

**INSPECTIONS FOR CGMP COMPLIANCE ENSURES:**

- Each drug product meets quality standards
- Each drug product meets strength standards
- Consumers are safe from ineffective drugs

**Author**

Joseph Acker was appointed president of SOCMA in March 2003. Previously, he was president and CEO of DanChem Technologies and president of Hickson DanChem. Acker began his career in 1966 with Merck & Co. From 1976 to 1988, he worked at FMC. In 1988, he joined ChemDesign as president and general manager of Specialty Chem. In 1995, he became vice president of Bayer and president of ChemDesign.

# TROUBLE WITH TRUST

**The public places great confidence in the pharmaceutical industry. An individual has a reasonable expectation in the safety and performance of any product bought over the counter. But while the public believes in the products they use, SOCMA president Joseph Acker takes a less indulgent view.**

**T**he US FDA performs an excellent job of inspecting domestic facilities to determine if the industry's accepted current good manufacturing practices (cGMP) are adhered to in the production of active pharmaceutical ingredients (APIs). Inspections determining compliance with cGMP confirm that each pill or each injection received meets the same quality and strength for its approved use and keeps consumers safe from defects and ineffective drugs.

However, the industry is increasingly facing a greater challenge from far-flung manufacturers of generics and over-the-counter drugs. Globalisation has put enormous amounts of pressure on profit margins, resulting in multinationals no longer creating their own APIs, but rather purchasing them through complex supply chains, which can lead to mislabeling, mishandling, contamination or substitution of the APIs being used. This means patients could be placed at risk from the very thing they hope will cure their illness.

**Inspection weakness**

This increasingly complex and global supply chain has also exposed a fundamental weakness in the USFDA's inspection process. The USFDA rarely performs foreign inspections of API facilities beyond the new drug approval stage, this despite estimates from the US General

Accounting Office that around 80% of all APIs are now being imported into the US.

The US FDA is required by statute to inspect every facility in the US at least every two years. According to its Center for Drug Evaluation and Research, the US FDA comes very close to meeting its annual inspection targets. While the it is not mandated to inspect every facility overseas, it is required to safeguard the public from poorly manufactured products.

Some of the difficulty lies with the fact that the US FDA cannot enter a foreign facility without the host country's invitation. The US FDA is encouraged to arrange cooperative partnerships that would allow inspections to take place. Most countries, when they have arrangements with the US FDA, have a long period of time between the notice of inspection and the actual inspection, giving any facility the time to either comply or disguise their deficiencies. Additionally, the duration of inspections is usually shorter than in the US and are limited to facilities the host country is willing to allow the US FDA to visit.

This lack of inspections is creating two very different regulatory enforcement regimes: domestically, companies are faced with regular inspections and compliance updates; while those produced overseas are rarely inspected, facing no accompanying

regulation from their home countries. The result is that facilities that are not inspected manufacture and sell products in the US that may not meet quality and performance requirements.

In the face of possible health impacts, this also creates an uneven economic playing field. In many parts of the world API regulation has been severely relaxed or absent, and when combined with a lack of enforcement, there is no incentive for manufacturers to invest in cGMP compliance. They do not have the added expense of making sure their processes are safe, clean and of high quality. Each step away from cGMP compliance results in cost savings and increases profit margins. This situation places the pressures of financial performance in direct competition with consumers' health and safety. The financial pressures on consumers are also affected, as they purchase increasingly less expensive generics, which are more likely to be susceptible to mishandled or poorly manufactured APIs.

It's only a matter of time before the public faces serious harm because of a lack of inspections.

Faced with the financial reality of the dual regulatory scheme, US manufacturers are unable to keep up, resulting in closure of domestic facilities and cutbacks in staff. The job losses also demonstrate another serious concern in the age of globalisation: with no domestic sources of pharmaceuticals, the US could be forced to wait to receive the drugs necessary in the event of a pandemic or catastrophic event. If a global pandemic were to take place, and there are no domestic manufacturers to treat a large number of people, the US would be on the verge of disaster. Will foreign producers – and their governments – fulfil orders for the US before producing enough of the APIs for their own internal needs?

#### **FDA enforcement**

So how can this problem be transformed? Where foreign API manufacturing regulation is little or nonexistent, the US FDA must step in and fulfil its mandate to inspect these manufacturing facilities at the minimum of every two years. Without meaningful US FDA enforcement, it means a large percentage of the medicines in the US using foreign-made APIs could be ineffective, or even harmful. This is must be rectified – and fast.

In January 2006, SOCMA, through its Bulk Pharmaceuticals Task Force (BPTF) formally petitioned the US FDA to increase inspections of the API manufacturing facilities outside the US. The petition gave several recommendations meant to improve the US FDA's process in determining which facilities to inspect.

One recommendation suggests that the US FDA considers a foreign manufacturing facility a significant risk factor when prioritising API facilities for inspection. The US FDA uses a risk-based approach using computer modelling when determining how inspections are prioritised, but domestic and foreign firms are not used together in the computer models.

This, and the fact that a foreign firm is the manufacturer, has no basis in the choice of facilities to inspect. Of those that are inspected, there is little or no follow-up to determine if the facility has come into compliance.

Other risk factors considered include specific products, processes used, past recalls, violations history and contamination potential. All these factors are based on a common-sense approach. By including a non-US based facility as a significant risk factor, the US FDA would allocate funds based on actual risk, and perform the necessary inspections. We have already seen what can happen when facilities are not inspected: in 1998–99, 17 patients taking gentamicin sulfate died, a tragedy subsequently linked to an API from a Chinese producer.

Naming a foreign facility as a significant risk may embolden the US FDA to prevent more APIs from coming into the US from countries where standards are known to be lax. It has the authority to prevent the sale of any drug it deems to be possibly harmful to consumers. Yet, it lacks the resources to do this. That is why in its petition BPTF called on the US FDA to monitor the impurity profiles of imported over-the-counter drugs for patterns that suggest underlying problems with cGMP as data to block importation of problem drugs. Warning letters and preventing the foreign APIs of bad actors from entering the US market are part of the US FDA's enforcement mechanisms.

This is why SOCMA, in conjunction with the European Fine Chemicals Group, issued a White Paper calling on US and EU authorities to step up enforcement efforts. While a full inspection regime similar to the one in the US is the ideal, SOCMA understands the financial strain the US FDA is under and that it cannot provide a full account of the drugs produced overseas.

#### **Government support**

But little is likely to change without congressional involvement. The US FDA's 2006 budget included cuts to foreign inspections at a time when inspections are needed most. If Congress does not provide the US FDA with sufficient resources to increase inspections, the US could face serious consequences.

The US has created a virtual regulatory regime, where the government performs perfunctory inspections and declares the drug supply safe – but it is not safe. The US has yet to detect large amounts of ineffective or harmful drugs coming into the US market and being consumed. SOCMA firmly believes the public is at risk and it is only a matter of time before the public faces serious harm because of a lack of inspections.

In an age of globalisation, with the constant movement of an increasingly mobile population, outbreaks of diseases such as SARS are only going to take on increasing significance to nations and their citizens. The US must prepare for this eventuality. One way to begin this process is to ensure the drug supply meets quality and performance standards. The US FDA must carry out more foreign API inspections and it needs to receive the financial and political support of the rest of the US government to make this a reality. **END**