

FDA's Hamburg declares no one can "inspect world on its own" for poor quality medicines

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It seems as if the US FDA is softening its stance on assessing the quality of pharmaceutical manufacturing facilities around the world in future, with an apparent desire to work more closely with other drug regulators. However, incorporating the regulators from countries such as India, China and Japan into a global inspectorate still looks problematical.

FDA Commissioner Margaret Hamburg told a gathering of regulators in Geneva last month, held to celebrate the 40th anniversary of the international GMP inspectorate scheme, the PIC/S that "Together, we can all do our jobs that much better, for as you know, no one country is capable of inspecting the world on its own, nor can we assure quality with inspections alone."

She went on to raise the question of how the quality of manufacturing can be assured as drug companies attempted to address production cost issues by relocating their facilities. "As manufacturers and distributors strategically relocate to countries with lower operational costs—and often countries with less mature regulatory systems and historically less active engagement in drug quality assurance—all PIC/S members must continue to think strategically about how we can pool our resources and truly work together for the common good."

The FDA only joined the PIC/S scheme in January of this year, a coup for a scheme that has been around since 1971. In part, the delay has been because the US has been (and is) rather protective of its home market, preferring itself to inspect the quality of any imported medicines into the US rather than rely on other regulatory inspectors. Every competent authority is charged with the duty to protect its market from medicines of questionable quality, but the onus to do so increased on the US especially after the political fallout that followed the contaminated heparin preparations that came from China in 2008 (scripintelligence.com, 24 November 2010).

She believed the work of the PIC/S is "more important than ever, given the realities of globalization". In the US, she noted that a "stunning" 80% of active pharmaceutical ingredients (APIs) in US drugs come from outside US borders and about 40% of the finished drugs themselves.

When the PIC/S was created in 1971, its decisions were legally binding – it acted like a "Mutually Recognised Agreement" for its members, but this changed dramatically in the early 1990s, when the European Commission did not want new EU members to join the scheme. At that point it then became non-legally binding, therefore allowing participating competent authorities to co-operate and share information of GMP inspection deficiencies informally (subject to confidentiality) while keeping complete control over imported medicines.

One source told *Scrip*: "The US FDA would never have joined the PIC/S scheme if it remained a legally binding scheme. The US would have had problems because it has never concluded a mutually recognised agreement on GMP with any country in the world."

The FDA chief told the PIC/S meeting of "a recent example" of its joint working in the GMP field which was "unprecedented" for the US agency. In that case, the FDA relied on the European Directorate for the Quality of Medicines to place a firm under Import Alert and prevent its API from entering the US.

Commissioner Hamburg declared: "We made this decision solely on EDQM's information, even though FDA had never inspected the manufacturing site. To make this decision, which was an unprecedented one for us, we learned about the deficiencies by monitoring an EU database; requested and reviewed EDQM's establishment inspection report; and had detailed technical discussions with the inspectors. Now, we are working to conduct a joint inspection of the firm with EDQM."

Last month the FDA also made efforts to share more of the data it has on GMP inspections, by making public its COMSTAT database, which contains its inspection results. "This means that every country, as well as every citizen, now has the benefit of knowing whether FDA has previously inspected a manufacturing facility and whether we found the facility to be in or out of compliance with our requirements and standards," she said.

FDA application was "long road" process

Commissioner Hamburg was quite open about the PIC/S application process, describing it as a "long road for us", but also believing that the PIC/S learnt something along the way.

She said: "Though not always easy, the PIC/S application process helped FDA to mature as an organization. The process required us to engage in rigorous self-examination. We improved our quality systems, focused on gaps in our regulatory processes, and became more cohesive internally."

But she added that the FDA believed the application process was "challenging and illuminating for PIC/S" as the FDA's system was so different from Europe's. "It took a lot of work to consider how to compare our system to those of many of the existing members. There was a great deal of productive dialogue ...[the PIC/S assessment team] were tough, but they were fair, and were willing to accept that different systems could be comparable and could get us to the outcome to which we all aspire."

Globalisation and outsourcing

She encouraged others to join the PIC/S, reminding delegates that the "world is poised for even further globalization. ... These realities challenge virtually all nations and make us increasingly connected and interdependent. In the US, at FDA, we tell Americans that there is no longer such a thing as an American drug supply; there is a global drug supply."

She highlighted how globalization and outsourcing have "redrawn the path that drugs navigate to reach the citizens of all of our countries, and the supply chain from manufacturer to consumer has become more and more complex ... involving a web of re-packagers and redistributors, including those online, that make oversight significantly more difficult."

China, India and Japan?

While PIC/S has 39 members and could have a further nine more in the coming years as more competent authorities signal interest in joining, it may become a victim of its own success. It will have to adjust to the new size, and it will need more resources. Soon it will have 50 members. It can take up to six years to join the PIC/S, with an average application taking three years, as it depends on the characteristics of the applicant and whether they

have a GMP system already in place. For example, Malaysia went through in less than three years.

The US FDA's application took about three to four years to finalise. As one source told *Scrip*: "It took the PIC/S some time to understand the FDA system on GMP inspections as it is so complex, and for the FDA to understand the PIC/S system."

Some key countries that are still missing from the PIC/S list are India and China (two major manufacturers of affordable APIs and finished pharmaceutical products) as well as the world's second largest pharma market, Japan. Others include Brazil (it has applied) and Mexico (apparently no contact has ever been made).

The PIC/S has had little contact with India and it has little information on how the country operates its GMP systems. "They seem to have a decentralised system," said one industry source.

Another regulatory source said: "We would like India to join the PIC/S to help in the sharing of information on GMP inspections. The PIC/S is a cost-saving measure for the competent authority as they do not have to rely on sending their inspectors abroad, but can rely, if they wish, on other regulators' reports."

While China has not made an application as yet, it did send one of its delegates from its regulator, the SFDA, to the PIC/S 40th anniversary party last month in Geneva. *Scrip* understands that China is interested in joining the PIC/S.

But would China's joining the PIC/S cause negative reactions for regulators who might be suspicious of a country known as a source of counterfeit/falsified medicines? In theory, no, since PIC/S is a co-operative technical arrangement, and is intended to be apolitical. That detachment from political can be seen in the fact that Iran has applied (although it is still waiting to be admitted) even though Israel (whose right to exist as a country Iran does not recognise) is a member. One source described PIC/S as more like the World Trade Organization, where all countries sit round the same table. Nevertheless, in practice, some countries or regions tend to have more influence on the debate (e.g., the US and EU) than others, as is also seen at the WTO.

Japan, too, has a decentralised system for GMP inspections, so it a complex system. So who could apply for PIC/S membership: the Japanese regulator, the PMDA, the separate GMP groups from each Japanese province, or a consortium of them all?