Enforcing GMP compliance for APIs in EU medicines

The legal basis for APIs for the EU market to be manufactured under GMP — a requirement already in place in the US since the 1970s — was created through a directive adopted in March 2004. Health authorities in the EU are now gradually increasing their enforcement efforts and are training their inspectors to check for GMP compliance of APIs used in medicines marketed in the EU. In November 2006, a majority in the EU Parliament voted in favour of an important 'Written Declaration' that proposes that only GMP-certified APIs will be allowed in EU medicines.

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The Active Pharmaceutical Ingredients Committee (APIC) — a sector group of Conseil European des Federations de l'Industrie Chimique (CEFIC) — first voiced the need for EU GMP API legislation in 1993 to help ensure the safety of medicines. In 2000, the International Conference on Harmonisation (ICH) finalized the harmonized API GMP Guideline Q7, which became legal in the US and Japan in 2001. The EU adopted a directive in March 2004 that includes the requirement for APIs in medicines for the EU market to comply with ICH/Q7A. Member States are transposing the directive into their national law: about half of them have completed this process, seven more are well on their way to completion, while seven others are still in earlier stages of adoption.

A basic principle of the EU directive is that API compliance for medicines for the EU market should be primarily assured by the qualified person (QP) of the manufacturer and/or importer of the final medicinal product. This strongly differs from US/FDA practice in which inspections of API manufacturing facilities are a key element of the approval process of medicines.

To be clear, the European Fine Chemicals Group's (EFCG's) concerns are not directed towards the manufacturers and users of APIs for medicinal products that are covered by patents. Instead, they are directed against the manufacture, trading and use of off-patent APIs, for which there is extensive competition in the marketplace and less control of quality standards along the — often long — manufacturing supply chain compared with APIs for medicinal products still under patent.

Foreign manufacturers

It was the 2004 APIC Lisbon conference that galvanized the CEOs of EU producers of off-patent APIs to put their case to the authorities and other stakeholders through the then newly formed EFCG. The presentations by EU medicines agencies made it clear that they were not contemplating inspection of foreign, off-patent API

manufacturers as a key part of their compliance enforcement strategy.

EFCG is aware that the large majority of off-patent APIs in EU medicines are imported, mainly from India and China. We are also aware that the number of European directorate for the quality of medicines (EDQM)-initiated inspections of non-EU API sites over the past decade has been very low indeed (less than 50), and of those that have been inspected, the number of serious noncompliance cases were at a worrying level.

Many thousands of manufacturing plants for off-patent APIs in those non-EU countries are unlikely to ever have been inspected by an EU official.

Inspections

EFCG believes that to guarantee the safety of EU medicines, serious consideration must be given to a focused inspections programme of off-patent, API manufacturers outside the EU and at the intermediary points inside the EU (importer, trader, broker), prioritized whenever possible by evidence of suspicious behaviour, but also including a random element.

Given the increasing pressure on prices of off-patent medicines, we feel that their safety is very likely to start presenting unacceptable risks to European citizens. Why? Because GMP-compliant companies know that compliance requires significant investment in people, as well as in equipment. It is unsurprising, therefore, that cost cutting, especially for off-patent medicines, is a factor that increasingly conflicts with compliance. What is less well understood is that the use of safe APIs forms a negligible factor in the cost of healthcare. The costs saved by noncompliance are only of relevance at "API business level" and have little, if any, impact on the price of final medicine to the patient.

EFCG remains concerned that the potential risk to public health presented by the strong possibility of non-GMP-compliant, off-patent APIs in EU medicines is increasing. It is important to keep reminding all stakeholders that without effective law enforcement, deterrence and sanctions, the quality of our medicines is compromised and the noncompliant operator is likely to continue business in the EU undetected.

Many thousands of manufacturing plants for off-patent APIs in those non-EU countries are unlikely to have ever been inspected by an EU official. But what we do not know is how many of them are Q7A-compliant. For the majority of EU medicines containing off-patent APIs the authorities have not confirmed (through their inspections of the API manufacturers or traders) that the APIs are Q7A-compliant and safe. Curiously, although most of the APIs come from Asia, the majority of inspections by EU inspectors are conducted in Europe where, according to the results of EDQM's inspections, very little serious noncompliance has been observed. Also, as CEP (Certificate of Suitability) statistics seem to indicate, EU off-patent API producers trigger the vast majority the API-related "variations submissions". Does this mean Asian producers never change their processes, or that they have inadequate change control procedures?

EFCG has accepted the challenge to initiate a change of mindset in off-patent API producers, users, regulators and politicians. We have given annual press conferences during CPhI, first in Brussels (2004), then in Madrid (2005) and last year in Paris. We have met with many stakeholders, regulators, politicians, industry representatives, media, nongovernment organizations (NGOs) and others. EFCG has also published several articles and has issued its "simple guide" to buying GMP and regulatory-compliant APIs.[1,2]

In 2005/2006, we performed a benchmarking exercise across the EU to assess the extent of readiness of the medicines agencies to enforce API compliance. The head of the Spanish Medicines Agency opened our Barcelona conference in April 2006 by announcing that her agency would be doubling the number of inspectors in 2007, which was very good news, but she was unwilling to commit to an increase in the number of overseas inspections. At that event, EFCG reported the results of the benchmarking exercise. It was concluded that there was a common understanding of the issues, a common shortage of inspection resources and there were only limited intentions to inspect outside of the Member States' jurisdiction.

A German lawyer speaking at the conference believed that the QP's personal legal liability is much less than what is generally understood. If this is so, the QP appears to be less accountable than a certified accountant who signs off the financial statements of public companies. In our opinion, this contrasts sharply with the importance of securing the safety of EU medicines.

Punishment

During 2006, more information became available on the 1990s Biochimica Opos API affair on illegal APIs.[3] More than €100 million have now been paid in fines and damages. An account on FDA's investigation showed that cefaclor manufacturing steps were secretly performed in unapproved facilities in Italy, France and Romania while fake production records were kept.[4] Manufacturing processes were very different from the original, authorized drug applications.

In 2005, a former manager of Biochimica Opos was arrested by the US authorities on entering the US at Miami airport. He was held in detention for 13 months and personally fined $16 million. The system in Europe heavily relies on individuals and companies obeying the law and much less on its enforcement. We have been unable to find significant examples of API-related sanctions within the EU that would deter determined, noncompliant manufacturers.

We were pleased to note that in 2006, the European Agency for the Evaluation of Medicinal Products (EMEA) started an EU-wide API programme that, *inter alia*, provides all the medicines agencies with a checklist for inspectors. EMEA stated that this initiative serves two purposes:

- To support and harmonize training on how to enforce and verify API compliance when inspecting dosage form manufacturers.
- To gather information to assess the compliance situation regarding APIs.

We are eagerly awaiting the outcomes of this data-gathering exercise and look forward to EMEA sharing any available data with us.

The APIC Audit Program has been completely revised to bring it in line with EMEA's guidance on the responsibility of auditing active substances manufacturers by the Manufacturing Authorization Holders for medicinal products in Europe. This audit programme now provides a third party option for auditing active substance manufacturers and is developing very well.

In 2006, another US initiative attracted our attention: the United States Pharmacopeia (USP) has launched its "Pharmaceutical Ingredient Verification and Qualification Program".[5] The USP website claims that "USP has established the world's most rigorous third-party verification programme for APIs and excipients". This essentially comes down to the USP granting its seal of approval after having performed a thorough, product-specific audit covering both GMP and — possibly — regulatory compliance (this latter aspect remains as yet unclear).

Equal footing

The leading US trade association representing API producers, Synthetic Organic Chemical Manufacturers Association (SOCMA),[6] joined EFCG last summer to develop a joint position paper arguing for the need of a level playing field to enforce GMP and regulatory compliance of APIs.[7] Whereas FDA is very tough, and sets high regulatory standards and hurdles for the APIs for prescription medicines, there is very little regulatory control over APIs for over the counter (OTC) products. There is neither a requirement for a preapproval inspection nor for regulatory (DMF) submissions. Therefore, for OTC products, any supplier that meets the specification seems acceptable. In contrast, APIs for OTC products in the EU must meet similar standards as those for prescription medicines.

The most recent development to recognize the lack of effective enforcement of European laws governing GMP compliance for APIs, has been the approval of the Written Declaration (0061/2006) in November 2006 by a majority of EU Parliament members. This states that worldwide GMP inspections of API manufacturers by European inspectorates should be mandatory for every API included in a medicine marketed in the EU, and that every such API should have a Certificate of GMP Compliance issued by an EU member state. The Written Declaration has been forwarded to the European Commission, the Council of the EU and the Member States for further action. This official position taken by the elected representatives of around 250 million Europeans is very similar to the one included in the APIC position paper of 24 December 2004 and adopted by EFCG as the cornerstone of its advocacy programme.[8]

Conclusion

In conclusion, EFCG believes that it has helped to advance the agenda on the need for the effective enforcement of GMP compliance of off-patent APIs, but there is still much more to do to convince the authorities to take further action. We see support for our actions from many quarters, particularly the EU Parliament through its Written Declaration, but we still do not have tangible progress on enforcement. Consequently, we would welcome the following recommendations by the EU authorities:

- To create an EU Foreign Inspection Service in concert with the EU medicines agencies with a capacity to inspect at least 100 non-EU API manufacturers per year for both GMP and regulatory related compliance. It also seems reasonable that those intending to export APIs to the EU should pay fees towards the costs of this service.
- The European medicines agencies should harmonize and coordinate the courses of action to be taken when a seriously noncompliant API is identified. This should include measures to block the import of such APIs into the EU by involving the EU Customs services. As a strong deterrent to others, effective sanctions must follow so that it becomes widely known that it does not pay to break EU law. EFCG is unaware of any progress on coordinated action by the European medicines agencies to deal with the consequences of suspended CEPs.

EFCG urges the Commission to recognize that legislation without full implementation and enforcement (via inspections), and without tough, appropriate deterrents and sanctions, is ineffective and a cause of increasing the risk to EU citizens, as well as leading to market distortions. Without proper enforcement and deterrents in place, GMP and regulatory noncompliance

by manufacturers of off-patent APIs will continue to threaten the safety of European medicines containing them and will remain a major competitive advantage to overseas suppliers. A recently published Chinese article on the API compliance situation in China would seem to support this view.[9]

An additional concern is the information given in a recent article reporting on corruption within the Chinese SFDA during the period 1998–2005.[10] It appears 170000 GMP and production licences may have been granted improperly with possible implications for public health. PTE

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Key points

- A new EU "Written Declaration" proposes that only GMP-certified APIs will be allowed in EU medicines.
- GMP and regulatory noncompliance threaten drug safety and the competitiveness of European suppliers.
- An EU Foreign Inspection Service is required to work alongside the EMEA to ensure GMP and regulatory compliance of off-patent APIs and adequate penalties must be introduced to deter noncompliance.