# Global API Sourcing: What Is Next for Suppliers to the European Union?

**Guy Villax and Chris Oldenhof**

**The authors discuss the preparedness of European regulatory authorities to implement and enforce the recent EU Directives 2004/27 and 2004/28, which require that all medicines marketed in the EU be made with active pharmaceutical ingredients (APIs) that comply with the harmonized GMP standard ICH/Q7A.**

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The Pharmaceuticals Business Committee (PBC) of the European Fine Chemicals Group (EFCG, Brussels, Belgium, www.efcg.cefic.org) brought together more than 120 delegates from the pharmaceutical industry supply chain and senior regulators from the European Commission (Brussels, Belgium, http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm), the European Medicines Agency (EMEA, London, http://www.emea.eu.int/), the European Directorate for the Quality of Medicines (EDQM, Strasbourg, France, http://wwwpheur.org), and the national health authorities of Spain, France, and Germany in Barcelona on April 27–28, 2006, to discuss the implementation and enforcement of the new European Union (EU) Directives 2004/27 and 2004/28 (amending EU Directives 2001/83 and 2001/82, respectively) designed to improve the safety of human and veterinary medicines. The deadline for the transposition of the directives into national law by the EU member states was Oct. 30, 2005.

The new laws require producers of medicinal products for the EU market to only

The European Fine Chemicals Group released the findings of a benchmarking questionnaire sent to 25 national health authorities in the European Union to measure their preparedness to implement and enforce EU Directives 2004/27 and 2004/28.

use APIs that comply with modern standards of "current" good manufacturing practice (CGMP) in order to deliver safer medicines to European citizens and animals. It is expected the greatest impact on the burgeoning global market will be on older, off-patent medicines that are increasingly used in Europe.

## New directives seeks to address changing supply chains for APIs

The new EU Directives are significant in that they address the changes that the global API market has undergone over the past 20 years. Roughly 80% of the total volume of APIs in EU medicines now originate in plants in China and India, and with a few exceptions, EU health authorities have never inspected these plants. The new EU Directives seeks to address that discrepancy by requiring every API producer, wherever located, be audited by those who use such APIs to supply medicines to the European market, namely the Manufacturing- or Import Authorization Holders to ensure compliance with the required GMP standard (ICH/Q7A). The authorities may in addition perform worldwide inspections of API manufacturers triggered either by suspicion of noncompliance or by a request from the API manufacturer.

The new laws result from Directives of March 2004 that had set a deadline of Oct. 30, 2005 for transposition into national law, and as of April 2006, less than half the member states had done so. This may be due to the complexity of the issues as well as to the hard work taking place behind the scenes to ensure the harmonization of the implementation process in Europe.

## Regulators offer updates on national and EU programs

Maria del Val Diez Rodrigalvarez, head of the Spanish Medicines Agency (www.agemed.es), who welcomed delegates to the EFCG conference, indicated that in Spain, inspection activities had grown by 37% over the last year, and that by next year (2007), the number of Spanish inspectors will double.

Emer Cooke, head of the inspections sector for the EMEA, clarified to the EFCG conference the expectations of inspectors regarding APIs when inspecting dosage-form manufacturers and API manufacturers, respectively. At the former, the focus will be very much on the audit program and audit outcomes of the involved API manufacturers and, if applicable, API traders, brokers and distributors. Audit reports should be available and accessible to the inspector. If middlemen are involved, full traceability to the API manufacturer is required, and contracts, referred to as "quality agreements" must be established between the producer of the API and the user of API so as to address all aspects of GMP compliance. Adherence to change control and submission of Variations also will be a point of attention.

Inspections of API manufacturers will normally concentrate on compliance with Part II of the EU Compliance Guide (ICH/Q7A) but, depending on how the inspection was triggered, may include in-depth coverage of compliance with submitted information, as in the drug master file (DMF), the certificate of suitability (CEP) dossier or the Marketing Application. Inspection outcomes will be posted in the upcoming EudraGMP Database to be launched in the second half of 2006. Limited public access to the database is still under consideration as is access by Mutual Recognition Agreement partners.

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New applications, renewals, and Variations for a Marketing Application will have to include a statement on API GMP compliance by the Qualified Person (QP) of the holder of the Manufacturing Authorization.

Third-party audits are acceptable provided that these are: (a) arranged by the Manufacturing Authorization Holder; (b) have contractual arrangements in place that define the responsibilities of the auditor, the purpose and scope of the audit and that the standard(s) against which the facility(ies) is (are) audited is defined and acceptable; and (c) are performed by an auditor that the Manufacturing Authorization Holder is satisfied with and who is competent and free of any conflict of interest. The inspectors expect to see such evidence in the files of the Manufacturing Authorization Holder.

Jean-Denis Mallet, head of inspections at the French Health Authorities (Agence Française de Sécurité Sanitaire des Produits de Santé, AFSSAPS, http://afssaps.sante.fr/) elaborated upon how the new API requirement impacted on the responsibilities of the Manufacturing Authorization Holder's QP. He explained that the principles of these responsibilities were already mostly covered by the original Directive 2001/83, but will now include more specifics on API Q7A compliance aspects.

Throughout the conference, regulators were keen to emphasize that the primary role of the watchdog over the quality of the API used in medicines is the QP of the Manufacturing Authorization Holder. The EU legal framework that assures the quality of medicines is centered around the QP, and it is for this reason that the regulators expect that every Manufacturing Authorization Holder has in its files evidence, gathered during an audit, that all of its API suppliers comply with GMPs. At the EFCG conference, the audience was repeatedly informed that the regulators do not see it as their obligation to verify through an inspection that all sources of API that are filed in the marketing application comply with GMP laws, a position that is at odds with practice in the United States.

## Audits

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of making audits by the Manufacturing Authorization Holders compulsory, instead of demanding that GMP inspections by the authorities be mandatory rather than optional. Regulators reminded industry that both sides have different responsibilities and that these need to be fulfilled. For example, having a GMP certificate cannot allow Manufacturing Authorization Holders to abdicate their obligation to gather additional information to satisfy that an API comes from a GMP-compliant source.

Another key issue raised by regulators at the conference related to the agreements that need to be put in place (quality agreements and contracts with third-party auditors), and how these contracts may need to stand up in court so that responsibility is attributed.

EFCG's conference chairman Guy Villax expressed the EU API industry's skepticism that all QPs could without exception be consistently relied upon to be independent referees in the decision-making process on APIs. Indeed, without an effective deterrent, the profit motive may, in those market segments where competition is very tough and a few euros price difference per kilogram of API is important, lead some to the use of lower cost, substandard APIs or to use APIs where GMP compliance is falsely evidenced by fraudulent practices.

## EFCG urges focus to Asia from Europe

The EU fine chemicals industry is concerned that there will be no level playing field until EU regulators refocus their API inspection efforts away from Europe, where fewer and fewer APIs are sourced and where GMP compliance is high, to Asia where GMP compliance is much less common but where 80% of the APIs for European medicines are sourced. This misdirected focus fails to deter non-GMP compliance and by extension, increases the risk to patients in Europe.

This is particularly important given the rise of the off-patent (generics) market in Europe. This segment of the pharmaceutical industry is growing at twice the speed of that of innovator drugs. In number of prescriptions, generics are already more than 50% of world pharmaceutical consumption. If over-the-counter (OTC) products are included, the percentage is much higher. This is a business characterized by intense competition and profound globalization. In addition, there is a trend for reimbursement mechanisms to use reference prices, so competitive pressure will push for the lowest cost API. In the absence of a referee, there is a predictable winner every time: the least scrupulous operator. There is currently no effective standardization of API producers across the globe as to what is an adequate level of GMP compliance in API manufacture. Therefore, without inspections, there is no mechanism to ensure a level playing field. Compliance with GMP is an investment in patient safety. Avoiding this investment offers financial competitive advantages

that may be decisive in market segments in which there are many different Marketing Authorization Holders for one product and in which competition is therefore tough. Such pressures are likely to be generating unacceptable levels of patient risk that could and should be avoided through enforcement.

### Issues of liabilities

An interesting perspective on the liabilities of manufacturers of dosage forms and APIs, respectively, and more in particular those of the QP, was presented at the EFCG conference by Horst Hasskarl, a German lawyer specializing in pharmaceutical law. Many in the pharmaceutical industry assume that the QP is personally liable for compliance matters relating to the released material and that the QP can face imprisonment and large fines. Hasskarl's analysis of the applicable laws showed that such personal liability is a myth: it will normally always be the company employing the QP that will be liable. This is an important clarification in view of the key role of the QP in the EU's legal concept of securing GMP compliance of the API.

The EFCG conference chairman Guy Villax remarked that accounting auditors, responsible for certifying financial statements, are personally financially liable for their work and opinions and that fraudulent practices lead to criminal proceedings. In light of Hasskarl's comments, the EU Commission's strategy for quality of medicines seems flawed as no such magnitude of liability rests on the shoulders of the QP. It is surprising to note that the person that is central to verifying the quality of medicines that are critical to the health of patients is under less obligations than those that sign off annual reports destined to healthy shareholders.

**The primary watchdog over the quality of the API used in medicines is the Qualified Person of the Manufacturing Authorization Holder.**

### EDQM outlines compliance issues

Corinne Pouget, head of the certification unit of the European Directorate for the Quality of Medicines (EDQM), offered the conference an overview of EDQM's experiences with roughly seven years of worldwide API inspections regarding compliance with GMP (ICH/Q7A or otherwise) and compliance with information submitted in CEP dossiers.

EDQM has granted more than 2,000 CEPs since 1994. In 1999, it initiated an inspection program under which 80 inspections have now been carried out, with about 50% of these in Europe and 50% in China and India. The outcomes of these inspections give reason for concern.

Only in very serious cases of noncompliance does EDQM suspend a CEP, explained Pouget. As of April 2006, 12 CEPs from 10 different CEP holders have been suspended. No details are known on whether the involved manufacturers had declared Q7A as their API GMP standard or any lower standard (which was still an option until re-

cently). One of these suspended CEPs has recently been restored after the manufacturer had completed the required corrective actions. These suspensions show a remarkably distinct geographic pattern: All suspended CEPs covered API manufacturing operations located in China and India. No CEPs related to API manufacture in Europe have been suspended. About half of the holders of the suspended CEPs were the Chinese and Indian API manufacturers, the other half were traders, brokers, or agents in the EU. In addition, the granting of "sterile grade" has twice been refused, once to a manufacturer in China and once to a manufacturer in India.

As was emphasized by a question from the audience at the EFCG conference, the suspension of a CEP suggests a possibility that an unsafe API has been used in Europe. EDQM grants a CEP as a result of a mere paper review. There is normally no preapproval inspection of the API manufacturer. As EDQM had been concerned for some time that the files submitted for inspection might not reflect reality, it began inspections for health and safety reasons even though it had no mandate to do so. As its selection process of who to inspect was "suspicion based," the high frequency of inspections in China and India with suspension outcomes (25%) cannot be directly extrapolated to the complete Asian API producer population. Nevertheless, the EU is still largely focusing its scarce enforcement resources on Europe instead of on the area that is, on average, more likely to be in noncompliance, namely India and China.

It was also emphasized that many APIs manufactured in Asia do not have a CEP, relying instead on European drug master files. As European inspectorates have never inspected these Asian API facilities, it is completely unknown if they comply with GMP at all.

**The EU fine chemicals industry is concerned that there will be no level playing field until EU regulators refocus their API inspection efforts away from Europe to Asia.**

The current trend that the major and ever increasing portion of APIs in medicines comes from India and China, where the incidence of inspections is lowest, leads to the conclusion that the average level of enforcement regarding the quality and safety of medicines on the EU market is decreasing. The quality of medicines may therefore be increasingly at risk with noncompliance unlikely to be identified.

### Evaluating noncompliance

More significantly when a CEP is suspended as a result of an inspection finding of serious noncompliance, such suspensions do not trigger any systematic action by the competent authorities in Europe. It appears that the EU has no transparent system for tackling this problem. EDQM does not know in

which member states and for which marketing applications any particular CEP has been cross-referenced. The competent authorities in each member state have no system to check what CEP suspensions impact on which marketing applications. So when such a CEP is suspended, there is no agreed course of action across Europe. This is a critical issue to be discussed with the European Commission, the Council of Europe, and the competent authorities via the Heads of Agencies. By issuing a CEP, EDQM indicates that a submitted dossier evidences a quality of API that is appropriate for a marketing application to be issued. Logic would suggest that the suspension of the same CEP by EDQM would require the sale of medicines containing an API from the same source to be suspended and/or recalled. The current situation of "no-action" by the regulators in the member states questions the credibility of EDQM—a situation that should not be allowed to continue.

The same question raised further issues, specifically "how can the importation into the EU of such unsafe APIs or final medicinal products containing these APIs, for which the CEP has been withdrawn, be stopped if part of these imports are not covered by CEPs but instead by drug master files?" The question remains unanswered.

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Another troubling aspect of the situation is the inflow of non-Q7A-compliant, and therefore unsafe APIs, which may have been legal before the Oct. 30, 2005 implementation date of the new EU directive, depending on the nature of the noncompliance. The new laws make compliance with ICH/Q7A now mandatory. This raises the question of whether the QPs that before Oct. 30, 2005 consented to certain practices have now changed their approach. This situation adds a further question mark to the crucial role the QPs are playing in the newly implemented legal structure on APIs in the EU.

### The role of traders in the API equation

The key benefits of a GMP-compliant trader were highlighted by trader Karl Metzger, quality and regulatory affairs manager of Welding GmbH & Co. (Hamburg, Germany, www.welding.de). Modern GMPs as enshrined in the new laws rely on transparency and traceability. The supply chain of APIs has had traditionally a strong involvement of traders, brokers, and agents whose key competitive attribute was to match users of APIs with producers of APIs, but typically striving to hide one from the other to remain in control of the business. Indeed, were traders to operate transparently, and not be able to provide other value-added services, they would quickly lose the business as producer and user would often choose to deal directly. Such is the extent of the traditional role of the trader as the old EU laws frequently referred to the "supplier" and almost never to the "manufacturer." Inspectors at

the conference repeatedly said that it was vital that the manufacturing authorization holder should know well the manufacturers of the APIs it formulates into medicines.

### Key concerns of regulators and the regulated

The recent EFCG conference also was useful in highlighting several key points to clarify and discuss the detail and consequences of the new EU directives. Key points that evolved included:

- Depending on its severity, noncompliance may lead to a range of sanctions against the Marketing- and Manufacturing Authorization Holders, *e.g.*, product recalls, withdrawal of marketing authorizations, staff suspensions and fines, and in the most severe cases, business closures and imprisonment.
- The speed at which the new compliance laws are being implemented varies across the EU member states.
- The new, API-related responsibilities of the QPs at the Manufacturing Authorization Holders may not yet have been made fully clear to them.
- The authorities may not be sufficiently aware of the true dimension of the commercial realities surrounding traders and brokers of APIs.
- Only a few EU member states yet had plans to increase the number of inspectors.
- The EU needs a transparent system for tracking APIs in relation to marketing authorizations.
- A strong appeal from industry delegates to the authorities for more inspections of API manufacturers outside the EU.
- In light of the evidence from inspections in China and India, it is necessary that EU authorities reassess their risk-based approach for prioritizing the location of their API inspections.

The parallel sessions at the EFCG conference also confirmed that across Europe, there is significant disparity in the understanding and implementation of the new laws. The role, position, and seniority of the QP are not the same across Europe – legally as well as culturally. There also seems to be a disconnection between inspectors from countries with considerable API industry tradition and those having little or no API industry. Also, inspectors that understand the realities of the shop floor seem to be more aligned with industry than both the regulators and politicians who are remote from "operations."

### Results of benchmarking survey

The EFCG conference in April also revealed the results of the EFCG benchmarking questionnaire sent to the 25 EU national health authorities to measure their preparedness to implement and enforce EU Directives 2004/27 and 2004/28. From the six responses received, the findings show there is reasonable alignment between the goals and views of industry and regulators, and consensus on key issues but that the "how-to-do" is not always clear. The complete report can be found on www.efcg.cefic.org. The authorities announced that they are planning their own monitoring survey during 2006–2007, with a focus on how API users are qualifying their sources of APIs.

## Conclusions and next steps

The European Fine Chemicals Group's (EFCG) board received a full report of the outcomes of the conference from the Pharmaceuticals Business Committee and concluded that there were three key issues that remained open and needed addressing in the short term:

1. Actions needed following the suspension by the European Directorate for the Quality of Medicines (EDQM) of an API manufacturer's certificate of suitability (CEP).

   At present, EDQM does send out an alert, but there is no system in place to quickly identify the consequences. An automatic suspension of the Marketing Authorization would seem obvious to safeguard patient safety. It was agreed that EFCG would discuss the matter with the Heads of Agencies.
2. Actions needed to raise the awareness of the Qualified Persons and their employers (especially those who source active pharmaceutical ingredients (APIs) for generic medicines) of their increased responsibilities under the new laws governing good manufacturing practices (GMP) compliance.

   It was agreed that EFCG would discuss the matter with the European Commission, Heads of Agencies, and associations representing Qualified Persons.
3. Actions needed to increase the number and frequency of European inspections of API manufacturing facilities in Asia, especially in India and China.

   It was agreed that EFCG would urge the competent authorities for more inspectors to be hired to inspect the facilities in India and China, which are responsible for 80% of the volume of APIs in European medicines.

The EFCG remains concerned that the downward pressure on the price of generic medicines by the national health authorities and health care providers, the intensity of competition in the generic pharmaceuticals industry, coupled with the high level of globalization of the API industry, are allowing low-cost Asian API producers to dominate the API supply for medicines in Europe. This trend has not seen a corresponding change in the geographic focus of the EU's regulatory supervision. Therefore, inadequate enforcement is increasing the risk component in European generic medicines to unacceptable levels. **PT**