FEDERCHIMICA
ASCHIMFARMA
Associazione nazionale produttori principi attivi e intermedi per l'industria farmaceutica

EFCG
EUROPEAN FINE CHEMICALS GROUP

Enterprise and Industry
European Commission
200, Rue de la Loi
B-1049 Brussels
Belgium

16th January 2008

For the attention of: Mr. Nils Behrndt
Member of Cabinet of VP Verheugen

Dear Mr. Behrndt,

With reference to the meeting at your office on 6th December, and to our subsequent letter to you dated 17th December 2007, as agreed, we enclose an Annex containing our additional proposals regarding the forthcoming report on "Supply Chain", and some additional considerations related to counterfeiting.

As agreed, we have divided our proposals into two categories:

1. Those that, in our opinion, do not require changes to the legislation but that would significantly improve the compliance situation for APIs in the shorter term, through a catalytic effect to be brought about by DG Enterprise & Industry.
2. Those that will require new legislation or changes to the existing legislation.

As mentioned in our previous letter, we are extremely concerned about the large quantities of mostly uncontrolled APIs that are entering the EU as such and -increasingly- also included in imported finished medicinal products, mostly through rogue players involved in API manufacture and trading. This is probably causing extensive damage to the health of patients in a way that is difficult to measure and is very likely to result in a future human health tragedy if not counteracted soon.

We see the almost complete lack of enforcement in the API area and the resulting lack of deterrence against such practices as the major cause for this serious problem.

In the attached Annexes we have provided our views and recommendations. We feel they provide the proper guidance for the immediate actions and legislative actions that are needed to address the concerns that the "*Written Declaration of the European Parliament on active pharmaceutical ingredients no. 61*" raised.

Our concern is the reduction of risk in medicines and the safety of the patient. The mentioned proposals, in our opinion, are the right combination of solutions that will assure the safety of drugs. We wish underline that the competent authorities must apply these measures as soon as possible. The food and agriculture sector provide recent successful examples where 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 active pharmaceutical sector. All the involved organizations, which took part to the meeting on December 6th 2007 by Enterprise and Industry of European Commission (i.e. Cefic, EFCG, Aschimfarma), are eager to collaborate with the Cabinet Verheugen. At our meeting we provided you with a number of comments that we feel provide the adequate background to our position.

We also believe that the EU Parliament took a leadership position at a global level when last year it passed a Written Declaration demanding greater transparency in medicines. It is becoming increasingly clear that the representatives of the citizens of Europe and of the USA are feeling that the truth about the origin of the medicines they are being prescribed is being hidden from them in an unacceptable way.

We remain available for any further clarification your may find appropriate.

Yours sincerely,

Guy Villax
Board Member
EFCG

Dr. Gian Mario Baccalini
President
Aschimfarma

- Annexes: 2

Annex I to
Letter to Enterprise and Industry
From Aschimfarma/EFCG
16th January 2008

Measures to consider regarding the Supply Chain

1. Short Term

- Enterprise & Industry should actively encourage the EU Member States to execute a significant number of API inspections per annum outside the EU territory. Currently, API inspection activities outside the EU - except those regarding products authorised through the Centralised Procedure and excluding the limited number of inspections performed by the EDQM - are completely restricted to the inspectorates of France and Italy. We recommend assigning a target to each of the other 25 Member States that will be in the same range as what France and Italy are each reaching per annum: ca. 20 inspections outside EU territory.

- Inspections at manufacturers of medicinal product, at traders and brokers and at API manufacturers should include a focus on possible API fraud. This implies that inspections should include focus on the purchasing and selling functions of the respective companies (See for detailed recommendations Annex II).

- Enterprise & Industry to promote an approach that will include inspection fees, to be charged to the to be inspected companies. This will resolve any issue on how such inspections should be funded.

- The EU should actively support and aim for extension of the recently initiated OMCL / EDQM analytical programme on sampling and analytical testing (authentication / fingerprinting) of APIs with emphasis on materials that have or may have entered the EU via middlemen (traders / brokers) where possible.

- Strong, publicised, deterrent sanctions should be taken against companies that are involved in deliberate API fraud and/or deliberate, severe API non-compliance. Marketing Authorisations, CEPs etc. should be suspended / withdrawn, rapid alerts should be issued and recalls should be initiated. A procedure that includes the above actions for the follow-up on CEP suspensions and withdrawals should, after having been subject to several years of delay, now be adopted and executed as soon as possible.

- EU inspectorates should include within their working terrain the major API Trade Fairs such as CPhI. Such fairs are well known to include numerous API manufacturers and middlemen and are a rich source for the detection of serious non-compliant situations.

- EU inspectorates should actively pursue information exchange with health authorities of countries where extensive knowledge on companies involved in fraudulent pharmaceutical practices is available, e.g. NAFDAC / Nigeria.

- The EU should exchange as much information as possible with reputed, trustworthy health authorities around the world - such as the US/FDA and Swissmedic/Switzerland - and should together with those authorities, pursue a coordinated, risk-based global approach for API inspections and their priorities.

- All 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.

2. Longer term

Having regards to:

"Written Declaration of the European Parliament on active pharmaceutical ingredients no. 61" dated November 30, 2006.

On November 30, 2006, the European Parliament, in plenary session, approved with 378 favourable votes the "*Written Declaration of the European Parliament on active pharmaceutical ingredients*" submitted by MEP Amelia Sartori and supported by all political groups, as well as by the Parliamentary Committee of Environment and Public Health.

With the approval of this Written Declaration, the European Parliament addresses to the Council of the European Union, the European Commission and the parliaments of the Member States, pressing for 1) *the submission, both by producers and importers of active ingredients, of a "Certificate of good manufacturing practice" delivered by the European Authorities following mandatory inspections at sites of production* and proposing 2) *to introduce the traceability of the active ingredient, with indication of its origin (ex., Country, Company, site of production), to discourage the relabelling or the repackaging of non-EU product, for better defence of public health.*

and to:

Respect of GMP for API quality and safety of medicines

To clearly understand the importance of the non-respect of GMP rules, it must be taken into consideration that all scientific studies carried out during recent years on the problems concerning safety of medicines for human use have concluded that the problems related to the quality of medicines, namely the active ingredients contained in them, are a source of risk for human health. The aim of mandatory inspections requested for by the European Parliament for the assessment of the actual compliance with GMP by companies producing API, EU or non-EU, is to ensure consumers of all Member States that each single active ingredient used in the composition of medicines produced and/or marketed within the EU is safe for human health whether made within the EU or imported.

The following changes to community legislation need to be considered:

1. ***Proposal for the modification of the community legislation concerning pharmaceutical products – mandatory inspections at EU and non-EU API sites of production.***

It is necessary to provide for an urgent modification to Community legislation on pharmaceutical products so that it provides for mandatory inspections for the assessment of

the GMP observance, both at the sites of production whether within EU or abroad. The net effect of such legislation is to make sure that only APIs for which a GMP Certificate has been issued by the EU, or by one of its Member States, will be allowed for use in the manufacture of medicinal products for the EU market. Such GMP Certificates should be included in the Marketing Authorisation Applications for the corresponding medicinal products.

In addition, the legislation should also contemplate that all API manufacturers should have reasonable access to inspection by EU authorities, upon their own request. Industry has made it clear that it would welcome user fees, provided they were equally applicable inside and outside the EU and would reflect the inspection costs.

2. ***Providing a legislative framework for a central EU body, such as the EMEA, to assume more than a simple coordination role, that makes them responsible for the management and implementation of the non-EU inspections programme to assure both the regulatory and GMP compliance of non-EU based producers of APIs and medicines. New legislation should also mandate the central EU body to act on behalf of the Member States in entering into agreements and relationships in activities related to anti-counterfeiting and to regulatory and GMP compliance of the production of medicines and active pharmaceutical ingredients, allowing it to recognize activities performed by like-minded and equally competent authorities from other states***

Currently there is no clear mandate on who is responsible to address the non-EU production sites. This results in either duplication of effort and/or absence of enforcement. It should be made clear that production sites located in Member States are the responsibility of the local competent authority. Responsibility for enforcement outside the EU should be handled centrally.

The EU should create a foreign inspection unit that will plan and execute a EU foreign API and medicines inspection programme that will include periodic re-inspection at a frequency that will ensure adequate oversight over GMP compliance as well as over compliance with submitted information in relation to the Marketing Application. For this purpose, an inspection frequency of once per 3 years would be appropriate.

This body would also be mandated to be the forum to promote active cooperation, exchange of information and collaboration of inspection activities with foreign medicines agencies that share in the same standards and objectives. This collaboration should be able to reduce duplication of inspections to deliver more effective deterrence results from fewer resources.
It should be noted that the most recent evidence shows that globalisation has made current enforcement practices obsolete. We cannot allow rogue players in the supply chain to find safe havens by just crossing the "state-line".

3. ***Providing a regulatory requirement that would provide patients with transparency on the origin of their medicines – in a way not inferior to what is provided today with textiles, toys or food products***

The labelling of all medicinal products should include details of the origin of the API it contains (manufacturer, production site and country of manufacture).

In the food sector, a rigorous, scrupulous and harmonised regulatory system is in force, which has imposed substantial systematic medical controls on the goods imported from non-EU Countries. It would seem logical to expect standards in APIs and medicines to be no lower. As globalisation intensifies, and undifferentiated generics become prevalent, the patient will not allow that information be hidden. Today our textiles, our toys and our food products all have a label that states clearly which country they come from.

4. ***Legislation should create systems to facilitate cooperation between the Member States' Customs Services and Medicines' Agencies so that only approved sources of medicines and APIs are allowed as imports into the EU***

Product labelled from non-compliant sources should be prevented from entering the EU. Procedures should be put in place at the EU borders to verify whether incoming API and/or medicine is compliant with EU laws and is authorized for use within the EU market. As similar systems are in place in the USA, it is recommended that the EU study the US/FDA and US Customs systems before designing and implementing a similar or preferably a better EU system. Such systems will need to include a unique coding system for identification of the API, medicine and its manufacturer (name, site location, country, packaging) both on the

label and in accompanying documentation – that need to be matched to a database that customs can consult if entry into the EU is to be allowed.

5. **Legislation that addresses traders and brokers that set themselves up between the producers of the APIs and the users of APIs**

The trading and brokering of APIs should be governed by a suitable licensing system. Deliberate actions that aim to reduce traceability, to misrepresent GMP or regulatory compliance, or businesses that have non-compliance at the centre of their business strategy should be classified as a category of counterfeit crimes.

6. **Legislation governing medicines approved based on an abbreviated process centered around "bioequivalence" testing should be requested to repeat such bioequivalence testing at regular intervals**

It is well known that accumulated changes of manufacturing site, or source of active ingredient, or batch size, may result in sufficient aggregate change to cause a medicine's formulation over time no longer to provide a bioequivalent profile.

Regular re-checks on bioequivalence of marketed medicinal products should be made mandatory and may also be made part of authority testing programmes of marketed medicinal products. The use of non-compliant APIs may seriously affect bioequivalence.

7. ***Legislation regarding the personal liability of the Qualified Person should be reviewed***

The regulations need to reinforce the role of the Qualified Person and need to formalize the QP's personal legal liability. Is it reasonable that the personal liability of a Qualified Person be substantially less than that of a Certified Accountant that signs off the audit of financial statements?

Annex II to
Letter to Enterprise and Industry
From Aschimfarma/EFCG
16th January 2008

Recommendations on inspectional approaches to uncover fraudulent API practices, aspects or Counterfeiting in API field.

What should inspectors do to uncover API counterfeiting practices?

API counterfeiting can occur at different entities in the supply chain:

- The (supposed) API manufacturer
- The exporting company / trader
- The importing company / trader
- Other API distributing / trading companies
- The dosage form manufacturer

Since the official documentation trail accompanying the supply chain in most cases deliberately conceals counterfeiting, inspections based on official documentation only (such as Marketing Applications, Drug master Files, CEPs, Certificates of Analysis and even Production Records) will usually fail to uncover API counterfeiting.

Taking API samples from the market and using appropriate analytical techniques for comparing these with authentic samples from the approved API manufacturer can be an important tool in identifying counterfeiting activities. The recently started cooperation between the OMCL network, EDQM and member companies of APIC (The Active Pharmaceutical Ingredients Committee of Cefic) will probably make the job of detecting counterfeit APIs much easier for the authorities because within this joint industry / authorities programme the latter obtain practical analytical methods for rapid API authentication from the original manufacturer. However, to turn this new programme into a success and to have it cover a significant part of all APIs on the European market will take at least several more years.

What inspectors can do today is to include a strong focus on possible counterfeiting and fraud within their inspectional approach. Each of the situations represented by the above five bullet points needs to be carefully evaluated in order to define the actions that would be needed to detect counterfeiting:
Some recommended actions during inspection for uncovering API counterfeiting in each of these situations are, for example:

(Supposed) API manufacturer

- Checking if this manufacturer secretly sources all or part of the API material elsewhere
- Scrutinizing purchasing records on externally sourced APIs
- Checking if API material with labels from producers not included in official documentation is present in the warehouses
- Checking reconciliation between volume of API produced vs. volume of API sold
- Analytical authentication / fingerprinting of API samples taken
- Obtaining a list of shipped batches, dates and clients (and end users if known) and then keep the data to cross-check during inspection of an API user's plant

Exporting trader

- Checking if the label of the original manufacturer has been replaced by a label from a different manufacturer
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- Scrutinizing purchasing records on externally sourced APIs and reconciliation between volume of API purchased from one company vs. volume of API sold as originating from that same company
- Checking if API material with labels from producers not included in official documentation is present in the warehouses
- Scrutinizing the entire labels production, -management and -reconciliation system for irregularities
- Analytical authentication / fingerprinting of API samples taken
- Detecting equipment that may be used for removing labels (e.g. a burner)

Importing trader

- Checking if after importation the label of the original manufacturer is replaced by a label from a different manufacturer
- Scrutinizing purchasing records on externally sourced APIs and reconciliation between volume of API purchased from one company vs. volume of API sold as originating from that same company
- Checking if API material with labels from producers not included in official documentation is present in warehouses
- Scrutinize the entire labels production, management and reconciliation system for irregularities
- Analytical authentication / fingerprinting of API samples taken
- Using data on the origin of the material to be obtained from customs to compare with data about the origin that is on file at the importing trader
- Detecting equipment that may be used for removing labels (e.g. a burner)

Other API distributing / trading companies

- Checking if after arrival in the warehouse the label of the original manufacturer is replaced by a label from a different manufacturer
- Scrutinizing purchasing records on externally sourced APIs and reconciliation between volume of API purchased from one company vs. volume of API sold as originating from that same company
- Checking if API material with labels from producers not included in official documentation is present in warehouses
- Scrutinize the entire labels production, management and reconciliation system for irregularities
- Analytical authentication / fingerprinting of API samples taken
- Detecting equipment that may be used for removing labels (e.g. a burner)

Dosage form manufacturer

- Checking if fraudulent actions with documentation take place aimed at hiding the true origin of the material
- Scrutinizing purchasing records on sourced APIs and reconciliation between volume of API purchased from one company vs. volume of API originating from that same company that is actually used in production of the dosage form
- Checking if API material with labels from producers not included in official documentation is present in warehouses
- Analytical authentication / fingerprinting of API samples taken vs. authentic samples of the approved API manufacturer
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- Obtain information from the approved API manufacturer(s) on the volume sold annually to the involved dosage form manufacturer and compare with the volume of API used annually in production of the dosage form.
- Verify that the batch numbers, dates, quantities of API from producer X that have been used match the data that were collected during the inspection of API producer X

Clearly, the inspectional approaches, when including a strong focus on possible API counterfeiting and fraud will differ quite strongly, from what is usual in a regular GMP inspection.

Counterfeiting in the pharmaceutical sector.

Damages deriving from the counterfeiting phenomenon in the pharmaceutical field are very high, since they affect the most important value for human beings: health.
The University of Würzburg in Germany has published, on assignment by the German Ministry for Health, a study which collects interesting and, at the same time, alarming data on the phenomenon of the marketing in the Common Market of counterfeited active ingredients in the years 2002-2003. In fact, in this study it results that most of the active ingredients circulating in the EU market comes from India and China, countries where between 10,000 and 15,000 API manufacturers are concentrated, and that approx. 33% of the active ingredients imported in the Common Market from non-member Countries are counterfeited API.

Recently some dangerous situations for the health of the EU citizen were published:

- On October 2nd-4th, 2007 during CPhI, the most important worldwide exhibition for APIs, many Chinese companies were accused by American Authorities for: patent violations, shipping counterfeit drugs. This situation was reported in an Article of the New York Times (dated October 31st, 2007) entitled "*Chemicals flow unchecked from China to drug market". I extract these words: "Pharmaceutical ingredients exported from China are often made by chemical companies that neither certified nor inspected by regulatory Authorities*".

- the Warning Letter (dated October 31st, 2007) issued by the US FDA to the Chinese company "Northeast General Pharmaceutical" for some products for which the mentioned company had two approved CEPs issued by EDQM.

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