Inspect & survive

SOCMA and the **EFCG** have united to call for a clampdown on the rogue elements. Andrew Warmington reports from CPhI Worldwide 2006

The Synthetic Organic Chemicals Manufacturers Association (SOCMA) and the European Fine Chemicals Group (EFCG) used CPhI Worldwide 2006 in Paris last month to launch a joint position paper on the enforcement of GMP in the manufacture of APIs.

SOCMA has some 300 member companies from the batch process industries, with a total of some 100,000 employees; it was also until this year the organiser of Informex. The EFCG is a CEFIC sector group, whose membership, either individual or via national bodies, represents some 200 companies with 50,000 workers.

In the immediate future, the joint position paper will be tabled at meeting with Congress, congressional committees that oversee the FDA and the Department of Commerce in the US.

In the EU, it will go to the Commissioners for Public Health, Trade, Enterprise and Defence, the European Medicines Evaluation Authority (EMEA) and heads of agencies, other trade associations and patient organisations.

The initiative began, according to Guy Villax, CEO of Hovione and chairman of the EFCG's Pharmaceuticals Business Committee, when he met with Joe Acker, president of SOCMA, at DCAT Week in New York in March. Acker remarked on the work EFCG had already been doing in the field and said that many similar issues existed in the US.

The two associations have subsequently worked together informally on various matters of mutual interest, culminating in the joint position paper. As Acker said in Paris, the paper may well be "a unique example of two trade associations coming together from the US and Europe who are in complete agreement with each other".

Entitled 'Uneven Enforcement Leads to Sub-Par Drugs and National Security Risks', the paper focuses mainly on the failure of health authorities to inspect adequately facilities producing APIs outside the developed world and the consequent risks that the associations believe this poses to public health and, potentially, security.

The paper thus echoes two separate documents that emerged in both regions in September. In the US, SOCMA's Bulk Pharmaceuticals Task Force (BPTF) submitted a Citizen Petition to the FDA, asking it to carry out more inspections of drug manufacturing facilities outside the US, in order to manage better the public health risks associated with the use of imported APIs and drugs.

Likewise, a Written Declaration (0061/2006) against counterfeit pharmaceuticals was tabled by five MEPs in the European Parliament on 4 September. This requested EU authorities to make the inspection of manufacturers and importers mandatory, in order to ensure that higher safety standards are met and qualified by a GMP certificate, and also proposed increasing the traceability of APIs.

This declaration is potentially very significant because, if 50% of MEPs sign it, it can go straight to the EC, who can then make inspections mandatory. The process would be far more rapid than it would be via the normal EU channels. The EFCG and the API Committee (APIC) both welcomed the declaration warmly, saying that counterfeit medicines are a serious public health issue and a €32 billion/year trade that is controlled by criminals.

The overall problem is that, despite the firm rules in both the US and the EU to make APIs compliant with cGMP, sanctions are not in place to deter non-compliance. Speaking at the launch event for the joint position paper, Villax, noted that four main interlocking factors have shaped the current situation and have combined to make the playing field very uneven.

Firstly, **cGMP** is becoming tougher. Compliance with cGMP and keeping up to date with the changing requirements is becoming more demanding and is - on average - 25% more costly than not complying. Compliance also makes operators less flexible than non-compliant firms and handicaps them in the race to get generics to market first when patents are about to expire.

Secondly, with the increasing **globalisation** of the drugs industry, APIs are being sourced more and more where they are cheapest. This is driving

Villax: Compliance is becoming a competitive disadvantage

rapid growth in the drugs market, but also means more complex supply chains, increasing the potential for contamination, mis-labelling and the substitution of one substance for another.

In addition, the consumption of **generic medicines** is growing twice as fast as the consumption of innovator drugs. This market is also, however, highly competitive. Lower costs are constantly being sought and corners are consequently likely to be cut.

Finally, the ever-increasing pressure from health authorities for **cost containment** is promoting greater use of generics and leading to decreased enforcement of quality standards through inspections. There is thus an ever-increasing danger of sub-standard products ousting compliant manufacturers from the market

The drugs world has moved so fast that legislation and the enforcement of it increasingly do not mirror the situation on the ground; plants in some areas are never actually inspected, so that compliance is uncertain at best. "In the absence of a referee, there is a predictable winner every time: the least scrupulous operator," said Villax.

Only 20 years ago, he added, EU- and US-based producers supplied 90% of the APIs consumed in the two markets and only 5% of prescription medicines were generic. Now, the respective totals are under 20% and over 50% respectively. The proportion of generics among over-the-counter (OTC) drugs in the EU and the US and among all drugs in other markets is even higher than 50%

Europe does, of course, have an inspection system, through the European Directorate for the Quality of Medicines (EDQM). In the seven years to April 2006, according to figures from the EFCG, it issued about 2,000 Certificates of Suitability (CoS).

However, over 90% of the inspections that the EDQM carried out in that time were in Europe. Only 80 facilities outside Europe were inspected, about half of them in China and India. Meanwhile, about 80% of the APIs on the European market come from abroad, mostly from India and China.

"The EU is not looking where it should be looking and thus has no filter to separate the wheat from the chaff in India and China, where some companies are excellent but there is no real brand value," Villax said.

Just as seriously, he added, the European authorities simply do not know who makes the APIs used in Europe. Although the EQDM has suspended 12 CoS from ten different holders in the past seven years, all of them in China and India, this means little in practice, because of the lack of a common procedures across EU member states.

Medicines with suspended CoS remain on sale in some states because national agencies are not always advised about suspensions or do not enforce them. In addition, there is little co-ordination between customs authorities and these agencies, no system is in place to identify or track producers and no NDC numbering system exists.

Many of the complaints about the situation in Europe are familiar. Indeed, it was in part with these issues in mind that the EFCG was originally launched at CPhI Worldwide in Brussels two years ago (*SCM*, January-February 2005, page 13). Since then, it has been urging the European authorities to enforce GMP requirements and adopt the FDA model of foreign inspection (*SCM*, December 2005, pages 19-20).

However, Acker said at the launch event for the joint position paper, all is not necessarily rosy in the US either. Although the FDA has a strict, pre-approval foreign inspection service and inspects all API producers for prescription medicines without exception, significant gaps remain in its coverage.

There is no real enforcement of GMP compliance by producers of APIs for OTC medicines, which comprise a substantial, rapidly growing part of the market.

About 50% of APIs for OTC medicines used in the US come from China and India, yet, according to the joint position paper, the FDA conducted a total of 163 inspections of non-US manufacturers of APIs in 2005. Of these, 14 (9%) were in China and 23 (14%) in India, most of the rest in Europe. These figures are clearly way out of proportion with market realities.

As the BPTF petition pointed out, almost as many API and other pharmaceutical manufacturing sites are registered with the FDA abroad as in the US; excluding those registered purely for medical gases, there are about 2,700, including about 440 in China and 330 in India, as against 3,300 in the US.

Although the FDA was "reasonably close" to its target of biennial domestic inspections in the years 1999-2003, the petition said, facilities abroad are inspected "infrequently, if at all". The number of inspections abroad fell from a peak of 249 in 2001 to 184 in 2003 and 2004, before falling again to 163 in 2005 as the FDA's inspection budget has been repeatedly cut.

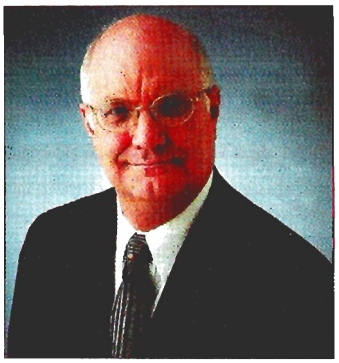
The petition argued that foreign facilities pose a greater health risk than domestic ones; Form 483s are significantly more likely to be issued to foreign firm and the deviations they find are generally more serious.

The unlikelihood and irregularity of inspections is likely to lead to complacency at best. "In the absence of a credible threat of reasonably frequent inspections, the 'c' in cGMP gets lost," the petition said

"FDA inspections are tough, but they are pre-announced and short. And, unless you are named on an NDA, you are very unlikely ever to be inspected," Acker continued. "Over 90% of the inspections are pre-approval, less than 10% are post-approval or for compliance. It is much easier to get your plant approved before you have put anything through it."

(Of course, the issue is not just about fraud or corner-cutting. As Villax later observed, the concept of change control is still not fully understood in parts of the industry in China. It is also not unknown for plants there to be physically dismantled and rebuilt elsewhere if they are no longer up to date.)

That the FDA foreign inspection service has real teeth is not in dispute,



Acker: FDA system still has loopholes

Acker added. It was an FDA inspection that uncovered systematic fraud in the Biochimica Opos affair, in which dual batch and production records were kept and a dual computer system operated.

This all ended in a Big Pharma company paying a fine of $33 million for its Italian subsidiary's criminal activity and the managing director of the subsidiary serving time in jail. And yet, as both Acker and Villax noted, the company's activity was not in breach of EU law at the time.

Thus, SOCMA believes that FDA inspections abroad are not proportional and are not true cGMP compliance inspections; the sanction of a follow-on inspection if corrective action is required is minimal. "The people are available but the agencies need to sort out their priorities. Governments have not kept up with the changes in the past years," concluded Acker.

Speaking to *SCM* later, Villax stressed that the FDA still represents the gold standard for inspections and should be the model for a better EU foreign inspection service. Arguments that FDA inspectors have no authority abroad are not the point.

"FDA inspectors might not have authority abroad but they have much more real power abroad than in the US. Their badge is their authority," Villax said.

"If they don't like what I am doing at my facility, they can tell their superiors in DC, and they will call customs and stop my exports to the US on the spot. They don't even need to gather evidence - unlike a US firm being inspected, I can't sue the FDA if I think they have made a mistake."

The other key point to realise, according to Villax, is that no company facing a realistic prospect of being inspected by the FDA ever cheats; they cannot hope to get away with it. However, with the rapid shift of API production to Asia in the past years, the authorities on both sides of the Atlantic have not been able to address the issue properly.

As a result, public health is potentially at risk. The joint position paper noted that even certain Indian companies that have even been blacklisted by authorities in Nigeria "because of their proven, deep involvement in exporting counterfeit medicines to that country, are still freely exporting APIs to the EU".

National security issues arise as well, the joint position paper continued, because the EU, the US and indeed Japan no longer make the basic medicines to fight against many common diseases or chemical warfare agents. "If there is a peak in demand, triggered by a pandemic or a terrorist event, there will be little domestic production capacity to meet public health needs."

Among many other drugs, it added, the joint position paper said, the main treatments for anthrax, ciprofloxacin and doxycycline, are no longer made in the West because every source of every key intermediate is Indian or Chinese.

To address these problems, SOCMA and the EFCG requested that medicine agencies and health authorities in the EU and the US should be given a mandate and the resources to "create a health care environment where all API manufacturers whose product is destined for EU or US consumers must comply with cGMPs, regardless of where they are located'.

This means more inspections in areas where GMP compliance is less likely to be happening. No medicine should be allowed on the market, the paper said, unless its Marketing Application includes a GMP certificate for the API. There should be no loopholes; every API facility should be inspected, to the same degree of thoroughness, regardless of location.

This last point had already been made in the BPTF petition, which had demanded three specific measures. First, it said that foreign and domestic firms should be ranked together in the FDA's computer programme to select manufacturers for inspection, so as to allow for better comparisons between them.

Secondly, being located abroad should be deemed a significant risk factor for determining facility inspections, alongside such factors as specific product, processes used, recalls, violation history and contamination potential. This is not the case at present

Finally, a programme should be created to monitor the impurity profiles of imported OTC drugs that are not the subject of an NDA, to examine patterns creating the appearance of underlying problems in cGMP compliance. This will enable the FDA to refuse entry to products appearing adulterated, the petition said.

On this particular point, the joint position paper added that, if the authorities will not impose "frequent and random GMP inspections" abroad to ensure that offenders are found out, impurity monitoring would be "a minimum but inferior surrogate" for them.

Villax also stressed at the launch event that this initiative is not about protectionism - as some observers have alleged - but about fairness and public health. "SOCMA and EFCG members have plants in the US and the EU, but also in China, India, Thailand, Taiwan, Japan and other countries," he said.

"We in the fine chemicals industry are pro-globalisation, there is no discussion at all about the fact that our competitive basis comes from taking advantage of globalisation, but we take a stand that the law must be enforced, that patient welfare is paramount and that we want a level playing field."

Is it feasible, however, to start the EU foreign inspection service that the EFCG wants? Villax said that he did not see any resource issue, merely reluctance on the part of the authorities to carry it out.

"I can guarantee that Europe has the largest proportion of trained QA people in the world - many of them from plants that have been closed down in recent years because of the trend to manufacturing elsewhere," he said. "Training them up to carry out inspections would be challenging and time-consuming but it could be done in a time-frame of five years or so."

But will this not lead to much higher API costs? Villax doubted that too, pointing out that although API prices are indeed higher in the US than the EU, many generic drugs are actually less expensive there than in many EU countries. This is essentially the result of inefficient distribution in the EU.

Moreover, the API represents only 2-5% of the sales price of a patented drug, or about 5-15% in a generic drug. "Better quality comes at a very small cost," Villax concluded.

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