

Enforcing the Quality of Medicines in a New World Order

The European Union (EU) and the United States of America (US) have rules in place to ensure the Active Pharmaceutical Ingredients (APIs) used to make medicines meet current Good Manufacturing Practices (cGMPs). Compliance with cGMPs is what ensures that each pill and medicated syrup we consume, each injection given to us, and each IV administered to us has the same identity and strength and the same quality and purity characteristics as the product approved by the Health Authorities in the EU Member States and in the US.

However, not everyone is playing according to the rules, and the European and American public are being put at risk in two critical areas: patient safety and regional/national security. This is a consequence of the huge changes in the pharmaceuticals market over the past 20-30 years, due to globalisation and the internationalisation of the supply chain.

We face a new world order

An analysis of the major market changes over the last 20-30 years shows:

- The break-up of the innovator-dominated, pharmaceutical value chain
- The rapid growth in the off-patent (generics and over the counter (OTC)) 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 that now fill 60%¹ of the prescriptions in the USA.
- 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.
- Today around 80% of the volume of APIs that are used to make medicines found in EU and US pharmacies come from abroad.^{2,3} A large and increasing proportion now comes from countries in Asia, up from close to zero 20 years ago.⁴
- 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 the centre of gravity 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.

¹ David B. Snow Jr., Maximizing generic utilisation: The power of pharmacy benefit management. *Journal of Generic Medicines*, page 28, October 2007.

² Presentation by Jurgen Hoose, Authority for Science and Health, Hamburg, to the 7th APIC/CEFIC European Conference on APIs, Lisbon 20-22 October 2004.

³ EMEA has stated ...approximately 80% of active substances used in the manufacture of medicinal products within the EEA are manufactured outside of the EEA... in Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials (page 60/101 of Compilation of Community procedures on inspections and exchange of information. <http://www.emea.eu.int/Inspections/docs/335103en.doc>

⁴ See “The World API’s market” publication by Dr. Giuseppe Tamburini, Milan, July 2005.

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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.

API manufacture is today almost as strictly regulated as the manufacture of medicinal products. 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. Today, dedicated, specialised companies all over the world who serve as suppliers to manufacturers of medicinal products manufacture many APIs.

Applying cGMPs in an industrial setting is complex and expensive. It requires depth and breadth of knowledge and training, plus a great deal of discipline and time. Not meeting cGMPs enables savings that have been estimated at 25% of operating costs (excluding raw materials).⁵ Compared to EU domestic facilities, uneven enforcement in foreign facilities means these sites can offer lower cost APIs with only a ‘voluntary’ regard for expensive cGMPs. Paying only cursory attention to cGMPs also allows for greater operational flexibility and faster product development which is decisive factor in the generics business where the first approval takes all the profits and remains with an enduring market share.⁶

The vast majority of medicines are no longer produced by the large multinationals; rather they are products whose patents have expired (generics) and medicines not requiring prescriptions (over the counter drugs or OTCs) that are supplied by a multitude of companies that very often do not make their own APIs but instead buy them from another company – who may just be a middleman.⁷

To illustrate the rapidly changing market, the number of ANDAs (Abbreviated New Drug Application) filed with the FDA in 2005 and 2006 is two and a half times greater than it was from 1994-2004 – and in last 18 months there were 36 new firms applying for ANDAs for the first time ever.⁸

Globalisation has caused unprecedented pressure on prices and profit margins and has driven these generic and OTC companies to buy their APIs at the lowest cost from plants that have never been inspected by any health authority from the EU or the US. In 2005, China alone – including European owned sites there – exported 39,700 metric tonnes of paracetamol; a 21% increase over 2004 and enough to produce billions of tablets.⁹

Globalisation has resulted in more complex supply chains, which increase the potential for contamination, mislabelling, or substitution of one substance for another, all of which increases the risk

⁵ ‘Managing the Cost of Compliance in Pharmaceutical Operations’; Frances Bruttin & Dr. Doug Dean / IBM Business Consulting Services, April 2004.

⁶ “...in the US Hovione and its customers also lost millions of dollars in sales because Opos-supplied generic firms got their approvals first. “ January/February 2005 Speciality Chemicals Magazine, page 4, Viewpoint – A Level Playing Field, Guy Villax, CEO of Hovione, calls on the European authorities to inspect API producers abroad.

⁷ Former FDA Commissioner, Dr. Mark McClellan, a strong advocate for generic drugs, in remarks before the First International Colloquium on Generic Medicine on September 25, 2003, said, “Generic drugs now account for the majority of prescriptions in the U.S., and the U.S. has some of the lowest-priced, safe generic drugs available anywhere in the world.” He went on to say, “As nations are working hard to find ways to tighten price regulations and shift costs elsewhere, we run a serious risk if product developers don’t think they can get a fair payment when they succeed. They will stop trying. They’ll turn to products where the prices aren’t regulated, like erectile dysfunction drugs and other lifestyle drugs.”

⁸ Tommy Erdei, UBS, strategic considerations within the API sector, presented at APIs Europe 2007, Stresa – Aschimfarma and CPA.

⁹ Reference: “Chinese Paracetamol Export Business Analysis in 2005” by Chinese Medical Export/Import Association, No. 2006-1.

to patients.¹⁰ Profit pressures in the generic and OTC medicines businesses pit quality assurance departments against the purchasing departments in the same company in an uneven fight. In absence of a referee, there is a predictable winner; the least scrupulous operator.

Because the EU regulatory framework is now out of date, the authorities cannot adequately deal with the effects of these changes in 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 API manufacturing and in the pharmaceuticals' supply chain, leading to detrimental effects on the health of EU citizens and on the competitiveness of the EU API industry.

The little evidence that we have shows overwhelmingly that the EU system is broken and that using short cuts has become a profitable business practice. All the 20 CEPs (Certificates of Suitability, the EU alternatives to DMFs for compendial APIs) hitherto suspended and withdrawn by EDQM were related to producers located in Asia, and about half of them were filings held in the name of “middlemen”, i.e. filings not held by the API producer itself. Non-compliant producers were only identified when inspections were performed and too few inspections are performed in the region that seems to have more problems. It is interesting to note that EU inspectors have looked at API plants that produce the very products that FDA does not include in its enforcement roster (the older OTC drugs) and interestingly it has suspended CEPs for such drugs making them barred from Europe but nothing stops them from becoming a US medicine.

Consequences of the new world order

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 working strongly against the European Commission achieving its two key objectives -to better protect the health of EU citizens and to strengthen the competitiveness of European companies- that EFCG strongly supports.

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.

Customers in the EU (and the US) may benefit from global competition in terms of cost of medicines but maintaining a minimum level of industrial capacity in key areas is essential to regional and national security. Pharmaceutical production capacity is a key issue from a security standpoint and we urge that

¹⁰ DeSorbo, MA. Balancing Act. Pharmaceutical Formulation and Quality. 8(2) 2006: 22-24.

steps be taken to stem the loss of domestic API manufacturing facilities. Requiring that foreign facilities meet the same quality standards as EU (and US) plants will not, in and of itself, assure that regional and national security is maintained. However, rigorous enforcement of the same standards across all pharmaceutical production venues will at least slow the departure to areas where a lack of enforcement results in lower costs of doing business and a higher risk to the health and safety of EU (and US) citizens.

EFCG feels that the EU competent authorities need to accept the existence of a new world order affecting the global pharmaceutical cluster 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.

Proposals for the transition step

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, EFCG has recommended to the European Commission that actions be taken to improve the Variation Regulations and the levels and focus of inspection and enforcement of the laws governing cGMPs.

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. However, 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 Marketing Authorisation Applications. 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. EFCG sees 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.

Inspection and Enforcement

EFCG 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. Respected market analysts recently estimated the cost of compliance as being in the region of 25% of site operating costs¹¹ (excluding raw materials). 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.

EFCG believes that the FDA has led the world in developing cGMPs that assure the quality of APIs. It is because of the FDA's enforcement activities that Europe was able to progress up the learning curve and become not only the home to the largest number of compliant API producers, but also the major contributor to the body of knowledge on cGMPs and compliant manufacture of APIs.

Many EU-based API manufacturers have been inspected by the US FDA and in some EU Member States, also by their own national authorities. However, in many other parts of the world where API inspection and enforcement have been largely absent, there is no incentive for manufacturers to incur significant extra costs necessary to meet cGMPs. The problem seems even more serious than 'mere' non-compliance with GMP. It appears that even companies in China and India that have been blacklisted by Nigeria's health authorities NAFDAC¹² because of their proven, deep involvement in exporting counterfeit medicines to that country, are still freely exporting APIs to the EU. Thus, the health of EU citizens is put at risk from sub-standard medicines. EFCG has noted that the FDA had issued Warning Letters to some of the leading firms in China.¹³ Is this the tip of the iceberg? Are fast growth and compliance difficult to reconcile? Whatever the answer, increased patient risk should never be a consequence of financial success.

Unlike in the FDA, the EU authorities are unable to say exactly how many factories supply the APIs used to make its medicines. The European Directorate arranges most of the API inspections performed by EU officials abroad for the Quality of Medicines (EDQM).¹⁴ In the 7 years that their inspection scheme has been in operation, around 80 API manufacturing sites were inspected with about half in India and China. These inspections yielded 20 suspensions of the Certificates of Suitability (CEP) from 13 different holders that had been issued by the EDQM. All 20 suspended CEPs covered API

¹¹ 'Managing the Cost of Compliance in Pharmaceutical Operations'; Frances Bruttin & Dr. Doug Dean / IBM Business Consulting Services, April 2004.

¹² See <http://www.nafdacnigeria.org/blacklisted.html>.

¹³ See warning letters addressed to Wockhardt (February 21) and Ranbaxy (June 15) - CDER's 2006 warning letters under at <http://www.accessdata.fda.gov/scripts/wlcfm/indexissuuer.cfm>.

¹⁴ The European Directorate for the Quality of Medicines (EDQM) is an institution of the Council of Europe. No other European Institution has done as much as the EDQM to start enforcing GMPs also at Asian producers of APIs.

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manufacture in China or India. Those CEPs had been relied upon by the Medicines Agencies across the EU to approve medicines for sale,¹⁵ but when they were suspended because of serious non-compliance no action was taken by the competent authorities – the EU medicines Agencies have no agreed procedure on how to act on such notification of suspensions.¹⁶ None of the EDQM inspections performed in Europe led to a single CEP suspension.

At the last count, the EU probably performed more than 30 inspections outside the EU in the last 12 months. The FDA performs about 200 foreign inspections per year to API producers and maybe 10% are in Asia. As an illustration of the 2 countries that are doing their best to correct the lack of proportionality in the geography of inspections versus location of API production – note:

- The Italian health agency has currently 139 API producers GMP approved. It performed 86 inspections between February 2006 and September 2007. The agency has indicated that on average, it performs 48 inspections in Italy and 6 abroad – and it has issued 5 GMP certificates to API plants outside of the EU.
- The French Medicines’ Agency performed a total of 77 inspections (in France: 8 distributors, 46 producers of which 1 covered excipients and the others APIs) – and abroad it performed 23 inspections (of which 9 with EDQM, 4 with the WHO and 4 with the EMEA).¹⁷

The continuing lack of adequate levels of inspection and enforcement will increase the risk of sub-standard (counterfeit) APIs entering the EU (and US) 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.

In an attempt to strengthen the rules affecting cGMP compliance for APIs, a majority of the Members of the European Parliament (MEPs) signed a Written Declaration¹⁸ in November 2006 that informed the Council of Ministers, the EU Commission and the Member State Parliaments of the benefits to the EU citizens if (1) producers and importers of APIs to the EU were required to submit a certificate of GMP delivered by the EU authorities following mandatory inspection of the production site irrespective of its worldwide location, and (2) to introduce traceability of the API’s country of origin via appropriate labelling of the final medicine in order to discourage re-labelling or repackaging of non-EC products in the interest of public health. The European Commission has informed the MEPs that it does not intend taken any action, instead waiting for the effect of recent regulatory changes to the law on GMP compliance for APIs to have sufficient elapsed time to allow for a proper assessment.

¹⁵ Presentation by Head of EDQM Certification Unit (Corinne Pouget) at the EFCG conference, Barcelona 26- 27th April 2006, see www.efcg.cefic.org. EDQM has issued over 2000 Certificates of Suitability (CEPs), but has inspected no more than 80 producers.

¹⁶ EFCG’s “Conclusions” on the Barcelona Conference, 27th – 28th April 2006, <http://efcg.cefic.org>.

¹⁷ Presentation by Lionel Viornery, AFSSAPS France, 2nd EFCG Conference, 24-25 May 2007, Berlin and Ana Rosa Marza, AIFA, “La Sicurezza del Fármaco nello scenario Europeo” APIs Europe 2007, Stresa, Aschimfarma and CPA.

¹⁸ European Parliament Written Declaration on pharmaceutical active principles No 0061/2006; DC\627587EN.doc

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As recently as October 2007, EFCG has strongly recommended to the European Commission¹⁹ 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, counterfeiting 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, EFCG has also recommended to the European Commission that consideration be given to the setting up of a ‘Global Regulatory Council’ of the major nations 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. Perhaps such a body could be built either on the Pharmaceutical Inspections Cooperation Scheme and/or the WHO’s recently announced procedure for assessing the acceptability, in principle, of APIs for use in pharmaceutical products.

As an interim measure, and to save EU resources, EFCG proposed a Mutual Recognition approach to provisional approval for those non-EU API manufacturers who have FDA and perhaps other mutually recognised approvals.

Conclusions

The United States Pharmacopeia²⁰, the PIC-S (Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme)²¹ - which FDA has recently applied to join- and the World Health Organization all have started to face the inevitable: the imperative need to make sure non-compliant APIs are prevented from reaching the market. The need to establish some kind of inspection-based verification of compliance in API plants is now on everyone’s ‘To Do List’.

In a globalized world, in an industry with very international supply chains, unscrupulous players cannot be allowed to take advantage of uncoordinated jurisdictions that enables them to always find a safe haven by crossing the “state line”. This new world order cannot be regulated by 20th Century structures and resources; the answer can only lie in global cooperation of all enforcement agencies.

Organisation

EFCG²² represents the interests of over 100 fine chemical manufacturers who have plants, primarily located in Europe, but also in Asia and North America, producing APIs, intermediates and

¹⁹ EFCG submission in response to the European Commission’s consultation on ‘The Future of Pharmaceuticals for Human Use in Europe’ October 2007 see http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2007/2007_07/consultationpaper-2007-07-19.pdf and <http://www.efcg.cefic.org/publications/items/2007-08.html>

²⁰ United States Pharmacopeia (USP) Verification Program for pharmaceutical Ingredients - see <http://www.usp.org/USPVerified/pharmaceuticalIngredients/>

²¹ Pharmaceutical Inspection Cooperation Scheme (PIC/S) – see <http://www.picscheme.org/index.php>

²² The European Fine Chemicals Group, a sector group of CEFIC – see www.efcg.cefic.org

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pharmaceutical excipients serving worldwide customers in innovator, generic and OTC pharmaceutical companies. Western Europe produces over \$12 billion of APIs.²³ A typical turnover for a member company is less than \$200 million pa.

EFCG represents an industry that has supplied APIs to the USA for the past 40 years.

EFCG is a sector group within CEFIC – The European Chemical Industry Council - the international organisation that represents national federations, companies and more than 100 affiliated associations and sector groups located in Europe. With the help of CEFIC, EFCG - together with its sister organisation – the Active Pharmaceutical Ingredients Committee (APIC) - 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.

²³ See “The World API’s market” publication by Dr. Giuseppe Tamburini, Milan, July 2005.