see Figure 3 above).

To enhance the harmonisation of the supervision and enforcement by European authorities, the EGA would like to reiterate the recommendations made in the previous sections on:

- The inclusion in the pharmaceutical legislation of specific provisions for all pharmaceutical business operators,
- The development of an adequate European operating license system (operated by Member States),
- The use of common European risk-assessment criteria (to establish criticality of product/partner, frequency of inspection),
- The need for equal levels of liability for all pharmaceutical supply chain actors.

To maximise the results of combating the counterfeiting of medicinal products sought by the European Commission, the following additional points should be taken into consideration:

- The grant or renewal of operating licenses of the supply chain business operators should be linked to their proven status of compliance with the applicable GXP<sup>19</sup> or other applicable standards. This should be part of the changes to the pharmaceutical legislation;

<sup>19</sup> GXP = GMP, GDP, etc.

- Each pharmaceutical business operator should bear the costs accrued in relation to the inspection of their premises.<sup>20</sup>

**Key ideas for changes to EC legislation:**

- (4.3.3.a) 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.
- (4.3.3.b) The competent authority shall carry out these inspections if there is suspected non-compliance with GMP.
- (4.3.3.c) The competent authority shall carry out repeated inspections in the exporting country if the third country applies standards of good manufacturing practice which are 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.

The EGA welcomes all aspects of the above proposals. We strongly believe that enhanced supervision and enforcement of the existing legal provisions are a key factor for success in protecting patients from substandard treatments or counterfeit medicines.

In terms of compliance to standards, unannounced inspections most probably represent the best way to enforce European legislative provisions.

To enhance the enforcement of the pharmaceutical legislation by European Authorities, the EGA would like to reiterate the recommendations made in the previous sections on:

- The use of common European risk-assessment criteria (to establish criticality of product/partner, frequency of inspection),
- The need for a European ‘inspection-database’ to optimise resources and avoid duplication.

To maximise the results sought by the European Commission in enhancing patient protection, the following additional points should be taken into consideration:

- A list of those other regions or countries which can be considered as having GMP standards, supervision, and means of enforcement equivalent to those applicable in Europe clearly needs to be made publicly available.
- Criminal enforcement procedures are needed both at European and National level to effectively combat the counterfeiting of medicines. To this end, enhanced

---

<sup>20</sup> As implied by equal levels of liability and clear definition of statuses

“horizontal” cooperation is necessary between health authorities, inspectorate, criminal investigators and customs staff<sup>21</sup>.

- Enhancing international co-operation (EU and non-EU) and harmonisation, particularly through recognition of inspections findings is crucial for matching global pharmaceutical industry characteristics. Further development of Mutual Recognition Agreements (MRAs) could contribute to the optimisation of resource allocation.
- The rationalisation of inspections and audits as well as a higher level playing field for GMP could be achieved through:
  - One unique publicly accessible official database (eg, EudraGMP) containing the findings of both inspections and audits.
  - On occasions, partnered inspection/audit (ie, by representatives of authorities and industry simultaneously on the field) which would contribute to standardise the level and quality of inspections and audits.
- The provision of a GMP certificate for an active substance supplier should remain optional for the registration of a medicinal product as the medicinal product manufacturer is in any respect responsible under the current legislation for ensuring, through audit, that its suppliers operate in compliance with GMP requirements.
- National inspectorates should clearly reconsider practices whereby inspections are prioritised on grounds of geographical “closeness” rather than on risk assessment.<sup>22</sup>

#### 4.3. Third party Auditors

The EGA welcomes the EC Proposal aimed at allowing third party auditing as an alternative and complementary approach to company auditing.

However, the currently available models for third party auditing (including accredited ones) do not provide adequate relief to the industry. The contribution to the rationalisation exercise is expected to remain limited under the current set of proposals:

- It is foreseen that third party auditors will be contracted by the medicinal product manufacturer for the audit of its partners (eg, active substance trader);
- The incurred costs are supported by the medicinal product manufacturer;
- Third party auditors represent an additional partner in the supply chain and need to be audited by a medicinal product manufacturer (contract giver).

---

<sup>21</sup> The UK presents a good example of an effective anti-counterfeit medicines structure with the associated forces of inspectors and criminal investigators (MHRA Enforcement & Intelligence Group (E & I)); <http://www.mhra.gov.uk/Howweregulate/Medicines/Enforcingthelaw/index.htm> and <http://www.touchbriefings.com/pdf/2404/ACF1C8.pdf>

<sup>22</sup> Please refer to an example presented in 8.2. of Inspections carried out by the “Raw Materials Inspection Unit” (“Unità Ispettiva Materie Prime”, Italy), (page 29).

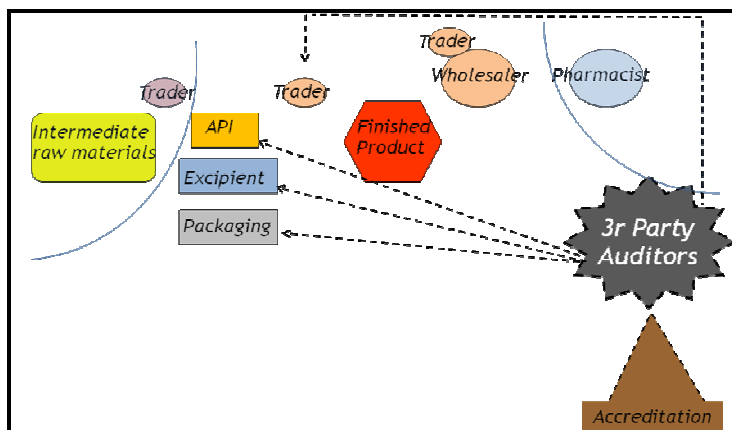


Figure 4: EC Proposed model for Accredited 3<sup>rd</sup> Party Auditing<sup>10</sup>

By definition, audits are the responsibility of the industry. It should be noted that, today, existing accreditation systems and organisations suffice when adequately operated. As such, there should be no need for a “special” or “distinct” accreditation by the authorities.

One proposal would be to define third party auditors in the pharmaceutical legislation along with the other business operators. Specific licensing requirements should be developed in relation to the specific scope of activities of third party auditors as part of the unique European licensing system. Their level of liability should be established as equal to that of all business operators of the supply chain involved. Third party auditors would then be subject to inspections, and certification.

By becoming a well-defined pharmaceutical supply chain business operator, the results of the inspection of third party auditors by the competent authorities should also be part of the EudraGMP database.

In line with our proposal to create a higher level playing field for GMP (unique audit/inspection database and partnered inspection/audit), the results of audits carried out by third party auditors on behalf of business operators should also be taken into account. This would further contribute to:

- the rationalisation of audits, and
- the optimisation of resources,
- the creation of a level playing field for 'strictness' of audits or inspections (standardisation of the level and quality of audits or inspections).

The current models foresee that medicinal product manufacturers bear the costs of auditing their suppliers. With the establishment in the pharmaceutical legislation of equal levels of liability for all actors of the supply chain involved, an alternative model whereby each business operator takes the responsibility for being audited (including costs of third party auditing) or inspected, could be foreseen.



## 5. Transparency

### 5.1. Increasing transparency concerning authorised wholesalers through a Community database.

- (4.1.6.a) Require GDP certificates to be issued after each inspection of a wholesaler.
- (4.1.6.b) Establish a Community database of wholesalers (including distributing manufacturers) documenting GDP compliance. This could be achieved via extension of the EudraGMP database.

Systematic issuance of GDP certificates is a desirable measure which is consistent with the measure aimed at subjecting all business operators to the pharmaceutical legislation. The issuance of a compliance certificate should be applicable not only to wholesalers, but also to all business operators who are subject to inspections (including traders, brokers or business to business platforms).

Making this information available will contribute to establishing a level playing field across the European Union through the collection and analysis of relevant data in the fields covered by the authorities. Improved identification of emerging risks may in the long term be a major preventive instrument at the disposal of the Member States and the Community in the exercise of its policies.

Transparency measures indirectly contribute to combating the counterfeiting of medicines in that they allow for a continuous re-evaluation of risk assessment audit/inspection plans through the broad diffusion of information to all stakeholders.

It is felt wise to envisage the expansion of the existing EudraGMP database to collect this information. Public access to the EudraGMP database is foreseen for mid-2008. The running costs linked to the expanded database will be increased accordingly.

By publishing these data, the database would ensure a level playing field for 'strictness' of inspections. It would further contribute to standardising the levels and quality of inspections.

Reference to the database could facilitate the link between the issuance (or renewal) of an operating license and the compliance status of a given business operator.

## 5.2. Mandatory notification procedure for manufacturers/importers of active substances

### Key ideas for changes to EC legislation:

- (4.3.1.a) Submit the manufacturing/import of active ingredients to a mandatory notification procedure
- (4.3.1.b) Render information on notified parties available in a Community database. This could be achieved via extension of the EudraGMP database.

Transparency measures are believed to contribute to a higher level of confidence between the authorities and pharmaceutical business operators, as well as amongst distinct European authorities and amongst distinct business operators.

However, when it comes to creating a mandatory notification process prior to manufacturing or import of active substances in Europe, the benefits of these additional administrative steps to combat the counterfeiting of medicines and to promote patient safety need to be balanced with regards to the potential increase in administrative burdens and the likely introduction of “weak points” (and the introduction of errors, eg, human error) in the multiplication of steps.

To maximise the results of combating the counterfeiting of medicinal products sought by the European Commission, the EGA would like to reiterate here the recommendations made in the previous sections on:

- the inclusion of specific legal provisions for all pharmaceutical business operators,
- the development of an adequate European “operating license” system, and
- the need for equal levels of liability for all pharmaceutical supply chain actors.

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

### Key ideas for changes to EC legislation:

(4.2) Directive 2001/83/EC would be clarified to the effect that imported medicinal products intended for export (ie, 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, eg, 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, eg, 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 EGA agrees with the European Commission proposal to clarify that the pharmaceutical legislation applies in a non-discriminatory manner to imported, exported or re-exported medicinal products (for placing on the market in a 3<sup>rd</sup> country), regardless of the actual trading or placing on the market in the European Community or internationally.

The medicinal products concerned should comply equally with the relevant requirements laid out in the pharmaceutical legislation unless otherwise requested by the authorities of the importing country or established by the laws, regulations, standards, codes of practices and other legal and administrative procedures as may be in force in the importing 3<sup>rd</sup> country.

Such provisions are consistent with the proposal to subject all pharmaceutical supply chain business operators to the pharmaceutical legislation. They are applied in other regulated industry sectors such as that of the Food Industry<sup>Y</sup>.

The EGA would recommend tighter and harmonised control measures on “bonded warehouses” as far as medicinal products are concerned, regardless of whether handling of the medicinal products involves repacking, re-labelling, over-labelling or any analytical sampling (ie, disrupting the medicinal product integrity).

To maximise the results of combating the counterfeiting of medicinal products sought by the European Commission, the EGA would like to reiterate here the recommendations made in the previous sections on:

- the inclusion of specific legal provisions for all pharmaceutical business operators,



Making Medicines Affordable

- the development of an adequate European “operating license” system,
- the establishment of equal levels of liability for all pharmaceutical supply chain actors,
- the creation of harmonised inspection standards.

## 7. Traceability

7.1. 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.

- 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, ie, 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).

The EGA recognises the fact that exchanging and/or opening the outer packaging of a medicinal product increases the risk of a product being counterfeited. However, the use of packaging equipped with a unique seal will neither stop nor prevent counterfeiting.

Other industries suffering from the same problem have used similar approaches without experiencing a decline in the counterfeiting of their products. In fact, the safety measures themselves were also counterfeited: *“Counterfeiters have come up with fake hologram stickers”*<sup>23</sup>. The use of a seal will only delay counterfeiters until the practice is sufficiently well-known to be circumvented. This will occur very rapidly because the manufacturer will have to give notice about this seal (and any subsequent changes to it) to the competent authorities and to all partners of the supply chain in order to make this feature known and to turn it into a recognised benefit.

Moreover, a fake medicinal product with a genuine seal will be perceived as a legitimate and safe medicine. Counterfeiters are able to produce fake seals very cheaply, creating a false feeling of safety and, thus, may create additional safety risks to patients.

Moreover, the introduction of seals as a measure to fight counterfeiting will have a dramatic impact on generic medicines companies. The costs imposed on the industry from implementing a unique seal will increase inefficiencies at the production lines and will

---

<sup>23</sup> Source: SAY NO TO PIRACY NEWS: <http://server1.msn.co.in/Computing/antipiracy/news.html>, Microsoft and Hollywood stand united against piracy, Source: ZDNET, 13 March, 2003.

diminish output, increasing production costs in an industry that is highly sensitive to the cost factor.

Furthermore, affixing a seal on the outer packaging creates a situation which does not facilitate the practical requirements of updating product information, such as updating a patient information leaflet following, for example, changes in safety information as the result of a referral.

In addition, the use of a unique seal raises other important questions regarding the cost-benefit ratio of the measure, the reduction of throughput on the production lines, and the resulting increase in cost for the pharmaceutical manufacturers and eventually for patients and payers.

## 7.2. Centrally accessible record to facilitate traceability of batches throughout the distribution chain

- 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.

Pharmaceutical manufacturers have been obliged by law since the early 1970s to record their batch numbers to facilitate the tracking and tracing of their batches through their own internal codes and procedures. There have been no complaints about this practice.

Implementing a system requiring information to be centrally recorded and centrally accessible by all actors using standard batch codes would affect the secrecy of vital strategic company information (see section **Error! Reference source not found.** in annex). It would reveal the increases and decreases in volumes shipped, show changes in product mix, breadth and depth of product lines, changes in routing, and other specifications.

It would also generate an increase in costs and would require drastic changes in the way that generic pharmaceutical manufacturers currently operate (see 8.4 in annex). Developing a unique and centrally accessible database would not guarantee the elimination of counterfeiting or a safer supply chain. In fact, centralising all batch numbers in a regulated order would facilitate the access of counterfeiters to the information required for their illicit activities.

The perfectly secure technical IT system does not exist. The risk of gathering and storing all the required information in a central database will raise questions of confidentiality, implementation, security and costs.

The existing fragmentation of information along the supply chain does not constitute a problem. Today's recall systems in the Member States are effective, efficient and easy to manage. No need for new systems has arisen as the result of ineffective recalls.

### 7.3. Mass serialisation for pack-tracing and authenticity checks on a case-by-case basis

- 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.

The EGA believes that, in the same way that a central database of batch numbers will not prevent a counterfeited pack from reaching the patient, mass serialisation at the pack level will also not achieve better results in thwarting counterfeiters, (for a graphic presentation of mass serialisation systems, see section **Error! Reference source not found.** in annex). Technical solutions do not constitute reliable prevention systems; the implementation of such measures will only stimulate counterfeiters to develop new skills and capabilities.

Although, the possibility of tracking and tracing a specific pack exists, the system does not secure all the possible links in the supply chain or stop the counterfeited pack from reaching the patient.

Additionally, the real cost of such solutions remain unknown; indicative figures are still inaccurate or do not take all aspects into account. Moreover, the high costs related to this kind of proposals represent a heavy economic burden to sectors where products are highly sensitive to cost increases, as is the case with the generic medicines industry. An increase of costs associated to non-effective measures is damaging to the competitiveness and sustainability of generic medicines companies. As a result, the EGA is pleased with the initiative from the European Commission to establish an impact assessment which is restricted only to medicines that are under a genuine risk of being counterfeited.

The benefit of a mass serialisation system at pack level is based on the authentication at each point of the supply chain (manufacturer, wholesaler and pharmacist) using expensive technology. However, should the system fail at the last point of authentication, the patient would still be at risk of receiving a fake pack anyway.

Having all the information in one central point by a centrally accessible database makes the database a delightfully (from their perspective) easy target for counterfeiters.

Recent initiatives from the different Member States using mass serialisation have been launched for several different purposes, mainly as a means to put a halt to reimbursement fraud. Since no single system has explicitly defined, nor implemented, parameters to measure either the occurrence of, or the increase or decrease in counterfeited medicines, we can only conclude that none of these were designed with the objective of stopping counterfeiting. Any reference to existing serialisation systems is therefore void with regards to the probable success in the fight against counterfeit medicines.

#### **Main conclusion on product integrity and traceability**

- Seals and technical solutions do not combat counterfeiting efficiently or effectively as they do not prevent the fake packs reaching patients. The EGA believes that business between certified/licensed partners only is the answer to stopping counterfeiting.

## 8. Annexes

### 8.1. Additional Explanatory Figures on GMP/GDP

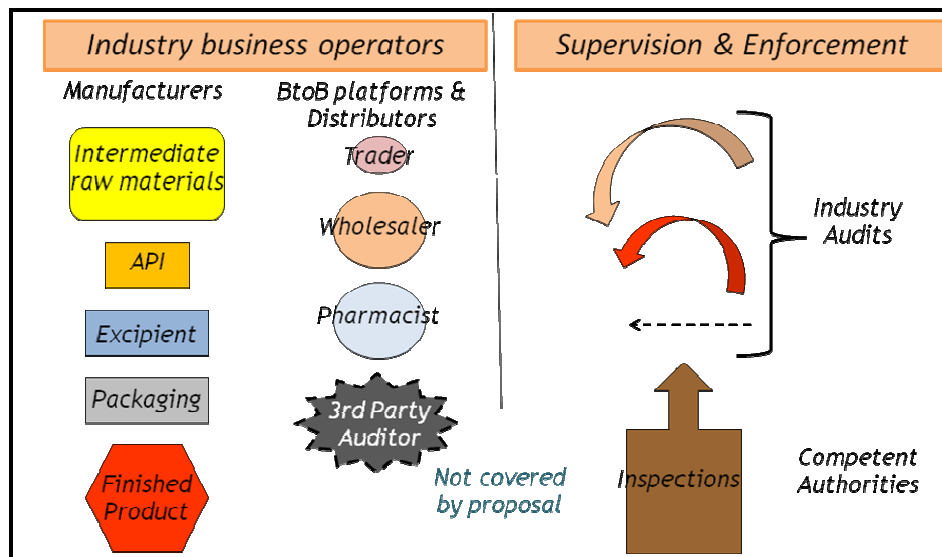


Figure 5: Key to Symbols

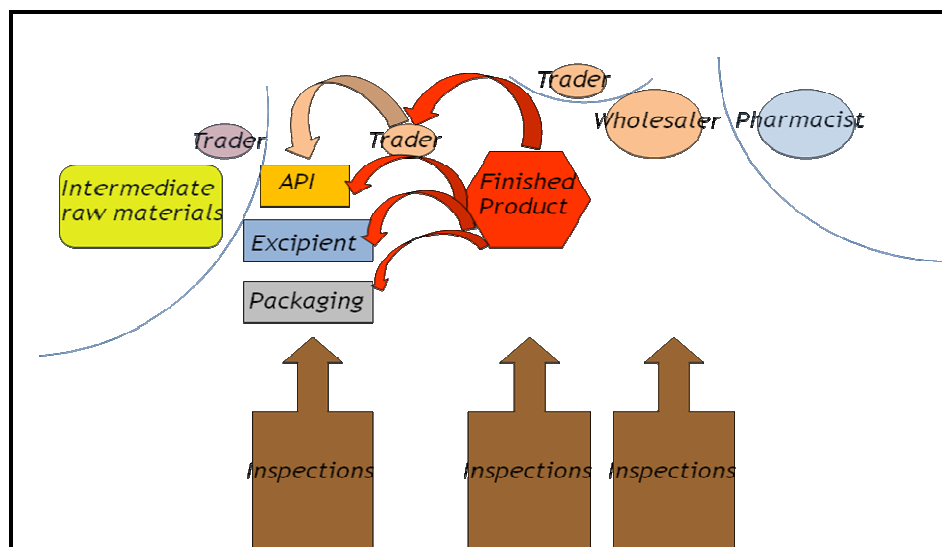


Figure 6: Current Audit and Inspection situation Europe

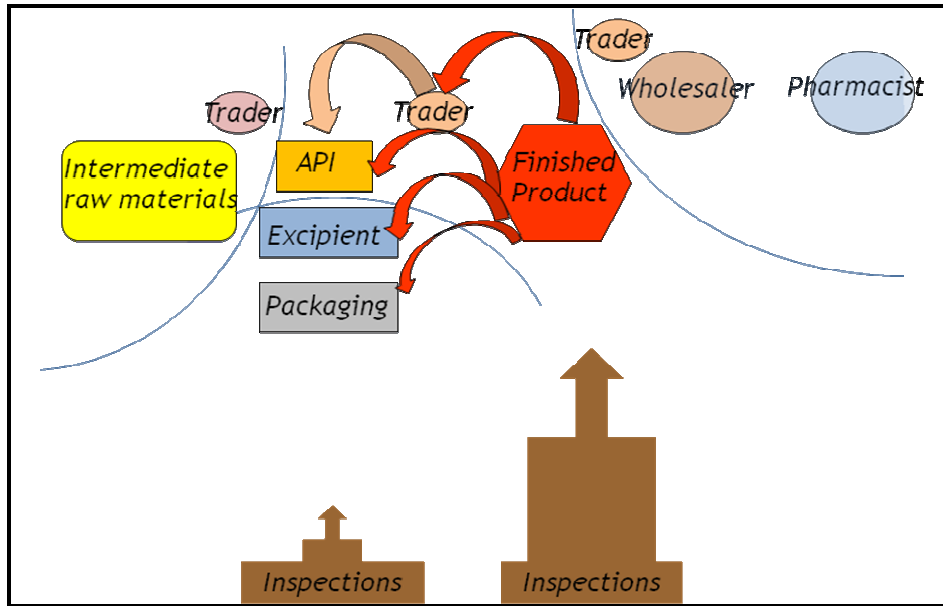


Figure 7: Current Audit and Inspection Situation Outside Europe

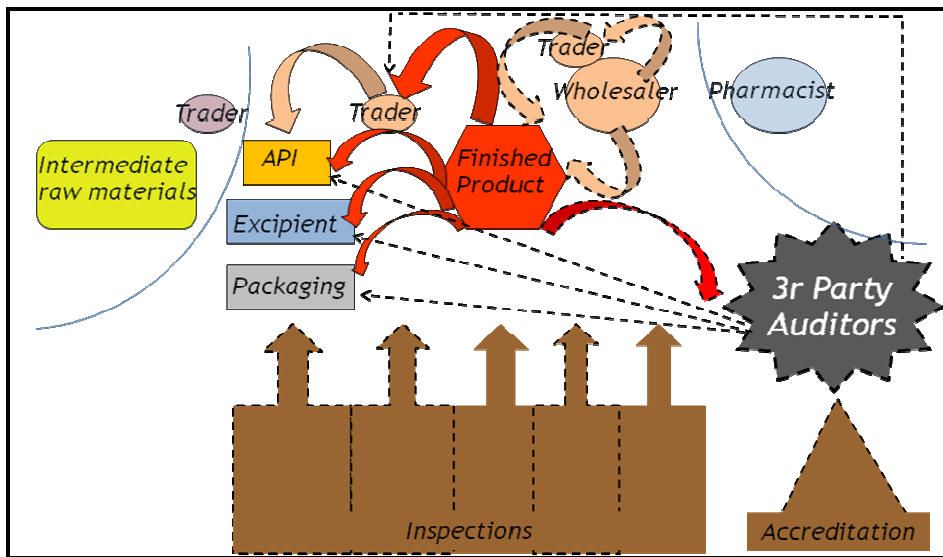


Figure 8: EC proposal



- Desired State

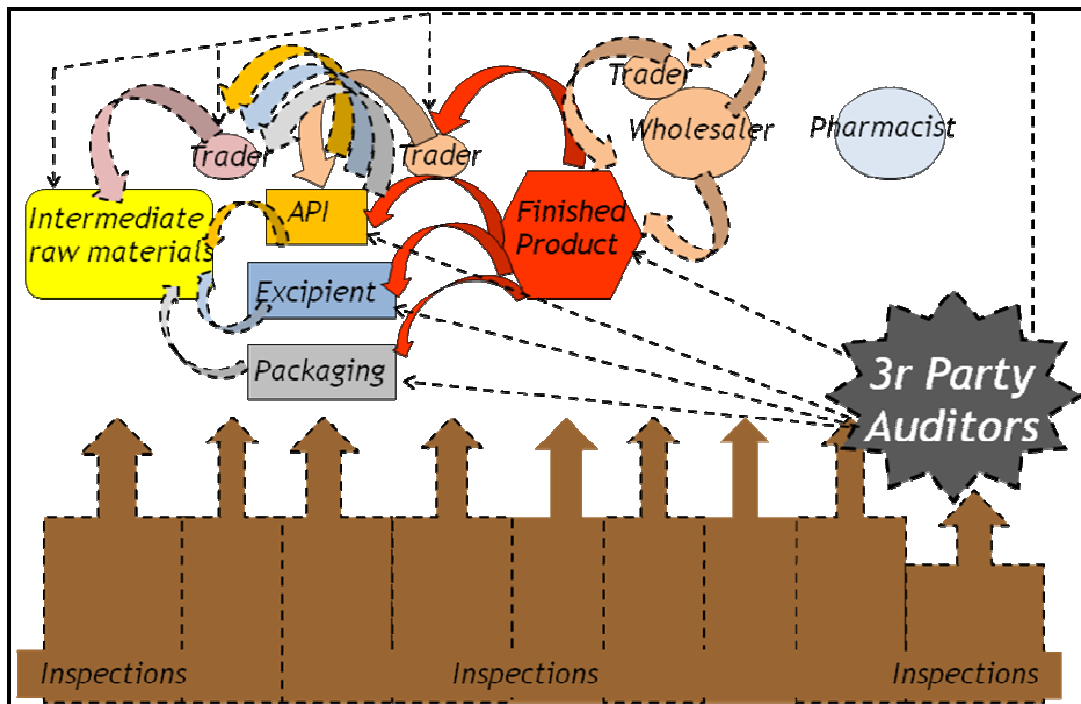


Figure 9: Desired State

### Desired State

- All business operators under the pharmaceutical law, including pharmacists & intermediate raw materials suppliers.
- Inspections cover all business operators.
- Audits prioritised based on risk assessment and rationalised through exchange of information within EU and internationally.
- National licensing activities harmonised at EU level according to common definitions of roles and responsibilities.
- Compliance is a condition for grant or renewal (maintenance) of license.
- Liability is shared equally by all supply chain actors.
- Audits prioritised based on risk assessment and rationalised through exchange of non-confidential information.

## 8.2. Example of Inspections carried out by the “Raw Materials Inspection Unit” (“Unità Ispettiva Materie Prime”, Italy)

A “Raw Materials Inspection Unit (*Unità Ispettiva Materie Prime*)” has been formed in 2003; this Unit takes care to inspect API manufacturers’ plants in order to assure that they are in compliance with Good Manufacturing Practice.

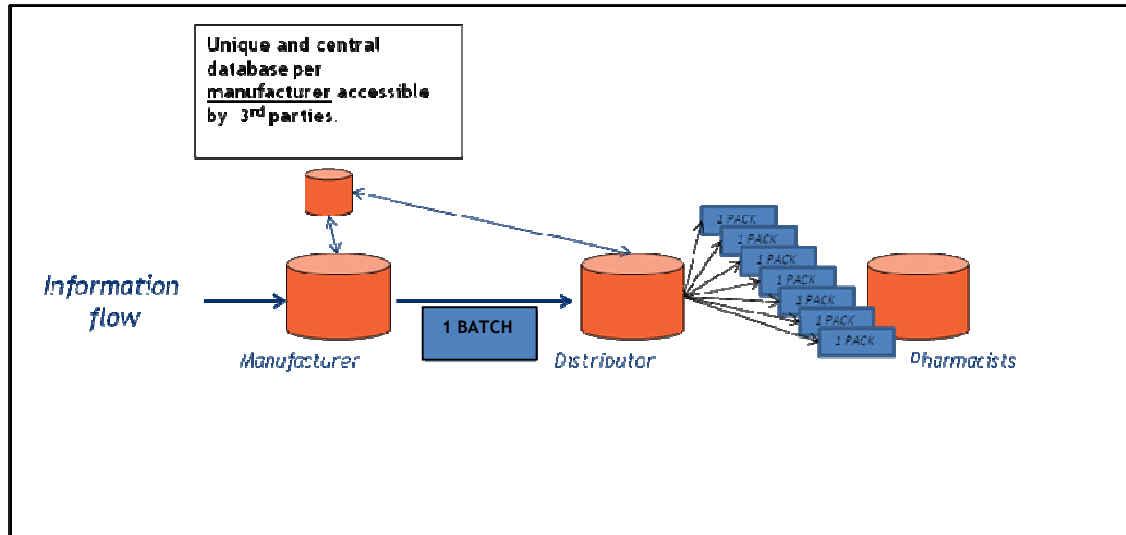
It consists of:

- 7 Inspectors from Istituto Superiore di Sanità (ISS)
- 2 Inspectors from Italian Medicines Agency (AIFA )
- 1 Coordinator

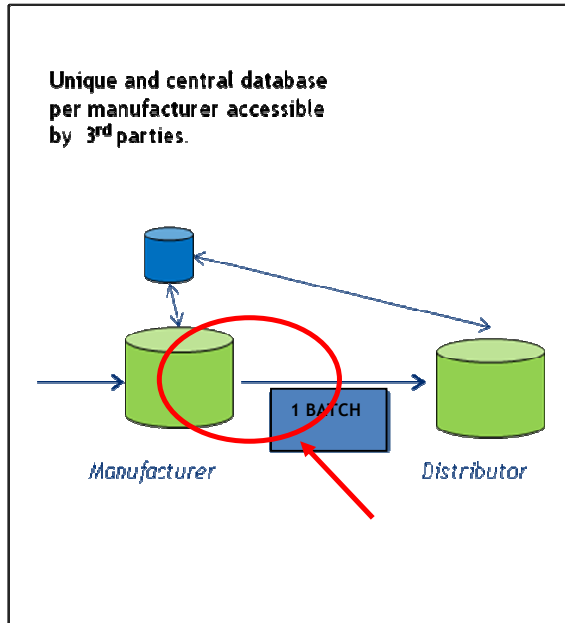
|             | ITALY    | EXTRA EU | TOTAL     |
|-------------|----------|----------|-----------|
| <b>2005</b> | 44 (84%) | 7 (16%)  | 51 (100%) |
| <b>2006</b> | 50 (84%) | 8 (16%)  | 58 (100%) |
| <b>2007</b> | 52 (87%) | 7 (13%)  | 59 (100%) |

### 8.3. EC Key Proposal 4.1.4. - "Centrally accessible record to facilitate traceability of batches throughout the distribution chain"

No real time information (one source)

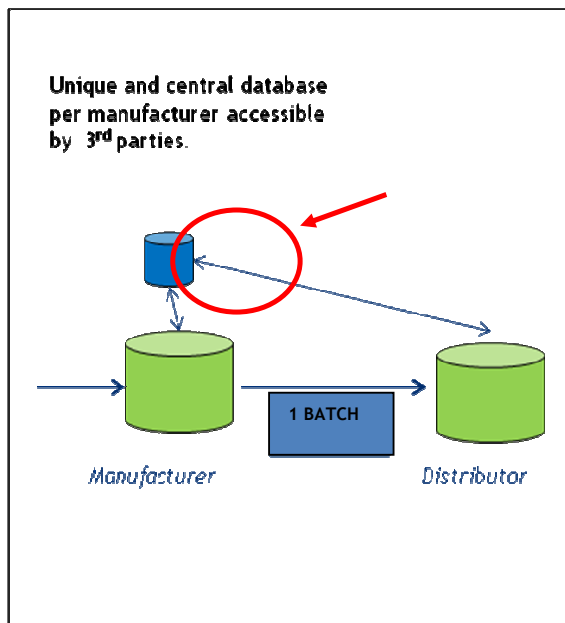


#### 8.4. EC Key Proposal 4.1.4. - Batch Level Model I - Generic medicines Manufacturers costs



##### Costs related with the production lines

- Cost of automating the production line
- Cost of equipment
- Overhead cost - people from different departments that will need to be included in the new process (mass serialisation pedigree or pack level):
  - Manager QC
  - Manager QA
  - Quality control employee
  - Quality Assurance employee
  - Logistics
  - One full time person per



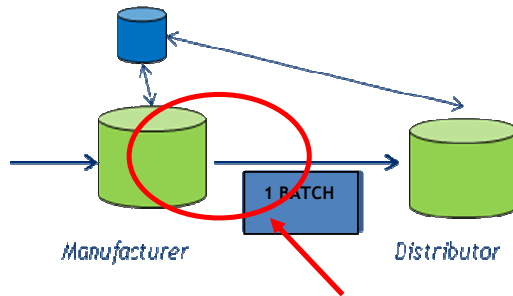
##### Costs related with the database

- World Standardisation of batch number (depending on the form/strength/presentation/country/company)
- Running the standardisation procedures
- Running and managing the database



Making Medicines Affordable

**Unique and central database per manufacturer accessible by 3<sup>rd</sup> parties.**



**Other consequences of the implementation of serialisation:**

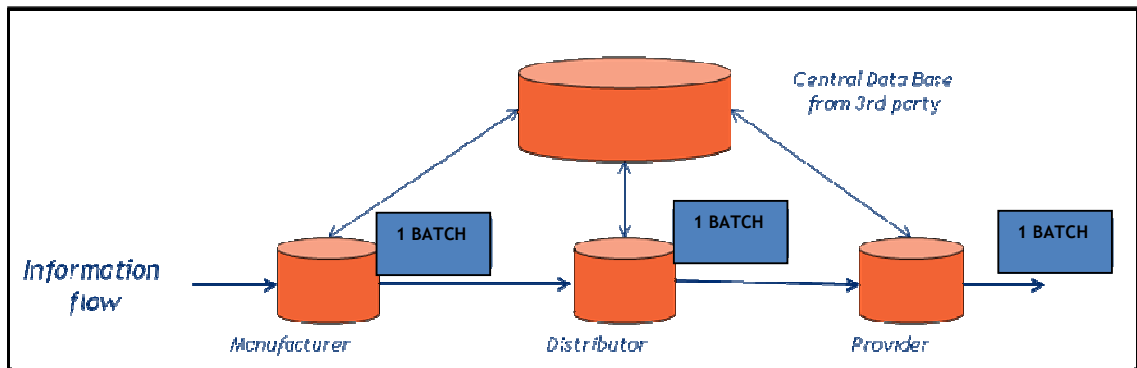
- Slow down of the production line
- Increase of costs related to the new system
- Training
- Implementation of procedures

8.5. EC Key Proposal 4.1.5. -“Mass serialisation for pack-tracking and authenticity checks on a case-by-case basis”

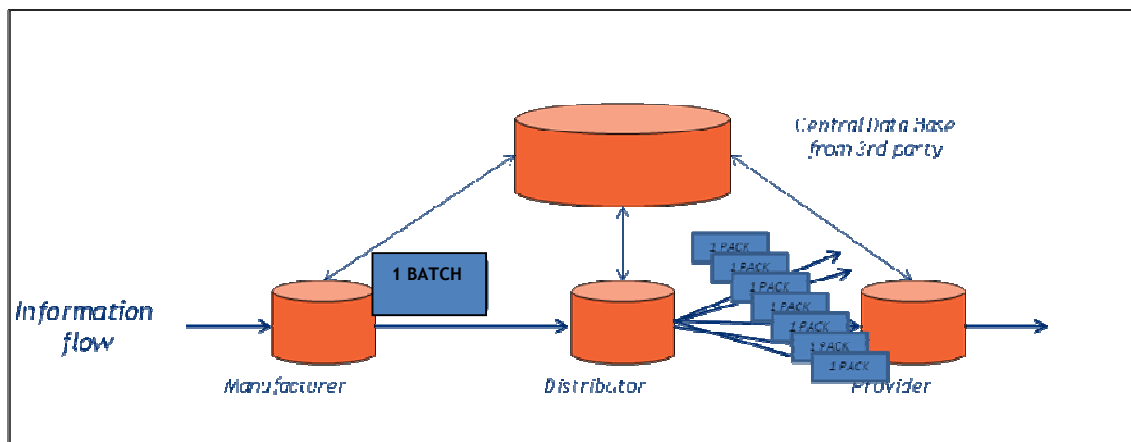
**Central data base**

- Point-to-point information sharing for day to day operations
- Duplication of data in a central database held by a 3rd party

- Option I - Individual Pack Level Model I (EFPIA model)



- Option II - Individual Pack Level Model II (using the batch level solution 4.1.4.)





---

<sup>i</sup> Regulation EC No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the principles and requirements of food law, establishing the European Food Safety Authority and laying down the procedures in matters of food safety.

“(12) In order to ensure the safety of food, it **is necessary to consider all aspects of the food production chain as a continuum** from and including primary production and the production of animal feed up to and including sale or supply of food to the consumer because each element may have a potential impact on food safety.  
(13) Experience has shown that for this reason **it is necessary to consider the production, manufacture, transport and distribution of feed given to food-producing animals, including the production of animals which may be used as feed on fish farms, since the inadvertent or deliberate contamination of feed, and adulteration or fraudulent or other bad practices in relation to it, may give rise to a direct or indirect impact on food safety.**”

<sup>iii</sup> Regulation EC No 178/2002

“Whereas protection of the consumer requires that **all producers involved in the production process should be made liable**, in so far as their finished product, component part or any raw material supplied by them was defective; whereas, for the same reason, **liability should extend to importers of products into the Community and to persons who present themselves as producers by affixing their name, trade mark or other distinguishing feature or who supply a product the producer of which cannot be identified**;

Whereas, in situations where several persons are liable for the same damage, the protection of the consumer requires that the injured person should be able to claim full compensation for the damage from any one of them;” (Council Directive 87/374/EEC on product liability)

“(30) A food business operator is best placed to devise a safe system for supplying food and ensuring that the food it supplies is safe; thus, it should have primary legal responsibility for ensuring food safety.”

<sup>iv</sup> For imported medicinal product, the level of testing is decided according to a risk-based approach (ie, level of compliance with EU standards)

- Option 1: If the medicinal product is shipped within the European Union (ie, in compliance with EU standards), minimal testing is required with an emphasis on identity testing of the active substance within the medicinal product. Countries with which Mutual Recognition Agreements (MRAs) have been signed are considered as countries of the EU.
  - Canada for instance, has an MRA with the EU. It is therefore possible to import medicinal products from Canada without full retesting. However in Canada, each imported batch of medicinal product does not need to be tested. In other words, medicinal products shipped from Asia through Canada might not have been tested yet when reaching Europe.
  - The situation of new EU Member States (EU Accession) is not always clear as to the applicability of one or the other options cited above.
- Option 2: If the medicinal product is entering the European Union from any other region in the world, maximal testing is required, including all tests listed on the certificate of analysis.



Making Medicines Affordable

---

<sup>v</sup> Regulation EC No 178/2002

*“(24) It is necessary to ensure that food and feed exported or re-exported from the Community complies with Community law or the requirements set up by the importing country. In other circumstances, food and feed can only be exported or re-exported if the importing country has expressly agreed. However, it is necessary to ensure that even where there is agreement of the importing country, food injurious to health or unsafe feed is not exported or re-exported.”*