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## **Excipient Compliance Challenges in Asia**

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In recent events affecting the pharmaceutical industry, the New York Times in February this year reported that tainted goods sourced back to a supplier in Asia killed four patients and caused 350 more to suffer from complications attributed to the contaminated material. Despite the fact that the material originated from Asia, the effects were felt across the Pacific when they manifested in Central America.

While the US Food and Drug Administration (FDA) was being asked to perform more and deeper inspections of materials originating from abroad, only 1,379 inspections of foreign facilities have been performed since 2002; there simply aren't enough inspectors compared to suppliers. The Washington Post in February this year reported that many of these inspections focus on areas where there are few quality concerns. Thus, there is a fundamental need for the North American industry to set and control its quality standards. Self-regulation, if done properly, is a better alternative than increased regulatory scrutiny. However, this will only be successful if undertaken proactively. If the present rash of incidences continues with the importation of foreign drug related materials from Asia, the FDA will have no alternative but to increase inspections, regulations and this could result in a lesser supply of inexpensive medicines and nutritional products. Costs will rise and this would ultimately harm the end user.



**While most Asian manufacturers follow high quality standards, many are operating far from what is expected in the US. This is an example of a poorly controlled manufacturer of excipients. (Source: Sancilio & Company, Inc.)**



**Most suppliers follow sophisticated procedures to maintain quality in their work place. This is an example of a packaging area of an average supplier. (Source: Sancilio & Company, Inc.)**

Excipient compliance issues in the pharmaceutical industry in Asia mimic that of the pharmaceutical industry experiences with compliance in Active Pharmaceutical Ingredient (API) manufacturing abroad. Due to the large number of manufacturers and supplies, drug manufacturers often take full responsibility for the quality of materials including the finished dosage form. Where the State Food and Drug Administration or SFDA (China's equivalent to the US FDA) requires that all raw materials, supplemental materials and components of drug products be housed in hygienic facilities and meet the requirements for pharmaceutical use, there are few measures in place to ensure that once those facilities undergo an initial inspection by SFDA, follow-up inspections would be forthcoming and regular.

It is estimated that nearly 80% of all drugs sold in the US contain components that originate in China or India. It is also likely that over 95% of nutritional products or their ingredients originate in these same countries. Considering that there are over 10,000 companies in China alone that produce these vital health care components, says one would expect an army of Quality Control auditors to be filling the skies to visit the suppliers of American healthcare. However, this is not the case, reports Bio Outsourcing Asia.

It also stands to reason that due to the large number of suppliers located in Asia, the US FDA simply does not have enough inspectors to visit the growing number of companies involved with products sold in and into the US. The only resolution to this growing issue is to shift the burden back to the industry to self regulate and audit suppliers on a regular basis.

The SFDA specifically mandates that "raw materials and supplementary materials required for the production of drugs as well as containers and packaging materials, which come into direct contact with drugs shall meet standards required for pharmaceutical use". This language is lax and the requirements are often vague. In 2005 the SFDA, in a push to ensure the quality of materials manufactured and distributed from China, published a Pharmaceutical Excipient Registration Regulation proposal, which calls for the excipient and facility, associated with that excipient to be registered and monitored. Since that time, however, no additional provisions have been published and monitoring is minimal at best.

While an article in the New York Times in February this year says as the SFDA and the FDA are falling short “not for lack of trying, perhaps, but from lack of resources” when it comes to inspections and follow-up inspections, manufacturers should be encouraged to clearly explain to consumers that all quality issues are addressed when drugs are obtained at the pharmacy counter. The industry will benefit as consumers demand manufacturers to ensure the quality of their excipients and raw materials.

In addition to the irregularity of facility audits in Asia, “what you see” is not necessarily “what you get”. While there are many modern and sophisticated facilities at one’s disposal, they are difficult to identify without prior experience doing business in Asia. The variation between the most modern facilities and the “mom and pop” operations can be staggering, to say the least.



Many companies operating in Asia have limited budgets available for preventive maintenance and repairs. Thus, even the most sophisticated companies tend to “degrade” rapidly with time. Doing routine (annual) inspections is a must to ensure consistent quality. (Source: Sancilio & Company, Inc.)

Resources providing lists and directories of Asian suppliers are available. However, they are usually written in the native tongue and most foreigners are unable to find specific items. To further complicate the search for a qualified partner, most manufacturers deal both directly and through other trading companies. Most of the trading companies may also change manufacturers at will without notifying the purchaser of changes. In one of our most recent trips to China, we realized that many Chinese manufacturers are now employing contract manufacturers to reduce their growing costs. These secondary manufacturers are normally located in remote parts of Asia such as Vietnam. Thus, many materials obtained from China may not be from the country but from other less developed industrial nations.

Many of the brokers who advertise their services to locate suppliers focus their search on trading companies with whom they have a previous arrangement. This might be convenient, but it may not yield the best quality material, or be the most cost effective. These brokers may actually be affiliated with specific factories that pay them a commission for locating business and they are often less than impartial.



The size of an organization is not reflective of its facilities. The pictures above show the diversity of what pharmaceutical supplier operations look like from the outside. Both facilities operate under the umbrella of larger organizations that have comparable sales and very impressive websites. It would be impossible to distinguish the two without a visit and an audit. (Source: Sancilio & Company, Inc.)

It is necessary to hire experienced native auditors who can bridge the language gap, source and locate facilities, which operate with a high level of quality, and exclude those which do not meet stringent quality standards. In basic explorations “whether pharmaceutical products or discovering new continents” successful efforts come from having experienced, local guides who know the language, customs and business environment. As US companies continue to rely on Asian sources for APIs, excipient compliance and self regulation following the US FDA and SFDA rules and regulations is the safest, most cost effective route to delivering top quality products to pharmaceutical consumers.

Authors’ Note: Over the past 15 years, Fred D. Sancilio, PhD, President of Sancilio & Company, Inc., has been a frequent visitor to many Asian pharmaceutical suppliers, and has developed a unique perspective on how to do business there. The observations and potential pitfalls noted in the body of this text do not exemplify any one country or region in particular, but is consistent with the practices and culture throughout Asia. However, since China has developed the largest number of potential US suppliers, most of the discussion that follows focuses on potential Sino-American related issues.

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