

# 'PharmAsia News'

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Pharma News from Asia

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## Global Drug Regulators And Manufacturers Grapple With How To Ensure Global Quality Standards (Part 2 Of 2)

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***[Editor's note: This is part two of a two-part feature on ensuring drug quality, as discussed at the Fifth IFPMA Asian Regulatory Conference in Kuala Lumpur. Part one appeared in [PharmAsia News, March 17, 2008.](#)]***

KUALA LUMPUR, Malaysia - Manufacturers often have more than one source of active pharmaceutical ingredients to maintain a constant state of supply, which could mean regulators would have four to five sites to inspect, GSK's Quality Assurance Director Malcolm Holmes told participants March 11 at the Fifth IFPMA Asian Regulatory Conference in Kuala Lumpur.

"Industry says to the regulators that you shouldn't have to look at all of us," Holmes said.

"Thankfully there are harmonization efforts, but there are also local regulations based on risk. They should be harmonized, but they aren't."

Two key principles that have been incorporated into European GMP standards are: the level of effort has to be proportionate to the level of risk, and the level of effort put into the reporting mechanism must be proportionate to the risk. These principles apply to regulators as well, Holmes said.

The International Conference of Harmonization established roughly 10 guidance documents that cover quality topics for implementing GMPs. The Association of Southeast Asian Nations and the Global Cooperative Group are finalizing discussions on implementing Q8, Q9 and Q10, which cover how to prioritize pharmaceutical development, risk assessment and quality systems, respectively. The documents together are a paradigm shift in the way CMC GMP may be done in companies ([PharmAsia News, March 17, 2008](#)).

"ICH Q8, 9, and 10 offer a real opportunity for step change," Holmes said. "Local management is under pressure to inspect foreign companies as much as domestic companies."

U.S. FDA announced March 14 that it will establish permanent offices in Beijing, Guangzhou and Shanghai, staffed by eight full-time employees and five local Chinese nationals, following the safety scare over Chinese-imported heparin API. The U.S. agency plans to hire and place staff in the three locations over the next 18 months, pending authorization from the Chinese government ([PharmAsia News, March 16, 2008](#)).

## **Failing Regulatory Muster Not An Option**

It takes industry roughly 120 man-power days to present for an inspection, according a recent 2006 survey, Holmes said. "Industry cannot afford to fail an inspection. If it does, the QA manager will probably get fired. Also the patients may not be able to get product from your site. If that happens from a misunderstanding, that is really bad news," Holmes said.

One company surveyed had 15 inspections in 2006, and 10 in 2005, according to Holmes. Yet another site had 46 inspections in one year by 10 different inspectorates.

Regulators should be able to share inspection reports with other regulators, he said, as one way to get around this growing problem.

## **Learning From EU Inspectorate?**

Asia might do well to look to the European Union as a solution for API manufacturing inspections, David Cogburn, principal scientific administrator for the inspections sector of the European Medicines Agency, told conference attendees.

Under the EU Marketing Authorization, each manufacturing site must hold a manufacturing authorization; each site also must have a qualified person who has legal responsibility to certify that every batch complies with the requirements of the marketing authorization. Manufacturing sites for API, including packagers, brokers and importers are also listed on the MA.

EU GMP guidelines are laid out for both medicinal products and APIs, with annexes providing detail on specific areas, which are modified when necessary.

"The basic approach is self regulation by the active manufacturer with the expectation that this is done through audits of their suppliers," Cogburn said. Self audits are not looked at by inspectors, he said, but audits of suppliers should be available for review.

Inspections are conducted only where there is perceived risk, Cogburn said. "A GMP certificate has little value in and of itself," he said, noting that the EU's main concern is the distribution chain itself.

Issues have arisen when the manufacturer was unaware of the original source of the active substance, and questions about traceability are becoming more complex with more parties involved in the supply chain.

Third-party audits should be available for inspections, Cogburn said, and can also be used in a risk-based approach.

Still, the primary means for verifying GMP compliance is via inspections of MA holders, not the suppliers of APIs. The approach is based on shared responsibilities and obligations and includes the API manufacturer and the intermediaries in between.

"There has to be a new climate of transparency for this to work," Cogburn said, which is "important because of limited resources and the large number of API manufactured globally. The risk-based approach assures the best use of resources."

The European Commission is expected to issue a resolution calling for tighter control of API manufacturers, mostly because more APIs are manufactured outside the EU, and a perception that there is not a level playing field prevails, Cogburn said. The resolution is expected in April.

"Whatever the EU Commission comes up with, there will be lessons to be learned about how to ensure GMP status," he said.

## **Pharmaceutical Inspection Cooperation Scheme Offers Shared Inspections**

"Both industry and regulators are under constant pressure to do more with less," Holmes stressed. "Regulators do this by becoming members of PICs."

The Pharmaceutical Inspection Cooperation Scheme is a mutual recognition agreement between regulators that aims to assure countries are adhering to ICH standards such as GMP. Malaysia is the 26th member of PICS; Singapore is the only other Asian country that is a PICS member.

ICH Q7A, which sets GMP standards for APIs, was adopted by Australia's Therapeutic Goods Association in 2001, and by PICS in May 2001.

"We realize it is important for us to comply with international standards in terms of quality, safety and efficacy, and GMP standards have evolved from WHO standards to current EU standards adopted by PICS," Malaysia's National Pharmaceutical Control Bureau - Center for Compliance and Licensing Deputy Director Abida Syed Haq told conference attendees.

"Our industry needs to penetrate in foreign markets, which is not easy because there needs to be international confidence in the quality of the medicines and level of GMP implemented," Haq said.

"I think people need to know that we practice those standards. So Malaysia's ascension to PICS was to open foreign markets and it has opened doors to the pharmaceutical market."

Malaysia's GMP inspectors benefited by attending PICS seminars and participating in expert circles as well as joining auditors programs, Haq said. "We benefit from having a good rapport with other regulators."

At the ASEAN level, the group has agreed to use the PICS level of GMPs, Haq said, which will "benefit us as well as the auditors to utilize resources in a more effective and efficient manner."

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