CEFIC RESPONSE TO

THE EC PUBLIC CONSULTATION ON COUNTERFEIT MEDICINES FOR HUMAN USE

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

Dear Sir, Madam,

Please find hereunder the contribution to the European Commission's *"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"* (11 March 2008),

I have read this attachments sent me by our represented in APIC *(Active Pharmaceuticals Ingredients Committee)* / EFCG.

The Association CPA (Chemical Pharmaceuticals generic Association) is completely agree with what was said. In particular I would like to put attention on 4.3.3 and especially on the key ideas for changes to EC legislation where it is suggested inspections unannouced. I agree with what mentioned.

Moreover I hope that the inspections are conducted by Qualified Personnel belonging to a special section of the EMEA(Not to inspectors freelance / or consultants).
I also hope in the certainty of penalty should act in bad faith including extradition. (see FDA rules)

Best regards
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1. Introduction

APIC and EFCG have been active in the fight against API counterfeiting for many years through discussions with the authorities and stakeholders in the EU, USA and China. We have published widely on the subject via articles and conferences to help raise awareness of the issue.

We greatly value the opportunity to submit our response, as we consider this consultation to be an extremely important step in helping to prepare for the better protection of the health and safety of EU citizens and to sustain the competitiveness of EU manufacturers of active pharmaceutical ingredients (APIs) by removing illegal players from the medicines production chain. These reflect the Commission's objectives for pharmaceuticals in general.

While welcoming the prospect of new legislation, we believe current legislation, though imperfect, if properly enforced with severe penalties for offenders, would significantly reduce the escalating risk driven by globalisation and hyper-competition in off-patent medicines. This makes decisive action imperative and urgent as there is little or no deterrent to ensure at least a reasonable level of compliance with the laws governing the manufacture and use of APIs destined for the EU market.

Overall View of the Consultation Document

Our overall view of the consultation document is that while its overall intention is to be applauded, we consider it falls short of what is needed to combat the counterfeiting of APIs. For example, while we strongly support the para on page 4 that reads: *"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",* we see no evidence in the paper of how it will be transposed into a set of clear and effective measures.

While recognising that the consultation is wider than just APIs, our contribution will focus on the need for an improved, harmonised regulatory framework and enforcement actions to maximise the security of the global supply chain that begins with the manufacture of APIs destined for use in medicinal products sold in the EU.

In this respect, we would have preferred para 2 on page 1 of the Introduction to read: "The European Commission has launched a study to assess various policy options to prevent counterfeit medicinal products from entering the EU market". As written, it implies that the scope is restricted to counterfeiting that originates within the EU, which we assume is not what is intended.

We are concerned that the Impact Assessment is being done in parallel with the consultation process. We feel this is very unusual and, without further consultation, may lead to some discrepancies regarding the future development of a revised legal framework.

In this context, we consider that the definition of what constitutes a counterfeit API and a counterfeit medicine is of vital importance.

Definitions

Firstly, of all the term "Counterfeit APIs" needs to be defined. Secondly, it needs to be considered if the health issue for patients, which is the key aspect of this matter, is limited to these Counterfeit APIs or whether the problem related to APIs is broader than that.

In 2005 APIC has issued a definition of Counterfeit APIs, directly derived from EFPIA's definition of Counterfeit Medicines:

Counterfeit medicines are any brand (or generic) medicines and active pharmaceutical ingredients (APIs) that are deliberately and fraudulently mislabelled by unauthorised parties with respect to source and/or composition and/or therapeutic quality.
(EFPIA, June 2005)

The APIC definition of Counterfeit APIs:

Counterfeit APIs are active pharmaceutical ingredients for which source and / or quality are falsely represented on the label, on the Certificate of Analysis or otherwise.
(APIC, August 2005)

With as a very important, directly derived conclusion:

A medicine that contains a counterfeit API is a counterfeit medicine.

It is therefore quite worrying that one can e.g. regularly hear the presumption being made that in the EU not a single case of counterfeited off-patent medicinal products is known until now. When using the appropriate definitions this statement clearly loses its basis.

Moreover, it is important to point out that a class of APIs not covered by these definitions forms an equally dangerous one: the severely, deliberately (GMP- and/or Regulatory-) non-compliant APIs.

The new “umbrella” term “Rogue APIs” is proposed to cover both Counterfeit APIs and seriously, deliberately non-compliant APIs:

Rogue APIs are APIs that are counterfeit and/or severely, deliberately non-compliant.

The common denominator for the two sub-types of Rogue APIs lies in what is also the core of the entire issue, namely potential harm to patients caused by unsafe APIs:

- A medicinal product that contains a counterfeit API is a counterfeit medicinal product that may harm or even kill the patient.
- A medicinal product that contains a severely, deliberately non-compliant API is a severely non-compliant medicinal product that may harm or even kill the patient

Note that Counterfeit APIs are normally severely, deliberately non-compliant ones but severely, deliberately non-compliant APIs are not necessarily always counterfeits. This is why we need to take both API types into consideration.

What is yet lacking is a detailed definition of “severely, deliberately non-compliant APIs”. We think the key to this definition should lie in the word “deliberate”. In other words: This should apply when there is involvement of one or more parties that may be expected to be fully aware of EU GMP- and regulatory requirements, but who are yet knowingly bringing severely non-compliant APIs into the supply chain for the EU market.

A recent good example is contaminated heparin - a counterfeit, off-patent API manufactured in China. The FDA suspects that the heparin had been deliberately mixed with a lower cost, dangerous contaminant to save costs and raise prices at a time of shortage of raw heparin. Here human greed for financial gain outweighed any concern for human safety! The FDA has so far reported 62 heparin-related deaths in the USA since 2007, because of patients having been treated with this counterfeit API.

Non-compliance of an API with GMP does not make the medicine containing it a counterfeit. It just makes it non-compliant. However, a serious breakdown in regulatory compliance (e.g., a break in traceability, mis-labelling, any kind of fraud or fabrication in related documentation used in the buy/sell/registration operation) will make the API a counterfeit API. Counterfeit APIs are normally severely GMP non-compliant. It is imperative that the definition of a counterfeit medicine recognises that when a medicine contains a counterfeit API it is a counterfeit medicine.

Many counterfeit APIs originate from manufacturers in countries where the health authorities are presently working with much lower standards than those in the EU - notably China and India. The oversight by the local authorities of APIs exported to the EU from such countries is completely lacking, relying instead on the vigilance and ethics of the purchasing company. Therefore, the protection of EU citizens against counterfeit APIs must depend on adequate EU-based systems for oversight and enforcement of the law along the full extent of the global supply chain. Our experience tells us that the proposals set out in the consultation paper do not go far enough to protect EU citizens from exposure to counterfeit medicines. As such, we have made proposals to overcome these deficiencies. (See para 5 for a summary)

2. Counterfeiting of Medicinal Products – an Increasing Threat to Public Health & Safety

We agree with the Commission’s observations on the worrying trends of counterfeit medicines, and the factors that have facilitated the rise in counterfeiting, especially that the trend is not restricted to innovator products. For example, the off-patent gentamicin and the more recent, heparin case, both resulted in patient deaths.

The ‘blurred line between counterfeit and sub-standard APIs in medicinal products’ will disappear if the above definition of ‘Rogue APIs’ that we have proposed be accepted.

Regarding the cases of unilateral action by certain Member States (e.g., Italy), we understood that these have arisen to protect local patient health and safety and to reduce the impact of non-compliance on the local economy. They have also helped raise Commission awareness of the seriousness of the counterfeit problem.

We applaud the Commission's commitment to international cooperation. What is surely a global problem requires a global solution. This may take a long time to bear fruit. At present, there is an urgent need to regulate the activities of all operators along the distribution chain - to introduce clarity and certainty to the legal responsibilities of supply chain intermediaries, such as traders and brokers, as well as Qualified Persons.

3. Legislative Strategy and Impact Assessment

We are delighted to note and support the para on page 4 that reads: *"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."*

We wish again to stress the need to transpose this statement into a set of clear and effective measures both in the short term and within the legal proposal, including the provision of the necessary resources to implement and enforce the law.

We would also again like to mention our concerns that the Impact Assessment is being done in parallel with the consultation process. We feel this is very unusual and, without further consultation, may lead to some discrepancies regarding the future development of a revised legal framework.

4. Key Ideas for Better Protection of Patients against Counterfeit Medicines

We agree with your synopsis of the scope and the challenge and the 3 areas of regulation to be addressed. As we represent European manufacturers of APIs (and their intermediates), our response will focus on *4.3 "Tightening requirements for manufacture, placing on the market of active substances and inspections"*, but we will also comment on the other areas where the impact of APIs in relevant.

We have been advocating for many years for the need for better enforcement of existing regulations covering APIs, wherever in the world they are manufactured and that are destined for use in medicinal products in the EU.

The referenced Written Declaration of 4 September 2006 was actively supported by APIC and EFCG. That this has now been recognised by the Commission as an indicator of the need for improved legislation to cover the earlier stages of the medicines' production chain is indeed gratifying.

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

We fully support the proposed key idea (4.3.1, page 12) for changes to EC legislation that would require all manufacturers and importers of APIs to be part of a mandatory notification procedure and for the information on notified parties to be available on a Community database (EudraGMP). However, such framework should be designed in such a way that it cannot be used in a fraudulent manner.

4.3.2 Enhancing Audit and Enforceability of GMP

We are surprised to note the first bullet point in the key ideas box on page 13, making regular audits of API suppliers (manufacturers and intermediaries) mandatory, as we believe them to be already mandatory.

Both the authorities and the industry should have adequate testing methodologies in place designed to detect Rogue APIs.

It is essential to ensure the provision of sufficient resources for the effective supervision and enforcement of all existing and new legislation. The lack of such resources is an underlying cause for the ineffectiveness of current legislation. Those who counterfeit choose to ignore the law as they recognise the low probability of being caught. Any new legislation to combat counterfeiting must, therefore, be fully enforced.

The provisions of existing laws are often not observed by all EU manufacturers and importers of medicinal products, e.g., mandatory audits of API suppliers for GMP compliance.

4.3.3 Enhancing GMP Inspections

As India and China are supplying around 70 - 80% of the off-patent APIs used in EU medicines, we have long-argued for an increase in the number of official inspections of manufacturers of APIs in such high risk countries.
The risk of non-GMP compliance in India and China is high due to the prevalence of lower GMP standards and the existence of numerous API manufacturers in those countries who are hardly or not complying with any GMP and registration principles. There are strong indications that many of such highly non-compliant manufacturers are presently supplying the EU market, mainly through traders and brokers, while not being inspected.

This has not only put the health and safety of EU citizens at more risk, but it has created a non-level playing field for EU API manufacturers. As a result, this has reduced their competitiveness and innovation capacity, and it has led to a loss of jobs and the closure of many efficient EU plants with much better HS and E profiles than the less regulated majority of API plants in India and China.

We, therefore, fully support the case for a significant increase of the number of GMP inspections in third countries in order to minimise the risk of non-GMP compliant APIs entering the EU either directly or in medicinal products. The law already provides for such inspections, but the lack of resources and the inclination of the EU authorities to inspect based on geographical proximity rather than risk to the patient, works against effective enforcement. As such, we propose that the priorities for inspection by the authorities should all be subject to the same risk-based priority setting procedures, in collaboration with other overseas inspectorates who already inspect to EU standards, such as the USA, Canada, Australia and Switzerland, to avoid duplication and to share resources.

We reject the principle that inspections should be carried out only if a suspicion of non-compliance exists. Non-compliance can normally only be discovered by audits and inspections, and we favour a significant increase in the number of inspections in third countries, especially unannounced inspections to act as a deterrent for non-compliance. The cost of inspections should not be an issue as the manufacturer or supplier should pay for them if they wish to secure the approvals needed to continue in business.

While cooperation with the authorities in third countries is desirable, we believe it is far too early to negotiate bilateral agreements with higher risk countries, such as India and China.

5. Summary of APIC /EFCG Priorities for Legislation and Enforcement to Protect EU Patients against Counterfeit APIs

Cefic have provided a number of documents to the Commission over the recent past advocating the improvements we believe would help reduce the risk to patients from exposure to counterfeit medicines containing sub-standard, counterfeit APIs.

There follows a summary of the highest priority improvements that we propose be considered as part of the legal proposal for APIs under heading ***4.3 "Tightening requirements for manufacture, placing on the market of active substances and inspections"***

1. Mandatory GMP Certification of APIs

Only APIs covered by a GMP Certificate issued by a EU competent authority following a successful inspection should be allowed for use in the manufacture of medicinal products destined for the EU market. Such GMP Certificates should be included in the corresponding Marketing Authorisation Applications and, for importation into the EU, should be part of the documentation to be checked by EU Customs. These and other proposed requirements should also cover APIs imported into the EU as part of a medicinal product.

2. Prioritising Worldwide Inspections of API manufacturers & middlemen based on risk

Worldwide API inspections by European competent authorities should be prioritised through a risk-based system taking into account the geographical location as an important criterion for determining risk. In addition, the involvement of middlemen (brokers, traders, distributors etc) should be a key criterion for assuming increased risk. Involved middlemen should all be subject to inspections with the very highest priority.

3. Creation of a central EU unit to coordinate all worldwide inspections

The proper training and management of EU inspectors to deliver the proposed risk-based approach, would benefit from the creation of a central EU management unit - a function that could well be added to the EMEA structure - which could also coordinate all API inspections to be undertaken worldwide to ensure an efficient and effective use of resources.

All EU API inspection outcomes, whether positive or negative, should be made available - preferably in detail - to the public, through the EudraGMP Database on the EMEA Website.

4. Making the detection of fraud and counterfeiting top priority during inspections

API re-inspections should take place on a regular basis (every 2-3 years). The possibilities of fraud and counterfeiting should be the focus of the API inspectional approach. The second EFCG / Aschimfarma letter to Mr. Behrndt details how these aspects might best be dealt with during the various types of inspections. EU inspections at manufacturers of APIs, medicines, and at traders and brokers, should be trained to look for possible API fraud by focusing on a company's purchasing and sales functions.

5. Eliminating inspection resource issues via a fees-based approach and MRAs

Any problems relating to insufficient resources for worldwide API inspections should be resolved through inspection fees to be charged to the to be inspected companies.

Mutual Recognition Agreements (MRA's) and information exchange with major, reputable authorities from other countries should cater for resource as well as knowledge sharing. Presently, we would advise very strongly against MRA's with high-risk API manufacturing countries such as China and India, as we believe that, despite their announcement to the contrary, the authorities there still have a long way to go before an adequate level of trust is generated.

EU inspectorates should exchange information with countries with extensive knowledge of companies involved in fraudulent practices, e.g. NAFDAC / Nigeria.

6. Mandatory methods of API identification along the supply chain

Both the authorities and the industry should have adequate analytical testing methodology in place designed to detect counterfeit APIs.

7. Provision of an IT system to help Customs to stop importation of counterfeit APIs

A system should be implemented that will allow EU customs to prevent identified counterfeit APIs entering the EU. The system should help prevent entry into the EU market of all APIs

originating from specific manufacturers and middlemen who have a proven record of being involved in counterfeit API business.

8. Introduction of tough sanctions and penalties for counterfeiters

Strong publicised measures, sanctions and penalties should be introduced against all parties that are involved in deliberate API fraud and/or deliberate, severe API non-compliance.

9. Introduction of a licensing system for middlemen, such as traders, brokers

Legislation should be enacted to enable the licensing of API supply chain middlemen (such as traders, brokers, importers and distributors) that operate in the supply chain between the producers of the full enforcement of the law.

10. Clarify the legal liability of Qualified Persons

As to the liability of the Qualified Persons we would recommend that the EU would carefully assess how this is legally arranged in Switzerland.

Conclusion

In order to combat the provision of counterfeit medicines for human use, Cefic welcomes the opportunity to respond to this consultation process and asks that Commission and the Member States seriously consider the implementation of the above short term and longer term proposals.

The food and agriculture sector has shown how the application of harmonized legislation has had positive influence for the health of the EU citizen. We ask that the same enthusiasm and rules be implemented in the API and medicines sector.

END