Pfizer Submission

DG Enterprise and Industry 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

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Introduction

Pfizer welcomes the opportunity to participate in the consultation process which has been initiated by DG Enterprise and Industry. The risks posed to the safety of patients by the increasing entry of counterfeit medicines into the EU market is a matter of the gravest concern. It is essential that the scale of these risks is fully recognised by the regulatory authorities throughout the European Union and that the necessary legal and enforcement responses are put in place as speedily as possible. The priority given to this task by Vice-President Verheugen in his statement in the European Parliament on 15 January last is welcomed by all those who recognise the seriousness of the threat posed to the health and safety of Europe's citizens.

Before commenting on the specific proposals contained in the consultation document, a number of contextual points are relevant.

The Context

The trade in counterfeit medicines is highly profitable for those who engage in it. As noted by the WHO, major international criminal organisations have targeted this trade and have developed sophisticated methods of counterfeiting medicines and packaging, and routing counterfeit into the legitimate supply chain. It is particularly attractive since the profits to be gained are greater than those made from trade in illegal drugs, whereas the penalties are significantly less severe.

Their capacity to access the legitimate supply chain is facilitated by its complexity, lack of transparency and fragmentation. Whereas the supply chain historically involved relatively straight forward movement of product from manufacturer to wholesaler to pharmacist, today it is characterised by much greater diffusion involving many further intermediate traders, including brokers, agents, grey traders and re-packagers. The growth in the number of intermediate traders which has been evident during the past decade is a function of the growth in parallel trade in medicines in the internal market. This is evidenced, for example, by the fact that, **in respect of one Pfizer product alone,** the number of traders with parallel importing licences increased from 18 in 2000 to 76 in 2006. The number of parallel importing licences granted for this single product increased from 62 to 660 in the same period.

Pfizer has described the complexity of the contemporary supply chains, insofar as it can given its fragmentation and lack of transparency, in earlier submissions to the Commission. The reality is that manufacturers cannot keep track of their products when these are moved into the intermediate markets between manufacturers and pharmacists. The supply chains have become longer and there are many intermediaries who see medicines as simply another commodity to be bought, sold and moved on, often without their handling the product or knowing its pedigree. The ease with which operators can enter the market is a source of serious concern. As implicitly recognised in the consultation document, the supply chains, as these are structured and regulated at present, facilitate access of counterfeit medicines into the market.

The regulatory and enforcement capacity of the public authorities have not kept pace with this rapid evolution of complex trading patterns in medicines. It is to be hoped that the present consultation process and the proposals which emerge from it will not only address the non-transparent nature of a supply chain which facilitates the entry of counterfeit medicines, but will also address the difficulties in the supply chain which are associated with repackaging errors, batch re-calls and stock-outs which also pose risks to the safety of patients.

In essence, the medicines distribution channel between manufacturer and patient needs to be brought back to the point where it is shorter, rigorously controlled in terms of the entry and quality standards applied to intermediate traders and is transparent at each stage in the process.

It must be remembered also that the adoption of new regulatory requirements will be of little value unless these are enforced rigorously by the EMEA and the responsible Member States' agencies. The latter are frequently under-resourced to carry out present mandates and, in some cases, do not give sufficient priority to targeting those engaged in the counterfeit trade. For these reasons, the Commission must put in place an oversight system which seeks to ensure compliance by Member States with the terms of the measures proposed.

The Need for Accompanying Measures

While the present consultation is concerned with identifying measures which can be adopted to improve the regulation and safety of medicines in the supply chain, these should be accompanied by wider measures to address the risks posed by counterfeit medicines.

Pfizer has supported the adoption of the Commission's proposal for a Directive on criminal measures aimed at ensuring the enforcement of intellectual property rights. While it can be argued that the minimum penalties advocated in that proposal in respect of those dealing in counterfeit medicines are not commensurate with the risks posed to patients and health systems, the intention to establish a criminal offence with minimum harmonised penalties throughout the EU is to be welcomed. It must be hoped that the current difficulties in securing the adoption of the proposal are overcome so that the serious nature of this activity is recognised and addressed in the criminal law systems throughout the EU.

It is known that much of the counterfeit medicine which is found in the EU originates in third countries. Pfizer welcomes the initiatives of DG TAXUD, DG MARKT, DG TRADE and DG JSL in seeking the cooperation of the authorities of these countries in addressing the source of the problem more rigorously and systematically. The initiatives which DG TAXUD is taking to mobilise Member States' customs authorities to address the issue with greater priority are also to be welcomed.

The task facing us in Europe requires increased collaboration between relevant national, EU and international agencies. Pfizer welcomes the engagement of the Commission in the WHO's IMPACT project and welcomes the proposal by the Council of Europe's Ad Hoc Group on Counterfeit Medicines in its Model for a Network and Single Points of Contact (SPOCs) to combat counterfeiting of medicines and pharmaceutical crimes. The model proposes integrated national networks of personnel from the Drugs Regulatory, Customs, Police and Justice authorities and close collaboration between SPOCs within the EU and globally. The extent to which the proposed SPOC model can be quickly established within and between Member States should be examined in the present consultation process.

While the consultation does not address the issue of internet sales of counterfeit medicines, this is a growing and dangerous trade. Pfizer believes that further discussions on how this matter can best be addressed should take place as a matter of urgency.

Pfizer's Response to Specific Ideas for Change by Section

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

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

Key ideas for changes to EC legislation submitted for public consultation
a) Clarify that the obligations for wholesalers apply to all parties in the distribution chain, except for those directly distributing or administering to the patient. Brokers, traders, 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.

Pfizer's Response

Pfizer supports these proposals. As noted above, the supply chain at present is characterised by fragmentation, lack of transparency and, frequently, by the absence of adequate standards of care which are essential in the interest of patient safety. This is evidenced by the frequency with which re-packaging errors occur, the difficulties in implementing effective batch re-calls of product and, sometimes, shortages of medicines in particular markets as a consequence of their export by intermediate traders to other markets. The tightening of regulatory requirements, as the consultation document notes, can also make a real contribution to protecting against counterfeit medicines. Indeed, it is essential to this purpose.

Within the distribution chain, only those entities which hold a wholesaler authorisation should be permitted to **hold, distribute or trade** in medicines and we support the extension of the wholesaler authorisation requirements and accompanying obligations stemming from the pharmaceutical legislation to brokers, agents and traders. However, we have a more fundamental concern with the involvement of agents, brokers and traders in the medicines supply chain. If these entities do not actually handle product in the way that a normal wholesaler would, how can they comply with the various obligations in the legislation and GDP, and how in reality can they confirm that the product they are dealing in is genuine? In light of these concerns, we question whether these entities should have a role in the medicines supply chain at all, and ask the Commission to consider stricter regulation in this area.

All authorised wholesalers should be required to conform to GDP standards and these should be reviewed to include a requirement that a qualified pharmacist or other professional person with specified quality control qualifications is given clear and personal responsibility (consistent with the concept of a Qualified Person in the GMP and Pharmacovigilance context), with the owners/boards of the business, for ensuring that the standards required in respect of all medicines which they put into the distribution chain are met.

Clearly, the requirement of conformity with GDP standards must be backed up by regular, comprehensive and mandatory audits of such conformity on the part of all operators in the chain. Manufacturers do, and must continue to audit contract manufacturers. Member States' medicines regulatory authorities must be required to conduct regular audits, either directly or through qualified auditors reporting to them, of operations between suppliers. From present experience, it is clear that the adoption of standards in law will not achieve the safety purposes envisaged unless these are backed up by effective audits, enforcement and penalties for non-compliance.

NOTE: In idea (a) in the key ideas above, it is suggested that the obligations for wholesalers apply to all parties in the distribution chain, "***except for those directly distributing or administering to the patient".*** The intention behind the words in bold and italics is not clear and could be construed, for example, to apply to internet pharmacies. We presume this is not the intention in the present case, but believe the intention should be further clarified.

4.1.2. Tightening rules on inspections

Key ideas for changes to EC legislation submitted for public consultation

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

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

Pfizer's Response

The Medicines Regulatory Authorities or other Competent Authorities of the Member States must be given a clear legal responsibility to inspect the premises and quality standards applied by all operators trading in medicines in the distribution chain within specified timeframes. As noted, the adoption of a new regulatory framework will only prove effective to the extent that its terms are vigorously enforced by the responsible authorities. Manufacturers should be facilitated to collaborate closely with officials in ensuring that the latter are fully aware of the concerns and insights of manufacturers with regard to the safety of medicines within each jurisdiction.

The proposal to strengthen provisions for inspections and supervisions in third countries is necessary. The precise means by which optimum outcomes can be achieved need further elaboration.

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

Key ideas for changes to EC legislation submitted for public consultation

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

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

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

Pfizer's Response

Security features on medicines packs are essential to seeking to ensure the integrity of medicines supplied to patients. Various pack security features are used by manufacturers to achieve this objective. So far as medicines packs are concerned, the most effective solution we are aware of at this time is tamper evident packaging applied to the patient specific units by manufacturers at the point of manufacture. Tamper evident packaging will clearly show when a medicines pack has been tampered with and, therefore, should not be dispensed to or be accepted by patients. This should be the first essential stage of the regulatory requirements so far as packs are concerned.

If the use of tamper evident packaging by manufacturers is to be an effective security measure, it is obvious that medicines packs must not be opened at any point in the distribution chain, save by the end-user (hospital or healthcare professional or the patient). The current practice whereby intermediate traders open packs for re-packaging for other markets in course of parallel trade destroys any tamper evident packaging and frequently other security features applied to them by the manufacturer. Similarly, the current practice whereby packs may be over-stickered or over-boxed in course of parallel trade can cover over or obliterate security features placed on the packs by the manufacturer.

For these reasons it is necessary to provide that the original marketing authorisation holder (manufacturer and those parties providing services under their supervision) and the end-user only are permitted to open the tamper evident packaging and that the practice of re-packaging (including re-boxing, over-boxing and over-stickering) is prohibited.

NOTE: Pfizer assumes that the proposed curtailments on the opening and repackaging of medicines packs would not apply to Investigational Medicines Products (IMP) used in the course of clinical trials. Were the prohibition on repackaging to apply to IMP it would prevent the use of comparators in clinical trials since these must be opened and repackaged in order to "blind" them. It should be made clear that this is not the intention of the present proposals.

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

Key ideas for changes to EC legislation submitted for public consultation

Require the possibility of tracing ownership and transactions of a specific batch. This should be achieved by making a specific record (pedigree) obligatory. The record should be accessible by all actors in the distribution chain.

Pfizer's Response

Pfizer supports the adoption of batch tracking through the supply chain. This will allow for ease of reconciliation in case of product re-call, through a more focussed and therefore rapid response in identifying the current owners and dispensers of product.

The responsibility for ensuring batch traceability should be passed through the supply chain, rather than developing a complex system which allows all actors in the distribution chain to access to this information. Responsibility for batch tracking should, therefore, be a condition of wholesaler authorisation and a condition of each purchase of pharmaceutical products. Access to batch tracking data should be granted to all parties up-stream of a particular sale to facilitate reconciliation in the event of a recall.

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

Key ideas for changes to EC legislation submitted for public consultation

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

Pfizer's Response

Pfizer agrees that the modalities of any future pack serialisation and tracing system should be considered in subsequent implementing legislation. The application of tracing serialisation codes on packs can only be effective if tamper evident packs and a prohibition on re-packaging (including re-boxing, over-boxing and over-stickering) are already in place. These steps are the foundation stones of a system which seeks to guarantee the integrity of medicines reaching the patient. Without taking these steps to ensure that the original packs and seals are in place, it will not be possible to feel confidence in any serialised tracing system.

While these initial, essential steps are being implemented, and when the improvements in authorisation, auditing and inspection outlined in sections 4.1.1. and 4.1.2. are put in place, the scope and type of pack tracing technology which are necessary can be assessed. Should it be decided that a serialised tracing system is required to supplement these measures, then one which authenticates the product leaving the manufacturer with the product being dispensed to the end –user, and which includes batch as well as pack details, seems likely to be best suited to the purpose. Pfizer, therefore, supports EFPIA's initiative to pilot an optimal solution now as a safeguard, should it be needed, following the implementation of the measures at 4.1.1., 4.1.2. ,and 4.1.3.

4.1.6. Increasing transparency concerning authorised wholesalers through a Community database

Key ideas for changes to EC legislation submitted for public consultation
• Require GDP certificates to be issued after each inspection of a wholesaler.
• Establish a Community database of wholesalers (including distributing manufacturers) documenting GDP compliance. This could be achieved via extension of the EudraGMP database.

Pfizer's Response

Both these ideas should be implemented. As indicated in response to the ideas posed in section 4.1.2. , GDP inspections by Member States medicines regulatory agencies should be obligatory within specified timeframes. The proposal that the listing of authorised wholesalers and the most recent certificates of their GDP compliance should be included in the EUDRA database with the requisite security provisions, is an essential element to improving the transparency and safety of the supply chain.

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

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

• the obligatory importation authorisation under the conditions set out under Article 41 Directive 2001/83/EC, e.g. relating to premises and the qualified person;
• the relevant obligations for the importation authorisation holders set out under Articles 46 and 48 Directive 2001/83/EC, e.g. relating to staff and access for inspection;
• the obligations stemming from Article 51(1)(b) and (2) Directive 2001/83/EC, relating to qualitative and quantitative analysis of the imported medicinal product; and
• the relevant obligations stemming from Directive 2003/94/EC on good manufacturing practice.
The corresponding rules on inspections would apply.

Pfizer's Response

Pfizer's welcomes the objective behind this proposal. Counterfeit product has been found in imported product intended for re-export or in transit. In principle and in general, it is appropriate and necessary that such movements should be subject to the rules for imports of medicines into the EU.

However, such measures are not required in the case of manufacturing companies whose standards of compliance are known to the authorities. Pfizer imports products for re-export on an on-going basis through a controlled site. The application of the proposal, especially the need to perform qualitative and quantitative analysis in re-testing of the medicinal products, would impose additional costs for analysis and release requirements, higher inventory costs, additional storage capacity and additional staff. In addition, it should be borne in mind that the tests carried out for normal release of products on the market do not test for adulteration specifically. Testing for

counterfeit material usually goes beyond the normal testing for release through the use of special testing techniques developed for this purpose.

Given that Pfizer's import/export and transit operations are known to the authorities and meet the highest GMP and GDP standards, it is suggested that the company, and other manufacturers which may be in this position, be granted an exemption from the requirements suggested. This will permit customs and medicines regulatory agencies to focus on importers/exporters whose activities are not so transparent and well-documented and which require further investigation.

A differentiating process on these lines has recently been introduced in EU customs law. It permits the granting of the status of Authorised Economic Operators to reliable economic operators who meet certain criteria and who are to benefit from simplifications provided for under customs rules and/or facilitations with regard to customs controls. This approach addresses appropriate risk management criteria in use of customs controls. A similar approach seems apposite in the present case.

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

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

Key ideas for changes to EC legislation submitted for public consultation
Submit the manufacturing/import of active ingredients to a mandatory notification procedure.
• Render information on notified parties available in a Community database. This could be achieved via extension of the EudraGMP database

Pfizer's Response

Pfizer supports the proposal to require all manufacturers and importers of APIs to be part of a mandatory notification procedure. Such a procedure is already in place in some Member States, for example in France where notification of all national manufacturers of starting materials is a recent requirement.

We fully support the Commission's proposal to make this information on notified parties available on a Community database (EudraGMP). A mechanism to enable information on counterfeit to be shared between regulators and industry should be built into the system to enable all stakeholders to be proactive in removing counterfeit APIs from the supply chain.

4.3.2. Enhancing audit and enforceability of GMP

Key ideas for changes to EC legislation submitted for public consultation
• Make regular audits of active substance suppliers on GMP compliance by manufacturers and importers of medicinal products mandatory. Auditors should be sufficiently qualified.
• Require, where scientifically feasible, control of active substances via sufficiently discriminating analytical techniques, such as fingerprint technologies, Near Infrared Spectroscopy (NIR), as a mandatory method for identification by the manufacturer of the medicinal product. Such a testing is meant to identify deviations of the manufacturing process and manufacturing site for each batch.
• Turn principles of good manufacturing practice for active substances placed on the Community market into a legal act of Community law (e.g. a Commission Directive) in order to enhance enforceability.

Pfizer's Response

Pfizer supports the proposal to make regular audits of API suppliers (manufacturers and intermediaries) mandatory. API manufacturers should be audited on a routine basis established through risk assessment. Acceptance of third-party audits by qualified auditors is considered to be a satisfactory alternative, especially in the case of small annual quantity of API supply.

Pfizer believes that regulators should be more proactive in performing inspections of API suppliers based on risk-assessment techniques. These should include inspections of non-EU API manufacturers and should focus not just on GMP compliance, but also on auditing for counterfeit. In this regard, it should be noted that the focus of inspections carried out for GMP compliance is different to that carried out to detect counterfeit. Pfizer believes that full knowledge of the supply chain and associated security measures should not only be part of an inspection/audit scheme, but also be part of vendor evaluation.

With regard to the suggestion that the introduction of discriminating analytical techniques may be feasible and warranted, Pfizer would point out that that tests are only as good as the sampling technique used and the decisions made as to what to test for in each case. An additional layer of testing as proposed will not yield the safety benefits desired. These can only accrue from the imposition and enforcement of effective quality management and security systems and processes throughout the supply chain.

When an acceptable quality history has been demonstrated and where the supply chain is known, we recommend the option to sub-contract the full testing to the API manufacturer, with the exception of the identification of the API at receipt, and provided that contracts are in place which clearly define accountability, roles and responsibilities. This would avoid unnecessary duplication of testing controls, hence better use of resources and quicker access to medicines for patients.

GMP for APIs is currently established as Part II of the EU GMP Guidance which is given legal standing due to the reference to compliance with it in Directive 2001/83/EC (Art. 47). However the Commission's proposal for a directive may have more impact especially in third countries and would facilitate communication and enforceability. As highlighted earlier, the lack of enforcement resources is an underlying cause for the ineffectiveness of the current legislation. Those who counterfeit choose to ignore the law as they recognize the low probability of being caught. Any new legislation to counteract counterfeiting of API must therefore be fully enforced.

4.3.3. Enhancing GMP inspections

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

The competent authority shall carry out these inspections if there is suspected noncompliance 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.

Pfizer's Response

Pfizer fully supports the proposal for the carrying out of announced and unannounced inspections. We strongly recommend a harmonized approach in relation to the issuance of GMP certificates, as opposed to the present situation where Italy alone requires a GMP certificate to be issued by an EU Competent Authority (effective from 1 January 2009).

The logistics of how the inspection proposal will be rolled out in parallel to the current legislation will need to be considered. For example, India and China supply some 70%-80% of the off-patent APIs used in EU medicines. We believe that these suppliers should be inspected by an EU Competent Authority. As it would take some considerable time and a high level of resources to carry out the inspections, we advocate the use of quality risk assessment to prioritize inspections.

We agree that Competent Authorities must carry out inspections in cases of suspected non compliance with GMP and believe that inspections planning must follow a risk based approach (including frequency and repetition of inspections). Since non-compliance can normally only be discovered by inspections, we favour a significant increase in the number of inspections in third countries, especially unannounced inspections, to act as a deterrence to non-compliance. Given the size of this task, we support appropriate international coordination of third country inspections. These could be carried out in a jointly planned risk assessment basis by Competent Authorities of the EU and other states, such as the US, Canada, Australia and Switzerland, which currently inspect to EU standards.