



'The Future of Pharmaceuticals for Human Use in Europe'
Cefic Input to the Consultation Process: Deadline for Submission 12/10/2007
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CEFIC is the organisation that represents national federations, companies and more than 100 affiliated associations and sector groups located in Europe. APIC and EFCG are two sectoral groups within CEFIC comprising producers of active pharmaceutical ingredients (API's), intermediates and pharmaceutical excipients from EU factories to worldwide customers in innovator, generic and OTC pharmaceutical companies. It provides a forum on scientific, technological, regulatory and trade related issues in the area of active pharmaceutical ingredients, and organizes an effective flow of information among the members, drawing upon their expertise.

The pharmaceutical supply chain starts with the GMP intermediates that are subsequently converted into Active Pharmaceutical Ingredients (APIs) before being formulated together with excipients to become medicinal products.

API manufacture is today almost as strictly regulated as the manufacture of medicinal products while also an increase in strictness of regulation covering excipients manufacture is currently under consideration. A large proportion of the pharmaceutical regulation in place does not take into account the existence of a separate highly regulated API industry. This means that compliance with API regulations and procedures is proving difficult and unworkable at times.

APIs and excipients are integral parts of the R&D phase and of production processes of medicinal products. However, today many APIs and excipients are manufactured by dedicated, specialised companies who serve as suppliers to manufacturers of medicinal products.

Q1. Do you agree with the analysis of the main challenges outlined above? Do you see other challenges?

AI. While the main challenges outlined in the Commission's 19th July 2007 brief are broadly correct, over the past 20-30 years there have been huge changes in the market due to globalisation and the internationalisation of the supply chain.

During this time, the volume and type of EU legislation, regulations and guidelines applying to the manufacturers of APIs and intermediates have increased dramatically. Today the API industry is being regulated to a level similar to the downstream pharmaceutical industry that manufactures final medicinal products.

Because the EU regulatory framework is now out of date, the authorities cannot adequately deal with the effects of these changes on the EU API industry. The regulators are struggling to cope but the system is obstructing their efforts. This situation has increased the risk of non-compliance remaining undetected in the API manufacturing and

supply chain, leading to detrimental effects on the health of EU citizens and on the competitiveness of the EU API industry. The Commission's review of 'The Future of Pharmaceuticals for Human Use in Europe' is therefore most welcome.

An understanding of the major market changes over the last 20-30 years shows that other, new challenges do exist and need attention, viz.,

- The break-up of the innovator-dominated, pharmaceutical value chain
- The rapid growth in the off-patent (generics) market driven by the demand for lower health care costs by national health service providers serving an ageing EU population during a period of relatively low economic growth
- Companies that neither produce the formulated medicines nor make the API now supply the majority of generic medicines.
- Patent legislation differences, globalization of know-how and free trade has led to the emergence of the production of off-patent APIs in the low cost economies, especially in Asia, where regulations and GMP requirements are still very limited as compared to EU legal requirements.
- Higher operating costs in GMP-compliant API manufacture in Europe, coupled with a dramatic increase in additional, industry-related EU regulations, has made Europe, once the cradle of the pharmaceutical industry, increasingly uncompetitive to produce off-patent APIs. This is causing EU off-patent API manufacturers to be pushed out of their home market by competition from Asia.
- EU law now requires a Qualified Person employed by a pharmaceutical company to assure the quality and compliance of APIs used in every batch of its medicines before sale. This requires back-up documentation and audit activities proving that the regulations governing its production have been met in full, including the use of GMP-compliant APIs.

The consequences of all the above-mentioned changes are undermining the quality and safety of medicines in Europe, are creating a non-level playing field for EU API manufacturers by lowering their ability to compete, are acting as a barrier to innovation to improve competitiveness and are detrimental to improving protection of both the environment and the safety of workers in API factories.

These changes are, therefore, working strongly against the Commission achieving its two key objectives (which Cefic strongly supports), viz., to better protect the health of EU citizens and to strengthen the competitiveness of European companies.

The EU regulatory framework, which affects the full length of the supply chain - from intermediates, to APIs to formulated medicines - has not kept pace with these dramatic changes in the marketplace. Much of the EU pharmaceutical regulation now in place essentially ignores the existence of the separate, but now highly regulated, upstream API industry. As a result, compliance with API regulations and procedures are proving disproportionately difficult if not unworkable at times. This must be corrected as the consequences are having a detrimental effect on EU manufacturers of APIs and intermediates and on the health of its citizens.

The lack of effective oversight, inspection and law enforcement by the authorities has encouraged non-compliant, illegal trade, especially involving the importation of APIs into the EU - mainly from Asia - via certain brokers and traders. This is due not only to their

ability to offer lower prices from a lower, non-compliant cost base, but also the opportunity to import sub-standard (counterfeit) APIs with a low chance of being caught.

Failure by the authorities to reverse this trend will encourage more of the EU-based players in the pharmaceutical supply chain to move to non-EU countries, taking with them many skilled jobs, sources of income and taxes and opportunities for investment.

Q2. Do you see other areas than those already targeted by the Commission where regulatory action should be taken?

Q3. What would you suggest as concrete measures to ensure the safety of medicines supplied in the EU, addressing in particular counterfeit medicines, and provision of high quality and affordable medicines also to 3rd countries?

Q4. What can be done to improve Europe's international competitiveness?

A2, A3, A4. Cefic feels that the EU competent authorities need to accept the existence of a new world order affecting the manufacture and supply of medicines in the EU and that they should therefore create a tailored regulatory framework for the full length of the pharmaceuticals supply chain, including APIs and their intermediates suitable for the 21st Century.

As a transitory step, the EU authorities must provide sufficient regulatory resources to effectively enforce the present regulations in the short term, and to fully enforce a new, integrated regulatory framework in the medium to long term.

The new regulatory framework must enable the delivery of a more effective and efficient public service than exists at present and be driven by the need to meet the Commission's twin objectives of (1) better protection of the health of EU citizens and (2) strengthen the competitiveness of EU companies by removing regulatory and non-regulatory barriers, which stifle innovation and impede access to foreign markets.

Unless these actions are taken, the EU-compliant, API manufacturing industry of the pharmaceutical cluster will be forced to exit serving the off-patent (generics) industry, and will focus on only serving the US market and the global Innovators.

During the transition step and to help deal with the design a new framework, Cefic recommends the following actions be considered:

1. Variations Regulations

The EU Variations Regulations are causing serious problems for the dedicated API industry.

Current regulation requires most changes to API manufacture to be separately assessed by the authorities for each resulting medicinal product. At best, when just a few parties are involved, this introduces delays and costs into the process. But one change in an API operation may often trigger the need for in total up to many hundreds of Variations to be submitted by the pharmaceutical companies for all their various MAAs. Clearly, such situations are unworkable. Ethical API companies will decide not to implement the change, whereas those with lower ethical standards will probably make the change without notifying customers or authorities.

The challenge is to define a new regulatory approach for APIs to both foster innovation in API manufacture and to maintain or improve the safety of medicines. We see 3 options:

1. The separate authorisation of APIs. This would solve all procedural problems.
2. A shift from inspection of post-approval documents to on-site inspections. If both customer and supplier apply modern quality management systems, the management of change will be secure. In “API to multi-customer” situations, this shift implies change management at multiple interfaces - a difficult task but feasible and more workable compared to oversight based on a full assessment of regulatory submissions.
3. Introduction of the concept of ‘Quality by Design’ to the pharmaceutical manufacturing and legislation process based on the principles of enhanced process understanding and strict process control. These principles have been accepted into policy by the FDA and EMEA but are not yet adequately translated into practice at the approval level for new product registrations never mind Variations.

We believe that all these approaches would deter those who might be tempted to choose not to notify any changes in API manufacture and, therefore, should improve the safety of EU medicines.

The current rigor of control in *Variations* is grossly ineffective as there is seldom any check by EU inspectors that GMP operations are also regulatory compliant, and that what is carried out in the factory truly reflects the information on file that led to approval. Compliant firms are again disadvantaged compared to those who do not respect change control requirements.

2. Inspection and Enforcement

Cefic believes that the present strict API regulatory framework requires a robust system of inspection and enforcement with tangible sanctions (to act as an effective deterrent) for those companies that are out of compliance. The cost of compliance was recently estimated by respected market analysts as being in the region of 25% of site operating costs. The juxtaposition of these costs with the competitive advantage of non-compliance (facilitated by the lack of adequate inspections) leads to the only logical conclusion that inspection should be (as with final medicinal products) an integral part of the API regulatory process.

The continuing lack of adequate levels of inspection and enforcement will increase the risk of sub-standard (counterfeit) APIs entering the EU market from less ethical producers who, by avoiding these costs, enable unethical traders and brokers to supply APIs to pharmaceutical producers based at a much lower price than compliant producers. Not only should the new regulatory framework allow for the public punishment of those companies for whom non-compliance is at the heart of their business strategy, but also it should reward compliant firms with mechanisms for less intervention and faster approvals. Indeed, we recommend that inspection and enforcement of API laws should be performed along similar lines as for final medicines.

Cefic strongly recommends the following actions to improve the oversight and enforcement of the regulations for APIs:

- increasing inspection resources and enforcement sanctions
- increased publicity of deterrents by the authorities
- creation of a central foreign inspection service for API producers to plan and coordinate non-EU inspections to ensure GMP and regulatory compliance by all non-EU producers that wish to export to the EU, and to uncover criminal activities such as fraud, counterfeits and deliberate non-compliance.

- creation of a publicly available database of the results of inspections disclosing compliant and non-compliant producers
- creation of a supervised EU licensing system for brokers, traders and distributors
- creation of an API producers registration and identification system for use by EU Customs
- the personal legal liability of Qualified Persons to become law.

To help deal with the growing counterfeit problem, consideration should be given to the setting up a 'Global Regulatory Council' of the major nations (USA/FDA, EU/EMA, China/SFDA, India/?, Japan/?, Australia/? etc) to agree how to work together to minimise illegal behaviour in the production and supply of all medicines worldwide, and to ensure alignment and cooperation in the fight against deliberate non-compliance and counterfeiting. As an interim measure, and to save EU resources, Cefic proposes a provisional approval for those non-EU API manufacturers who have FDA and perhaps other mutually-recognised approval.

3. Excipients

With the implementation of the Directive 2001/83/EC amended by Directive 2004/27/EC, it is now mandatory that all APIs and in due course a set of 'Certain Excipients' (yet to be defined) used in pharmaceutical manufacturing must be GMP-compliant. However, it should be taken into account that a combination of excipients normally contributes by far the largest weight and volume to a medicinal product.

Cefic believes that the manufacture of excipients is not sufficiently regulated and controlled as it should be to protect the health of EU citizens. The European Pharmacopoeia (EP) defines the excipients specification and the required analytical methods to assure their quality. However, in many cases, only very limited data on impurities is available due to the variety of production processes being used. Consequently, drug quality and drug safety are not sufficiently assured. Based on their limited regulation and the lack of legal enforceability even with today's low standards, these chemicals pose a potential risk to the quality of medicines. Cefic, therefore, recommends that for common excipients – by far the large majority – are subject to the GMP requirements of the amended General Chapter <1078> of the US Pharmacopoeia (USP) with ISO certification, and that for the remaining very small group of Special and Novel excipients (including the yet-to-be-defined 'Certain Excipients') are covered by the GMP requirements of Directive 2001/83/EC amended by Directive 2004/27/EC.

Q5. What can be done to foster convergence and transparency as regards pricing and reimbursement in the EU?

No response

Q6. Do you think the current regulatory framework can accommodate emerging technologies like regenerative and personalised medicine, as well as nanobiotechnology?

No response